DOCTOR OF PHILOSOPHY

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Physicochemical Characterization of Solid Dispersions Prepared Using Hot-Melt Extrusion Technology

Osama Abdel Razzaq Ahmad Abu Diak, B.Sc., M.Sc.

This thesis is submitted to the Queen's University Belfast for the Degree of Doctor of Philosophy

School of Pharmacy
Faculty of Medicine, Health and Life Sciences
Queen's University Belfast

September 2009
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Dedication

To my father, my mother, my wife Lamees,

my children Zaid and Yusuf
I would like to express my sincere thanks to my supervisors Dr. Gavin Andrews and Prof. David Jones for their support and encouragement they offered me in this work.

My sincere thanks also go to HIKMA pharmaceuticals for sponsoring my PhD study at Queen's University Belfast. I would like to thank Mr. Samih Darwazah for allowing me to continue on my postgraduate studies and Dr. Ibrahim Jalal for his help on donating celecoxib raw material.

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Finally, I offer my regards to all staff and postgraduate students at school of pharmacy, Queen's University Belfast, for their kindness and help.
The main aim of this thesis was to investigate the feasibility of HME to manufacture solid dispersions of poorly soluble drugs, bicalutamide (BL) and celecoxib (CX), and to characterize the physicochemical properties of the prepared melt extrudates by different analytical techniques. Hot melt extruded solid dispersions of BL were prepared using polyethylene oxide (PEO) or polyvinylpyrrolidone (PVP) as hydrophilic carriers, whereas PVP or Eudragit 4155F was used to prepare the hot-melt extruded solid dispersions of CX. The solid state properties of the prepared solid dispersions were characterized using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) techniques. FT-IR and Raman spectroscopic techniques were also employed to characterize the solid state properties of the hot-melt extrudates.

BL was present mainly as an amorphous form in PEO solid dispersions prepared at drug : polymer ratios of 1:10 and 2:10, whereas solid dispersions at a ratio of 3:10 contained a significant amount of BL in the crystalline form. BL was molecularly dispersed within PVP melt extrudates at all prepared ratios (1:10, 2:0 and 3:10). It was shown that BL-PVP solid dispersions were physically more stable than BL-PEO solid dispersions. This physical solid state stabilization of amorphous BL by PVP may be attributed to the anti-plasticization effect of PVP on amorphous BL and the formation of new intermolecular interactions between BL and PVP that were stronger than the intermolecular interactions between BL individual molecules. Conversely, the physical instability of BL-PEO solid dispersions may be attributed to the solid state plasticization effect of PEO on BL and the lack of any strong specific interactions between BL and PEO. In vitro drug release studies showed significant increase in the dissolution properties of BL from the prepared solid dispersions in comparison to pure BL or the physically mixed samples of BL with the polymer. These results suggest the efficiency of HME in producing solid dispersions of BL that have enhanced dissolution properties and hence potentially improved oral bioavailability, particularly given that BL has absorption properties that are limited by its in-vivo dissolution properties. The increase in drug release from the solid dispersions was dependent on the polymer concentration in the melt extrudates. The
higher the polymer : drug ratio, the greater the improvement in the dissolution properties of BL. The significant increase in the dissolution properties of BL may be attributed to the effect of the polymer in enhancing the wetting properties of BL and the presence of BL in an amorphous form within the melt extrudates.

PVP was efficient in stabilizing the amorphous form of CX in both the solid state and during dissolution. The prepared hot-melt extruded solid molecular dispersions at 50 and 70% w/w PVP concentration remained stable without evidence of re-crystallization after storage for three months (40°C, 75% RH). Conversely, these results were only achieved using a high concentration of Eudragit 4155F (90% w/w) suggesting that PVP was more efficient in stabilizing the solid state properties of amorphous CX. This physical stabilization effect exerted by PVP may be attributed to its anti-plasticization effect on amorphous CX and the presence of strong intermolecular interactions which were stronger than the intermolecular interactions between the amorphous CX molecules. Conversely, it was shown using the Gordon-Taylor equation, that ideal mixing between CX and Eudragit 4155F in which the adhesive forces are equal to the cohesive forces existed in the CX:Eudragit 4155F binary system at 1:9 and 7:3 ratios. Conversely, non-ideal mixing existed in the midrange compositions of CX:Eudragit 4155F at 3:7 and 1:1 ratios suggesting that the adhesive forces between CX and Eudragit 4155F were weaker than the cohesive forces in such systems. Additionally, the glass transition (Tg) values of CX-Eudragit 4155F solid molecular dispersions were significantly lower than the Tg values of corresponding CX-PVP solid molecular dispersions. The polymer concentration dependent physical stability of CX-Eudragit 4155F solid dispersions may be attributed to the increase in the local viscosity of amorphous CX due to the formation of solid molecular dispersions and hence a reduction in the molecular mobility of the amorphous drug molecules.

Both PVP and Eudragit 4155F solid molecular dispersions generated supersaturated concentrations of CX which were maintained for up to 72 h achieving drug concentrations that were significantly greater than the equilibrium solubility of crystalline CX. The supersaturated drug concentrations achieved by Eudragit 4155F may be attributed to the solubilising effect of the polymer on CX particularly given that Eudragit 4155F significantly increased the solubility of crystalline CX at PBS 7.4
in which Eudragit 4155F had been dissolved or from the physically mixed samples. The solubilising effect of Eudragit 4155F on CX may be attributed to the formation of a soluble complex during dissolution as was confirmed by solution $^1$H NMR. Conversely, there were not any solubilising effects of PVP on CX either in PBS 7.4 in which PVP had been dissolved or from the physically mixed samples. However, the efficient stabilizing effects of PVP on the supersaturated concentrations of CX may be attributed to drug/polymer interactions as was confirmed by solution $^1$H NMR.

CX has poor compaction properties that make formulation into solid dosage forms difficult. HME was efficient in developing hot-melt extruded tablets of CX using PVP as a model hydrophilic matrix. It is well known that drug release rate from hot-melt extruded tablets is slow because of the high density of these tablets. Supercritical carbon dioxide (scCO$_2$) was used efficiently to enhance the drug release rate of CX from the prepared hot-melt extruded tablets. Exposure of the tablets to scCO$_2$ resulted in the formation of foamed like structure of increased porosity and hence increased surface area.

Hot melt extruded Eudragit 4155F polymeric matrix was efficient in releasing CX to in-vitro simulated colon medium (pH 7.4). The solid state properties of the hot-melt extrudates and the drug release properties were highly dependent on the extrusion temperature used to manufacture such tablets.
INTRODUCTION
1.1 Solid states properties of pharmaceutical materials

The solid phase is the most commonly encountered phase in the pharmaceutical industry. Most materials, either active pharmaceutical ingredients (APIs) or excipients, are in the solid phase. In addition, the most common pharmaceutical dosage forms e.g. tablets or capsules are solids. The solid phase can be classified into two major types, based on the order of molecular packing, crystalline or amorphous sub-phase (Cui, 2007).

1.1.1 Crystalline state

The molecules in the crystalline form are packed together with both short-range and long-range orders. Short-range order refers to the way that the neighboring molecules sit next to each other; while long-range order refers to the regularity or periodicity that molecule pack, first through "neighboring" (short-range) and then propagate to an "appreciable" distance, to form a phase (Cui, 2007). Crystalline solids can exist in multiple forms, such as polymorphs and pseudopolymorphs (solvates).

1.1.1.1 Polymorphism and pseudopolymorphism

Polymorphs arise when the drug substance crystallizes in different crystal packing arrangements and/or different conformation. Polymorphism in crystalline solids is defined as materials that have the same chemical composition but different internal lattice structures and/or different molecular conformation, and therefore possess different physicochemical properties (Vippagunta et al., 2001). The polymorph with the lowest free energy is the most stable polymorph and consequently has the lowest aqueous solubility because during dissolution water molecules need higher energy to overcome the intermolecular forces within the crystal lattice. There is a tendency of phase transition to the most stable polymorph. Thermodynamically, this condition is governed by loss of entropy to reach a high order condition. This is typically what could happen when a certain material is exposed to high temperature or humidity levels. The increase in the temperature and humidity acts as an energy input where the material can overcome any forces (which are relatively minimal) to transform into the more stable polymorph. In general, polymorphs are divided into two groups: monotropic and enantiotropic. In monotropic polymorphs the more stable crystal form has a higher melting point and enthalpy of fusion than the less stable
crystal form. When the higher melting form has a lower enthalpy of fusion, then the polymorphs are called enantiotropic (Rodriguez-Spong et al., 2003).

Pseudopolymorphs or solvates are crystalline solid adducts containing solvent molecules within the crystal structure. If the solvent is water, a solvate is termed a hydrate. Desolvated solvates are generated when a solvate is de-solvated and the crystal retains the structure of the solvate. Because crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties (density, hardness, tablettability, refractive index, melting point, enthalpy vapor pressure, solubility, dissolution rate, stability) which can significantly affect the manufacturing and the bioavailability of drug substances. The effect of polymorphism and pseudopolymorphism on the dissolution rate and hence the bioavailability of the drug substances has led to an increased regulatory interest in understanding the solid-state properties of drug substances (Vippagunta et al., 2001).

1.1.2 Amorphous state

An amorphous solid (glass) is similar to a crystalline solid that it may have short-range molecular order but it has no three-dimensional long-range order of molecular packing or well-defined molecular conformation that normally exists in a crystalline material. The position of molecules relative to one another is more random in an amorphous solid, typical of the liquid state. Thus molecules in amorphous form have physical properties different from those of their corresponding crystalline forms. In other words, amorphous solids have macroscopic properties of a solid and the microscopic structure of a liquid. Due to the high internal energy, amorphous solids possess enhanced thermodynamic properties, molecular motions, and chemical reactivity as compared to crystalline solids (Hancock and Zografi, 1997).

When a crystalline material is heated above its melting point (T_m), it transforms into the liquid state. If the liquid is cooled slowly then the material can re-crystallize to the crystalline form. This distinction between the two states can be seen as the drop in energy when the material is cooled down to give the solid crystalline form which represents a lower volume and enthalpy state. If the cooling rate is very
fast so that crystallization is prevented then the rubbery state (supercooled liquid) is obtained. This form has the properties of a liquid with appearance of a solid. Upon cooling of the sample, glassy amorphous form is obtained at the glass transition temperature (Tg). Increased viscosity will prevent the formation of crystal nuclei and instead a frozen glassy form is obtained. The difference between the glassy and rubbery states of the amorphous form is the molecular mobility. Molecules in the rubbery state exhibit faster relaxation rates (minutes to hours) than molecules in the glassy state (days to months) (Hilden and Morris, 2004). Hence, the glassy state represents the frozen state of the material where the molecules retain the structure of a liquid while they have high viscosity similar to solids. Due to the increased enthalpy and free volume of the amorphous form the tendency of amorphous materials is always to transform into the crystalline form. A thermodynamic representation of the transformation of the crystalline to amorphous form and vice versa is shown in Figure 1.1 which presents a schematic diagram of the enthalpy (H) or specific volume (V) of a solid substance as a function of its temperature. At a Kauzmann temperature ($T_K$) the crystalline form has higher entropy than the amorphous form. Hence, this theoretical temperature can define a limit where the amorphous form has minimum molecular mobility (Hancock and Zografi, 1997).

Figure 1.1 Schematic diagram of the variation of enthalpy (or volume) with temperature (Hancock and Zografi, 1997).
The main rationale to prepare the amorphous form of poorly soluble drugs is that it has a higher apparent solubility than the crystalline form. Due to the lack of order at long range distances there is no need for energy to break up the lattice as in the case of crystalline form. This can lead to enhanced dissolution and bioavailability, which is the focus of much pharmaceutical research. Conversely, the amorphous form has the highest free energy which means the lowest stability among the other solid forms and hence there is a possibility that during processing or storage the amorphous state may spontaneously convert back to the crystalline state (Hancock and Zografi, 1997). The most common means by which amorphous solids may be generated are summarized in Table 1.1.

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1.1.2.1 Aging of amorphous materials

Relaxation and crystallization of amorphous solids are the most important physical changes that occur to amorphous materials. These changes can occur as a result of the high energy of amorphous materials. Relaxation in the glassy state is often referred to as structural relaxation, physical aging, or annealing, and has strong temperature dependence. The relaxation rate is maximum close to the Tg while negligible relaxation occurs at temperatures far below it. The term "structural relaxation" refers to changes in atomic/molecular arrangements that occur during relaxation. Relaxation of amorphous materials, which can be detected either during storage or even directly after preparation, occurs due to configurational changes in the molecules so that it transforms from the nonequilibrium frozen glassy state to the equilibrium state. The molecular mobility below the glass transition temperature is slow so it is possible to predict the physical stability of amorphous materials by measuring the relaxation times. The effect of annealing time and temperature were investigated by many studies. Shamblin and Zografi (1998) studied the effect of additives on the enthalpy relaxation of sucrose. The enthalpy relaxation of sucrose decreased by formation of solid molecular dispersions having single Tg in the order dextran \( \approx \) PVP > PVP/VA > trehalose while there was no effect when these additives were physically mixed with sucrose. The enthalpy relaxation of amorphous lactose was studied at different aging temperatures and periods below the Tg (Haque et al., 2006). The enthalpy relaxation increased with increasing aging time and temperature indicating that the molecular mobility in amorphous lactose was higher at temperatures closer to Tg.
1.1.2.2 Factors affecting crystallization from the amorphous state

Since molecules in the amorphous state are thermodynamically metastable as compared to crystalline state, the potential for crystallization during processing and storage is always present. Crystallization from the amorphous matrix has been linked to the molecular mobility in the amorphous matrix and recent research has focused on developing the link between these two fundamental properties of amorphous materials. The roles of different factors in crystallization from the amorphous state were reviewed (Bhugra et al., 2008). Many studies were focused on studying crystallization of amorphous materials and the factors affecting the stabilization of these materials (Crowley and Zografi, 2003; Alie et al., 2004; Hancock et al., 1995; Andronis and Zografi, 1998). Crowley and Zografi (2003) found that particle size had a large effect on crystallization rates in amorphous indomethacin alone or in the presence of low concentrations of PVP molecularly dispersed (Crowley and Zografi, 2003). It was concluded by Alie et al., (2004) that the crystal growth process are controlled by the intramolecular oscillation of small dipolar groups (βα-relaxation) not by the molecular motions responsible for αa relaxation mode in a range of temperatures >Tg. Hancock et al., (1995) concluded in a study conducted on amorphous indomethacin, PVP and sucrose that glassy pharmaceutical solids should be expected to experience significant molecular mobility at temperatures up to fifty degrees below their glass transition temperature. Andronis and Zografi (1998) measured the dielectric relaxation times of supercooled indomethacin as a function of temperature and relative humidity above Tg. It was shown in this study that sorbed water lowered the dielectric relaxation times of supercooled indomethacin as a result of its significant plasticizing effects (Andronis and Zografi, 1998).
Humidity and temperature are the most important factors which induce crystallization of amorphous materials.

1.1.2.2.1 Humidity

Humidity is the water content in the environment surrounding the solid sample. The most common way to describe humidity is the relative humidity (RH) which describes humidity as the ratio between the partial vapour pressure of water ($p_{\text{water}}$) and the saturation vapour pressure of water ($p_{\text{saturated}}$).

$$RH = \frac{p_{\text{water}}}{p_{\text{saturated}}} \times 100\%$$

Equation 1.3

Water is the most common plasticizer (Tg = -150 to -130°C) hence quantification of water in air is essential to understand the physical stability of amorphous materials. Buckton and Darcy (1995) showed that the amorphous region of lactose has been plasticized by water adsorption allowing sufficient freedom of molecular movement to facilitate crystallization.

Humidity is not a constant value and may change with changing the temperature. If the temperature increases then the ability of air to dissolve more water vapour increases while the opposite will happen if the temperature decreases. The residual moisture content of a solid sample is in equilibrium with the air vapour. The moisture content of the sample may significantly decrease the stability of the amorphous form subsequently resulting in re-crystallization. The increase in moisture content of the sample means that drug molecules can have enhanced mobility facilitated by the plasticization effect of water molecules.
1.1.2.2 Temperature

The effect of temperature on the stability of amorphous drugs is very important (Bhugra et al., 2006). This effect is attributed to increased thermal energy which encourages the self association and phase separation in amorphous solid dispersions. Crystallization could be prevented by storing the amorphous drug at temperatures below the glass transition temperature (Hancock et al., 1995).

The combination of both the relative humidity (RH) and temperature is fundamental to understanding the increased mobility of the amorphous molecules. This mobility can be predicted to understand the spontaneous conversion of the amorphous form and therefore to define the best storage conditions of the amorphous material.

1.1.2.3 Mechanism of crystallization

The crystallization process starts with the formation of nuclei (nucleation). This step starts with the formation of tiny small crystals in the supersaturated phase. This step is followed by the attachment and association of the phase molecules to these nuclei to form larger crystals. The crystal growth process proceeds until an equilibrium state is reached between the saturation of the medium (the solvent or the carrier system in a solid dispersion) and the solid crystalline phase of the drug. The medium (solvent) can dissolve the drug and keep it in the amorphous form. Fast crystallization of the amorphous drug from the polymer means that the drug solubility that carrier has been exceeded and a supersaturated solution has been prepared. Although of significant benefit for improving the dissolution rate of poorly water soluble drugs, only a small number of solid dispersions have been successfully marketed, which may be attributed to the poor physical stability of formulations in the amorphous state (Serajuddin, 1999).
1.1.2.4 Stabilization of amorphous materials

The Tg is an important indicator of the stability of the amorphous state and it has been suggested that the Tg should be at least 50°C above the storage temperature to ensure stability over the shelf life of the product (Yoshioka et al., 1995). It is very important to analyze the Tg of the drug within the glass solid dispersion to know whether the glass solution formed with a specific drug and carrier for a given mass ratio will be in the glassy or rubbery state at the normal storage temperature (20-30°C) which is important for physical stability (Forster et al., 2001a). At storage temperatures exceeding the Tg a less viscous, rubbery state will form, with an increased tendency to re-crystallize (Lu and Zografi, 1998). The Tg of the drug can be increased by adding polymers with high Tg values that can form solid molecular dispersions (glass solutions) with the drug having a single Tg higher than the Tg of the amorphous form of the drug (anti-plasticization effect) (Van den Mooter et al., 2001). In drug/polymer systems, the stability of the amorphous form primarily depends on criteria such as drug polymer interaction, viscosity of the polymer, and the glass transition temperature of the system (Taylor and Zografi, 1997; Matsumoto and Zografi, 1999). The literature has shown that a higher glass transition temperature and viscosity usually show superior stability for the amorphous drug (Hancock and Zografi 1997; Hancock et al, 1995). The specific interactions between drug and polymer are important considerations for stabilization of the amorphous formulations. Therefore, the rational selection of polymeric materials is a key factor in developing stable solid molecular dispersions (solid or glass solution). Re-crystallization and nucleation of drug molecules from the polymer melt is retarded during the cooling of the extrudate due to reduced solute migration and the difficulty in nucleation in a highly viscous polymer medium. Furthermore, polymer viscosity is inversely proportional to temperature.
1.2 Solid dispersions

The term "solid dispersion" refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid-state prepared by the melting (fusion), solvent or melting-solvent method (Chiou and Reigelman, 1971). Solid dispersions are prepared to solve the problems associated with the bioavailability of poorly water-soluble drugs. When the carrier is dissolving, the drug will be exposed to significantly larger amounts of water (than if the drug was alone without the carrier) which can accelerate the dissolution of the drug. Moreover, the structure of the drug-polymer matrix has an important effect on the release mechanism of the drug. This is because molecular mixing can be totally different from physical mixing. Molecular mixing implies that the effect of the carrier is more significant than when physical mixing is used.

A biopharmaceutical classification system (BCS) categorizes the different drugs into four categories (Table 1.2) (Amidon et al., 1995). Class II drugs have low solubility in water and good permeability properties. A drug may be defined as poorly soluble whenever the dissolution rate is slower than the transit time in the gastrointestinal tract resulting in incomplete bioavailability. The dissolution rate of a certain drug can be assessed by its aqueous solubility as well as dose/solubility ratio. The dose solubility ratio is the volume of the gastrointestinal fluid necessary to dissolve the administered dose of the drug. When the volume required to dissolve the dose is higher than the available gastrointestinal fluid, a reduced bioavailability is expected. Therefore, the two factors (low aqueous solubility and high dose) result in reduced oral bioavailability.

| Table 1.2. The biopharmaceutical classification system of drug classes (Amidon et al., 1995) |
|---------------------------------|------------|------------|------------|------------|
| Class I | Class II | Class III | Class IV |
| Solubility | High | Low | High | Low |
| Permeability | High | High | Low | Low |
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Formulation of poorly soluble drugs for oral delivery now represents one of the greatest challenges to formulation scientists in the pharmaceutical industry. Due to the rapid increase in the number of poorly soluble drugs (Leuner and Dressman, 2000), with the recent advent of high throughput screening in the drug discovery process, resultant compounds are often high molecular mass, highly lipophilic and poorly water soluble (Lipiniski et al., 1997). It has been estimated that around 70% of all new molecular entities have poor bioavailability because of low aqueous solubility. This percentage is likely to increase due to a greater understanding of molecular targets of many diseases.

The modified Noyes-Whitney equation (Noyes and Whitney, 1897) describes how different factors influence the dissolution rate of a compound and hence how the dissolution rate of poorly soluble drugs can be improved:

\[
\frac{dC}{dt} = \frac{AD(C_s - C)}{h}
\]

Equation 1.4

where \(dC/dt\) is the rate of dissolution, \(A\) is the surface area of the compound available for dissolution, \(D\) is the diffusion coefficient of the compound, \(C_s\) is the saturated solubility of the compound in the dissolution medium, \(C\) is the concentration of drug in the medium at time \(t\) and \(h\) is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Based on Noyes-Whitney equation, improving the dissolution rate of a drug can be achieved by decreasing its particle size and hence increasing its surface area available for dissolution, optimizing the wetting characteristics of the drug surface, decreasing the boundary layer thickness or by improving the apparent solubility of the drug. Increasing the surface area available for dissolution can be achieved by grinding, but there is a practical limit to the degree of micronisation that can be achieved. Such fine powders may also be problematic in handling because of air adsorption, high dust formation and low apparent densities (Hülsmann et al., 2000). Lin et al. (1968) reported that the anticipated increase in the bioavailability from size reduction may not be achieved because of aggregation or agglomeration resulting in poor powder wettability. Salt formation can improve the solubility of a compound but
may often not be practical. The increased dissolution rate in the gastrointestinal tract may not be achieved due to the reconversion of the prepared salts into aggregates of the original compound (Serajuddin, 1999). Using surfactants or/and cosolvents to solubilize poorly soluble drugs leads to liquid formulations which are undesirable commercially and unacceptable by patients (Serajuddin, 1999). Additionally, using surfactants e.g. sodium dodecyl sulphate and tween 80 for drug solubilization was associated with toxicity problems because of the erosion of the cellular epithelium by these surfactants. Inclusion complexes of drugs with cyclodextrins (CDs) were highly efficient in increasing the solubility and the dissolution rate of many poorly soluble drugs and hence their oral bioavailability (Jambhekar et al., 2004; Basavaraj et al., 2006). The use of cyclodextrins is associated with some limitations such as the drug molecular size and the instability of the drug-CD complex upon changes in temperature and variable degree of solubilization when different methods of preparation are used (Challa et al., 2005).

Solid dispersions, first developed by Sekiguchi and Obi in 1961 (Sekiguchi and Obi, 1961), seem to be the most attractive option that can overcome all the limitations of the aforementioned methods to enhance the oral bioavailability of poorly soluble drugs. Formulating the compound as a solid dispersion either as a simple eutectic mixture or solid molecular dispersion (solid or glass solutions) can result in significant enhancement in drug solubility and hence its bioavailability. Once the solid dispersion is exposed to the aqueous media and the carrier dissolves, the drug is released as very fine, colloidal particles of greatly enhanced surface area. The lowest particle size that can be produced after disintegration of conventional capsules or tablets is approximately 5 μm whereas solid dispersions or solid solution release the drug as fine colloidal particles or oily globules of submicron size resulting in a faster dissolution rate and hence higher bioavailability (Serajuddin, 1999).
Solid dispersions combine the benefits of a local increase in the solubility and maximize the surface area of the active that is created as the carrier dissolves by contact with the dissolution medium (Serajuddin, 1999; Leuner and Dressman, 2000). Furthermore, an improvement in the drug wettability can occur (Yamamura and Rogers, 1996). Moreover, the carrier may affect the dissolution of a drug by a direct cosolubilisation or cosolvation (Leuner and Dressman, 2000). The drug may not possess the crystal structure in the solid dispersion, so no energy is required to break down the crystalline lattice enhancing the dissolution rate. Following the dissolution process, the drug is present as a supersaturated solution and in some cases the carrier may act as a precipitation inhibitor (Usui et al., 1997).

Chiou and Reigelman (1971) classified solid dispersions into groups (Figure 1.2): The prepared solid dispersions can be either one of these groups or combination with other groups.

![Figure 1.2. Categories of solid dispersions](image-url)
1.2.1 Eutectic mixtures

A simple eutectic mixture composed of two components which are completely miscible in the liquid state but only to a very limited extent in the solid state. The eutectic mixture can exhibit a faster dissolution profile than the physical mixture of the drug and the polymer as a result of the large surface area of the fine crystals released in the aqueous medium once the carrier is dissolved and through the enhanced wettability due to presence of the hydrophilic carrier. This approach has been used to improve the dissolution of poorly soluble drugs (Chiou and Niazi, 1976; Yong et al., 2003). When determining eutectic mixture compositions, it is important to decide the ratio of each component, which requires extensive experimental work (Law et al., 2002; Law et al., 2003; Vippagunta et al., 2007). Drug release from the eutectic mixture depends on the size of crystals formed, the ratio of the carrier to active, and the interaction between the drug and carrier. In addition, crystalline forms of drugs are associated with slow dissolution. Hence, a modification is necessary to ensure that fast and reproducible dissolution rate is obtained.

1.2.2 Solid molecular dispersions (solid or glass solutions)

A drug/polymer system can be defined as a solid molecular dispersion (solid solution or glass solution) when the drug is dissolved at a molecular level, that is, when the drug forms a one phase system with a polymer. In order to qualify as solid molecular dispersions, the drug/polymer system should satisfy the following criteria:

(a) The mixture of drug and polymer should show a single glass transition temperature.
(b) The drug should be present in the amorphous form (Goldberg et al., 1965; Goldberg et al., 1966).

In solid molecular dispersions, the particle size of the drug has been reduced to its absolute minimum i.e. the molecular dimensions (Goldberg et al., 1965) and the dissolution rate of the carrier determines the dissolution rate of the drug. Solid solutions can be classified according to their miscibility into continuous and discontinuous solid solutions. In a continuous solid solution, the components are miscible in all proportions. Discontinuous or partially miscible systems are the most
common types of solid solutions where the drug and the polymers are partially miscible. The ideal type of solid dispersion for increasing dissolution is the glass solution, in which the amorphous drug has a lower thermodynamic barrier to dissolution together with a maximally reduced particle size (Hancock and Zografi, 1997). In addition, the intimate presence of a hydrophilic excipient can increase wetting and lead to supersaturation in the diffusion layer (Chiou and Riegelman, 1971)

1.2.3 Drug carrier interactions in solid dispersions

Drug polymer interactions affect the miscibility of the drug within the carrier. An increase in the miscibility of the drug within the carrier means that solid molecular dispersions can be produced with more intimate mixing between the drug and the carrier and hence enhancement in both the stability and the dissolution properties can be obtained. The higher miscibility of the drug within the carrier, the more stable the solid molecular dispersions formed as the carrier will prevent the re-crystallization of the amorphous form of the drug by acting as a solvent for the drug in the solid state. The presence of strong drug carrier interactions reduces the hygroscopicity of the highly water soluble carrier especially if hydrogen bonding interactions are present between the carrier and the drug (Thypo et al., 2007; Forster et al., 2001b). Additionally, incorporation of the functional groups of the amorphous molecules with strong hydrogen bonding with the carrier will decrease their molecular mobility and will prevent the amorphous drug molecules from rearranging their intra and intermolecular forces to form crystals. The role of hydrogen bonding interactions between a drug and a carrier has been explained previously (Tantishaiyakul et al., 1999; Vasanthavada et al., 2005). The effect of hydrogen bonding in increasing the stability of the amorphous form of a drug has been explored and the formation of hydrogen bonding in solid dispersions was confirmed using different techniques (Forster et al., 2001b, Taylor and Zografi, 1998). Therefore, the rational selection of the carrier based on the miscibility with the drug and the possibility of formation of strong hydrogen bonding with the drug is very important to maintain the amorphous form of the drug within the solid dispersion during storage and to enhance the drug release properties of the drug (Konno et al., 2008).
1.2.4 Methods used for solid dispersions preparation

1.2.4.1 Solvent evaporation method

The problems associated with the melting methods like the thermostability and the difficulty in processing the polymers of high melting or glass transition temperatures were solved by the solvent methods. With the solvent evaporation method, the drug and the carrier are dissolved in a common solvent followed by the removal of the solvent by evaporation, spray drying (Lo et al., 1996) or freeze drying (Betageri et al., 1995). Tachibani and Nakumara (1965) were the first who used this method to prepare a solid solution of β-carotene in PVP. The most important prerequisite for preparing solid dispersions using this method is that both the drug and the carrier must be sufficiently soluble in the solvent. Temperatures used for solvent evaporation usually lie in the range 23-65°C (Kearney et al., 1994; El-Zein, 1998). It is very important for the solvents to be removed thoroughly since most of the organic solvents used have toxicity issues. The problem of residual solvents and the consumption of considerable volumes of organic solvents which is unfavorable in pharmaceutical industries due to associated hazards on the environment as well as on the working staff are considered the most important disadvantages of this method. In addition, solvent methods are time-consuming and expensive because of long processing and drying times. Based on the ecological and economic problems associated with the use of organic solvents in these methods, hot melt extrusion (HME) is the current method of choice for the manufacture of solid dispersions (Leuner and Dressman, 2000).

1.2.4.2 Hot melt method

With the hot melt method, the drug and the carrier are melted together and then cooled rapidly to yield a solid dispersion of the drug and the carrier. This method was used to prepare simple eutectic mixtures of sulphathiazole and urea (Sekiguchi and Obi, 1961). To form a solid molecular dispersions (solid solutions) by the hot melt method, the drug and the polymer must be miscible in the molten form. This method is unsuitable for thermolabile drugs as the heating process might result in the degradation of the drug or the carrier, so both the drug and the carrier must be thermally stable at the processing temperature. Because of this limitation, the solvent
method became more commonly used in the 1970s and 1980s until the advent of HME which has been applied to manufacture solid dispersions. The materials used during HME are only subjected to an elevated temperature for very short periods (1 min), enabling drugs and polymers that are somewhat thermolabile to be processed.

1.3 Hot-melt extrusion (HME)

1.3.1 Definition

Extrusion can be simply defined as the process of forming a new material (the extrudate) of uniform shape and density by forcing it through an orifice or die under controlled conditions such as temperature, mixing, feed-rate and pressure.

1.3.2 Industrial applications of HME with historical background

The industrial applications of the extrusion process dates back to the 1930s especially in the plastic and food industries (Mollan, 2003). Today HME technology is considered as one of the most important industrial processes in the plastic and rubber industries with more than half of all plastic products manufactured using this process (Kaufman and Falcetta, 1977) e.g. pipes, hoses, insulated wires, plastic bags and cables, plastic and rubber sheeting, and polystyrene tiles.

Today, HME has found its place in the pharmaceutical industry and the interest in the pharmaceutical applications of HME especially in manufacturing solid dispersions and controlled release drug delivery systems is growing rapidly with more than 100 research papers published in the last 12 years. In addition, the number of patents issued in the area of pharmaceutical applications of HME has steadily increased from the early 1980s (Figure 1.3) with international scope (Figure 1.4) (Crowley et al., 2007).
Figure 1.3. The number of hot-melt extrusion patents issued for pharmaceutical applications from 1983 to 2006 (Crowley, et al., 2007)

Figure 1.4. The number and percentage of hot-melt extrusion patents issued by country since 1983 for pharmaceutical applications (Crowley et al., 2007)
1.3.3 Advantages of HME

The advantages of HME technology make it an attractive alternative to traditional manufacturing processes used in the pharmaceutical industry (Breitenbach, 2002; Crowley et al., 2007; McGinity and Zhang, 2003).

- HME is a fast, simple, efficient and continuous process offering an efficient scale up from small scale laboratory equipment to large scale production machines.

- It is a solvent free process avoiding time-consuming drying steps and the problems relating to the use of organic solvents such as environmental pollution, explosion-proofing and residual organic solvent.

- HME is an anhydrous process, avoiding potential hydrolytic degradation.

- The short residence time of the raw materials inside the extruder during HME with the availability of thermoplastic polymers of low melting or glass transition temperatures and the efficient use of plasticizers in reducing the glass transition or/melt viscosity, enable HME to be more efficient in extruding heat labile drugs or polymers compared to other hot melt methods. Thermally labile drugs like hydrocortisone (Repka et al., 1999) and p-aminosalicylic acid (Verreck et al., 2006a) were successfully processed using HME. The decrease in the molecular weight of polylactic acid (PLA) was more pronounced after injection moulding of PLA with a somatostatin analogue to produce an implant compared to extrusion process indicating less \textit{in vitro} degradation of PLA after the extrusion process compared with an injection moulding process and hence a more stable implant formulation produced by the extrusion process (Rothen-Weinhold et al., 1999).

- Molten polymers during HME can act as thermal binders which upon cooling and solidification, form drug depots for producing highly efficient sustained release pharmaceutical products.

- More uniform dispersion of the drug within the polymeric carrier can be achieved by HME as a result of the intense mixing generated by the rotating screws that lead to efficient de-aggregation of drug particles in the molten polymer.

- Raw materials can be processed by HME regardless of their compression, polymorphic and particle size properties. Materials with poor compaction
properties can be prepared as tablets without a compression process by cutting an extruded rod to the desired dimensions.

- HME technology is suitable for both high dose and potent drugs. The efficient mixing that occurs in the barrel of the extruder during processing ensures good content uniformity of the drug in the finished product.

1.3.4 HME equipment

Extrusion process technology can be divided into two categories based on the mode of operation: ram extrusion (discontinuous) and screw extrusion (continuous). Ram extrusion operates with a positive displacement ram capable of generating high pressures to force material through a shaping die, while screw extrusion consists of a rotating screw or set of screws inside a heated barrel.

1.3.4.1 Ram extrusion

During ram extrusion, materials are introduced into a heated cylinder. After an induction period to soften the materials, a ram (or a piston) pressurizes the soft materials through the die and transforms them into the desired shape (Figure 1.5). High pressure is the operating principle of ram extrusion. The ram exerts modest and repeatable pressure as well as a very consistent extrudate diameter. The major drawback of ram extrusion is the limited melting capacity that causes poor temperature uniformity in the extrudate. Also, extrudates prepared by ram extrusion have lower homogeneity, in comparison with extrudates processed by screw extrusion (Perdikoulis and Dobbie, 2003). Ram extrusion was shown to be highly efficient in producing a fast release dosage form with uniform shape and density, containing carbamazepine as a water-soluble drug and polyethylene glycol as a carrier (Perissutti et al., 2001).
1.3.4.2 Screw extrusion

Screw extrusion consists of at least one rotating screw inside a stationary cylindrical barrel that provides more shear stress and intense mixing than ram extrusion. A screw extruder consists of three distinct parts: a conveying system for material transport and mixing, a die system for forming, and downstream auxiliary equipment for cooling, cutting or collecting the finished products (Breitenbach et al., 2002). Individual components within the screw extruder are the feed hopper, a temperature controlled barrel, a rotating screw, die systems and heating/cooling systems. Standard process control and monitoring devices include zone temperature and screw speed with optional monitoring of torque, drive amperage, and pressure and melt viscosity. Temperatures are normally controlled by electrical heating bands and monitored by thermocouples (Crowley et al., 2007). Specific screw features are displayed in Figure 1.6. The dimensions of the screws are given in terms of L/D ratio, which is the length of the screw divided by the diameter. Screws are designed with several sections, with the function of each section ranging from feeding, mixing, compression, and metering. Most screws are made from surface coated stainless steel to reduce friction and the possibility of chemical reactions (Steiner, 2003).
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Figure 1.6. Extrusion screw geometry (Breitenbach 2002).

A distinction can be made based on the number of screws incorporated in the extruder, resulting in single-screw, twin-screw or multi-screw extruders. As indicated by the name, the difference between a single-screw and twin-screw extruder is whether one or two screws are utilized in the machine. Also, they differ in the type of material transport and mixing abilities that take place in the extruder. In a single-screw extruder (Figure 1.7), one screw rotates inside the barrel and is used for feeding, melting and pumping the material in the direction of the die (a drag-induced type of transport), whereas the transport in a twin-screw extruder is to some extent a positive displacement type of transport, with a reduced degree of leakage flow since there is a possibility of exchanging material from one screw to the other. Single-screw extruders are less efficient than twin-screw extruders, and therefore have generally a longer equipment length. Twin-screw extruders have several advantages over single-screw extruders, such as easier material feeding, high kneading and dispersing capacities and less tendency to overheat the material. In addition, twin-screw extruders have the advantage of a shorter residence time, therefore, a smaller equipment size is required to achieve an equivalent output, and twin-screw extruders are currently used to process higher quantities of material. On the other hand, single screw extruders do have the advantage over twin-screw extruders in terms of their mechanical simplicity, are less expensive and hence provide high productivity-to-cost ratios. Single-screw extrusion is a fundamental operation for polymer processing in the plastic industry and not the preferred approach for the production of
pharmaceutical formulations (Mollan, 2003; Breitenbach, 2002; McGinity and Zhang, 2003; Crowley et al, 2007).

Figure 1.7. Component parts of a single-screw extruder (Breitenbach et al., 2002)

Twin-screw extruders were initially developed in the 1800s, with the concept of combining the machine actions of several available devices into a single unit. They had several significant engineering issues that were not fully overcome until the 1940s. A twin-screw extruder, as its name implies, consists of two screws usually arranged side by side allowing different configurations to be obtained and imposing different conditions on all zones of the extruder from the transfer of material from the hopper to the screw, all the way to the metered pumping zone. Twin-screw extruders are either co-rotating or counter-rotating extruders. In a co-rotating extruder, the screws rotate in the same direction while in counter-rotating extruders the screws are rotating in the opposite direction (Figure 1.8 and Figure 1.9). Co-rotating screws can rotate either clockwise or counter-clockwise, and both directions are equivalent from a processing standpoint. Counter-rotating screws can rotate either toward the centre or away from the center. The counter-rotating designs are utilized when very high shear regions are needed as they subject materials to very high shear forces as the material is squeezed through the gap between the two screws as they come together. Counter-rotating twin-screw extruders suffer from disadvantages of potential air entrapment, high-pressure generation, and low maximum screw speeds and output. These types of extruders are operated at lower speeds because of the pressure which is developed from the outward pushing effect as the screws come together in rotation. Co-rotating
twin-screw extruders can be operated at higher screw speeds and achieve higher outputs, while maintaining good mixing and conveying characteristics. Both rotational designs with twin-screw extruders have the basic processing advantages of positive conveying and effective mixing as compared with single-screw extruders. In general, co-rotating shafts have better mixing capabilities as the surfaces of the screws move towards each other. (Mollan, 2003; Breitenbach, 2002; McGinity and Zhang, 2003; Crowley et al, 2007).

These two primary types of the twin screw extruders can be further classified as non-intermeshing and fully intermeshing. The fully intermeshing type of screw design is the most popular type used for twin-screw extruders (Figure 1.8 and Figure 1.9) (Thiele, 2003). This design itself is self-wiping: the flight of one screw wipes the root of the screw on the shaft next to it causing material to transport from one screw to the other. In this manner the material is transported along the extruder barrel, thereby preventing material from rotating with the screw which is a significant advantage over a single-screw extruder. This arrangement in the twin-screw extruder eliminates stagnation areas, and ensures near complete emptying of the equipment (first in/first out principle) which prevents localized overheating of materials within the extruder (Breitenbach, 2002). In non-intermeshing extruders, the arrangement comes close to a single-screw set-up and has a lower degree of positive conveying. The non-intermeshing types are also described as double-screws as they are not true twin-screw extruders, they consist of essentially two-single screws side by side and work in a similar way as single-screw extruders. Non-intermeshing extruders are often used when large amounts of volatiles need to be removed and when processing highly viscous materials (Mollan, 2003).
Figure 1.8. Twin-screw configurations: (top) intermeshing co-rotating twin-screw extruder, (bottom) intermeshing counter-rotating twin-screw extruder (Mollan et al., 2003).

Figure 1.9. Twin screw design examples: (top) intermeshing co-rotating twin screw, and (bottom) intermeshing counter-rotating twin-screw (Crowley et al., 2007).
The modular design of the most commercial extruders with the segmented screw elements allow agitator designs to be easily optimized to suit a particular application such as high or low shear (Figure 1.10). Die plates can also be easily exchanged to alter the extrudate diameter and hence the spheroid diameter. This versatility allows processing of many different formulations on a single machine using polymers of a wide range of viscoelastic and melt viscosities, leading to good equipment utilization (Breitenbach, 2002; Nakamichi et al., 2002; 2003).

Figure 1.10. Screw and kneading elements (Breitenbach, 2002)
1.3.5 HME process

The extrusion channel is conventionally divided into three zones along the length of the barrel: feed zone (solid conveying zone), the transition zone (melting, compression), and metering zone as shown in Figure 1.11.

![Figure 1.11. Schematic of an extruder illustrating various functional zones including the hopper, solid conveying zone, melting zone, metering zone and die (Follonier et al., 1995).](image)

The starting material is fed from a hopper directly into the feed zone, which has deeper flights or flights of greater pitch (Figure 1.12). This geometry enables the feed material to fall easily into the screw for conveying along the barrel. Pitch and helix angle determine the throughput at constant rotation speed of the screws. The channel depth is usually widest in this zone to facilitate mass flow and the transfer of the solid material forward as a solid plug to the transition zone where it is mixed, compressed, melted, and plasticized. Compression is developed by decreasing the thread pitch but maintaining a constant flight depth or by decreasing flight depth while maintaining a constant thread pitch resulting in increasing pressure as the material moves along the barrel. This increase in pressure facilitates the removal of entrapped air. The polymer gradually begins to soften and melts as it enters the melting zone; melting results from the heat transferred to the barrel from the heaters as well as from the heat generated by friction as the polymer is sheared between the rotating screws and the barrel wall. The space between the diameter of the screw and the width of the barrel is normally in the range of 0.1-0.2 mm. The melt moves by circulation in a helical path. For producing an extrudate of uniform thickness, flow
must be consistent and without stagnant zones right up to the die entrance. The
function of the metering zone is to reduce pulsating flow and ensure a uniform
delivery rate through the die that is attached to the end of the barrel and dictates the
shape of the extrudate. The prepared extrudates can be further processed by auxiliary
downstream devices for cooling, cutting or collecting the finished products (Figure
1.12) (Breitenbach, 2002; McGinity and Zhang, 2003; Ghebre-Sellassie et al., 2003,
Crowley et al., 2007).

Figure 1.12. Illustration of a pelletizer used to chop rod shaped extrudates into
pellets or granules (Crowley et al., 2007).

1.3.6 Regulatory aspects of HME

The extruders designed for pharmaceutical uses are mostly identical in their
basic layout to the extruders used in the polymer industry with some differences to
meet regulatory requirements of the pharmaceutical industry like the metallurgy of the
contact parts that must not to be reactive, additive or absorptive with the product and
some specific configurations for cleaning and validation requirements. Cleaning is
accomplished by disassembly and removal of any excess material from the screw,
barrel, and die. These surfaces can then be swabbed and analyzed to satisfy cleaning
validation requirements (Crowley et al., 2007).
Chapter 1

HME is a mature engineering technology that can provide data about many processing parameters such as feeding rate, segmental temperatures, screw speed, pressure, melt viscosity, drive amperage, torque or applied vacuum. These data can contribute to the comprehensive documentation and the quality of the production lots and hence satisfy regulatory authorities. Oral pharmaceutical products manufactured by HME have been approved in the USA, European and Asian countries (Breitenbach, 2002).

1.3.7 Materials used in HME

The eligibility of the materials for HME is determined by the following physicochemical properties:

- melt viscosity, molecular weight, glass transition temperature and melting point (in the case of a semicrystalline polymer) should be considered to establish appropriate processing parameters. The temperature of the melting zone is normally set 15–60°C above the melting point of semi-crystalline polymers or the glass transition temperature of amorphous polymers. In general, polymers with low melt viscosities and high thermal conductivities exhibit a more efficient melting process (Crowley et al., 2007).

- the sensitivity of the materials towards heat and shear force. HME can only be applied when the products are thermally stable. For a number of drugs, proteins and other excipients, HME can not be used unless a plasticizer is added in order to reduce the viscosity of the mixture in the extruder and therefore to lower the process temperature settings (Verreck et al., 2005).

- thermoplastic properties: the ability of the materials to deform easily inside the extruder and solidify upon its exit.

- good powder flow properties, otherwise an erratic flow will occur forming a solid bridge at the throat of the hopper (McGinity and Zhang, 2003). Material transfer should be efficient in order to maintain an increase in pressure in the compression zone and the metering zone to insure efficient output of the extrudate. Inconsistent material feed may result in a “surge” phenomenon that will cause cyclical variations in the output rate, head pressure, and product quality. A force feeding device such as a mass flow feeder or side stuffer can be used to direct the materials onto the rotating screw (Doetsch, 2003).
Hot-melt extruded dosage forms are complex mixtures of drugs and functional excipients. Functional excipients may be broadly classified as matrix carriers, release modifying agents, bulking agents, antioxidants, thermal lubricants and miscellaneous additives.

1.3.7.1 Carriers

The carrier is usually a polymer or a low melting point wax. The selection of a suitable carrier is important in the formulation and design of a hot-melt extruded dosage form as the physico-chemical properties of the carrier often determine the processing conditions and the release kinetics of the active compound from the final dosage form. Carriers used in hot-melt extruded dosage forms have included water-insoluble polymers and waxes such as ethyl cellulose or carnauba wax in which the drug release rate is diffusion controlled. Water-soluble polymers have included hydroxypropyl cellulose, polyethylene oxide, poly(vinyl pyrrolidone) in which the drug is released by a diffusion and erosion mechanism (Keleb et al., 2001; Repka et al., 2000a, 2001a). Table 1.3 lists some of the most common carriers used to prepare hot-melt extruded dosage forms.

Formulation of a hot-melt extruded dosage form may contain some functional excipients that can function as a processing aid or drug release modifier. Citric acid monohydrate was found to be an effective solid-state plasticizer for Eudragit RS PO that facilitates the production of controlled-release matrix systems by HME (Schilling et al., 2007). In another study, citric acid monohydrate significantly increased the release of diltiazem hydrochloride from Eudragit® RS PO matrix as a result of enhanced pore formation (Schilling et al., 2008). Citric acid monohydrate, in this study, showed a faster and more complete drug release compared to systems with drug only or alternative pore formers.
<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Trade Name</th>
<th>Tg (°C)</th>
<th>Tm (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonio methacrylate copolymer</td>
<td>Eudragit® RS/RL</td>
<td>64</td>
<td></td>
<td>(Follonier et al., 1994; Kidokoro et al., 2001; Zhu et al., 2002b)</td>
</tr>
<tr>
<td>Poly (dimethylaminoethyl) methacrylate-</td>
<td>Eudragit® E</td>
<td>50</td>
<td></td>
<td>(Atken-Nichol et al., 1996; Repka and McGinity, 2000b)</td>
</tr>
<tr>
<td>methacrylate) esters</td>
<td>Eudragit® 4135F</td>
<td>48</td>
<td></td>
<td>(Young et al., 2002)</td>
</tr>
<tr>
<td>Poly (methyl acrylate-co-methyl methacrylate-acid</td>
<td>Eudragit® S</td>
<td>160</td>
<td></td>
<td>(Follonier et al., 1995)</td>
</tr>
<tr>
<td>(7:3:1)</td>
<td>Klucel®</td>
<td>130</td>
<td></td>
<td>(Repka et al., 1999, 2000a, 2001b; Sato et al., 1997)</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>Polyox WSR</td>
<td>133</td>
<td>-67</td>
<td>(Crawley et al., 2004b; De Brabander et al., 2002; Follonier et al., 1994; Follonier et al., 1995)</td>
</tr>
<tr>
<td>Poly (ethylene oxide)</td>
<td>Carbowax®</td>
<td>50</td>
<td>20</td>
<td>(Forster et al., 2001a; Hülsmann, et al., 2000; Perissuti et al., 2002; Follonier et al., 1995; Forster et al., 2001a; Forster et al., 2001b; Hülsmann, et al., 2000)</td>
</tr>
<tr>
<td>Poly (ethylene glycol)</td>
<td>Kollidon® V64</td>
<td>168</td>
<td>37-63</td>
<td>(Follonier et al., 2001a; Koele et al., 1999; Nakamichi et al., 2002)</td>
</tr>
<tr>
<td>Poly (vinyl pyrrolidone)</td>
<td>Methocel®</td>
<td>137</td>
<td>150</td>
<td>(Forster et al., 2001a; Hülsmann, et al., 2000b; Hülsmann, et al., 2001)</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone-phthalate methacrylic</td>
<td>Aquasol® AS</td>
<td>-175</td>
<td></td>
<td>(Nakamichi et al., 2001)</td>
</tr>
<tr>
<td>Methacrylic acid copolymer Type C</td>
<td>Eudragit® L100-55</td>
<td>-104.4</td>
<td></td>
<td>(Young et al., 2005)</td>
</tr>
</tbody>
</table>
1.3.7.2 Plasticizers

Plasticizers are typically low molecular weight compounds capable of softening polymers to make them more flexible. Plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains as a result of the inter-molecular secondary valence forces between the plasticizer and the polymer (Aharoni, 1998). Plasticizers are used in HME to improve the processing conditions or to improve the physical and mechanical properties of the hot-melt extruded dosage forms. In transdermal films, the addition of a plasticizer to the polymer matrix can improve the film's flexibility by influencing the product's tensile strength and elastic modulus (Aitken-Nichol et al., 1996; Repka et al., 1999). With the addition of a plasticizer, a HME can be conducted at lower temperatures and with less torque enhancing the stability of materials during HME. The most commonly used plasticizers in pharmaceutical dosage forms are triethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, polyethylene glycol, propylene glycol and triacetin. Recently, it was shown that surfactants can be promising plasticizers in producing solid dispersions by HME in addition to acting as solubilizers (Ghebremeskel et al., 2006).

To be used in HME, plasticizers must have good efficiency, stability, polymer plasticizer compatibility, and permanence. Permanence of a plasticizer during processing and storage is very important as the physical-mechanical properties and drug release rate of the hot-melt extruded dosage form is dependent on the permanence of plasticizers. The evaporation of highly volatile plasticizers from the dosage form during storage has been reported. Repka and McGinity (1999) demonstrated that the amount of plasticizer remaining in hot-melt extruded films over time was a function of plasticizer type and storage conditions.
1.3.7.3 Other processing aids

Antioxidants can be used in hot-melt extruded formulations to protect the polymers, drugs or other excipients that are susceptible to degradation by oxidation. Oxidative drug degradation during HME has been reported by Aitken-Nicol et al. (1996) and Repka et al. (1999). Hindered phenols and aromatic amines such as butylated hydroxyanisole, butylated hydroxytoluene and vitamin E are chain breaking antioxidants that inhibit free radical chain reactions. The O-H bonds of phenols and the N-H bonds of aromatic amines are very weak, so the rate of oxidation is generally higher with the antioxidant than with the polymer. Butylated hydroxytoluene was used as antioxidant for hydroxypropylcellulose and polyethylene oxide (PEO) during HME (Repka et al., 2005; Prodduturi et al., 2004; 2005). It has been reported that the thermal oxidation of polyethylene oxide was highly dependent on polymer molecular weight, the lower molecular weight polymer degraded more rapidly than the higher molecular weight polymer (100,000>600,000>1,000,000) (Crowley et al., 2002). In this study, the efficiency of different antioxidants to protect PEO from free radical and oxidative degradation were investigated, and it was shown that vitamin E, vitamin E succinate and vitamin E TPGS were efficient stabilizers for PEO while butylated hydroxyanisole and Vitamin E acetate were ineffective in stabilizing PEO during extrusion.

Waxy materials like glyceryl monostearate have been reported to function as a thermal lubricant during hot-melt processing (Henrist, et al., 1999a; Henrist and Remon, 1999b, 1999c; Bruce et al., 2005). Functional excipients can act as solid state plasticizers for certain polymers. Methylparaben acted as an efficient solid-state plasticizer for Eudragit RS PO resulting in a decreased Tg and melt viscosity (Wu and McGinity, 2003). In this study, it was found that methylparaben was as efficient as triethyl citrate (TEC) in reducing the torque during the melt extrusion process. Vitamin E TPGS has been reported to plasticize polymers and enhance drug absorption (Crowley et al., 2002; Repka et al., 2000a; Repka et al., 2001a). Pressurized carbon dioxide acted efficiently as a temporary plasticizer for PVP-VA64, Eudragit E100 and ethyl cellulose 20cps during HME (Verreck et al., 2006b).
1.3.7.4 Active Pharmaceutical Ingredients (APIs)

APIs can be either beneficial or detrimental to the properties of hot-melt extruded dosage forms and may facilitate or hinder the functionality of the other components in the formulation. Oxprenolol hydrochloride was shown to melt under the HME processing conditions resulting in a decreased viscosity of the extrudate to produce a material with poor handling properties (Follonier et al., 1994). Conversely, several drug substances have been reported to function as solid state plasticizers in hot-melt extruded dosage forms (Chokshi, et al., 2005; Zhu et al., 2002b, Zhu et al., 2006b). Tables 1.5, 1.6 and 1.7 provide a partial listing of some of the drug substances that have been formulated and processed by HME.

1.3.8 Characterization of physicochemical properties of hot-melt extruded dosage forms

HME is a non-ambient process requiring elevated temperatures that may affect the stability of drugs. High-pressure liquid chromatography (HPLC) is the most commonly used technique to investigate the stability of drug substances. Stability indicating methods should be developed so that the active ingredient is separated from the degradants. Additionally, polymers during HME may undergo chain scission, depolymerization or thermal degradation due to the effects of the mechanical shear imposed by the rotating screw and the relatively high processing temperatures (Zhang and McGinity, 1999). Differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and gel permeation chromatography are often used to monitor polymer stability.

It is very important to characterize the solid state properties and the miscibility of the drug with the carrier and to investigate any drug carrier intermolecular interactions within the melt-extrudates and the nature and the strength of these interactions. The solid states properties of the drug within the polymeric matrices depend on the degree of miscibility between the drug and the polymer during HME. Following HME, an API may be present in the crystalline form embedded in the hardened polymer phase, or on a molecular level intimately mixed in the polymer matrix (glass or solid solutions). In glass solutions, the drug is molecularly dispersed (solubilized) within the amorphous solvent (polymer), whereas in solid solutions
some drugs were reported to be concentrated in the amorphous regions of the semi-crystalline polymer (Delahaye et al., 1997, Schachter et al., 2004), and some drugs were reported to be solubilized in the crystalline matrix of the polymer (Chiou et al., 1971). It is challenging to precisely characterize amorphous solid dispersions, which are molecularly dispersed from those that are not due to the complexity of the systems, and different analytical methods may yield contrasting results. A screening system based on a dimeric moiety of polyvinylpyrrolidone (PVP) has been presented which is capable of comparing the solubility in the liquid to that in the solid (polymer) (Neumann et al., 1999). In general, dispersions in which no crystallinity can be detected are molecularly dispersed (Crowley et al., 2007). The methods that have been used to characterize hot-melt extrudates are summarized in Table 1.4.

Table 1.4. Common methods used for the characterization of hot-melt extrudates (adapted Crowley et al., 2007)

<table>
<thead>
<tr>
<th>Thermoanalytical Methods</th>
<th>Dissolution Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential Scanning Calorimetry</td>
<td>Powder X-Ray Diffraction (PXRD)</td>
</tr>
<tr>
<td>Thermogravimetric Analysis</td>
<td>Fourier Transform Infrared (FT-IR)</td>
</tr>
<tr>
<td>Hot Stage Microscopy</td>
<td>Fourier Transform Near Infrared (FT-NIR)</td>
</tr>
<tr>
<td>Microthermal Analysis</td>
<td>Fourier Transform Raman (FT-Raman)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spectroscopic Methods</th>
<th>Microscopic Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray Diffraction</td>
<td>Polarized Light Microscopy</td>
</tr>
<tr>
<td>Fourier Transform Infrared (FT-IR)</td>
<td>Scanning Electron Microscopy</td>
</tr>
<tr>
<td>Fourier Transform Near Infrared (FT-NIR)</td>
<td>Transmission Electron Microscopy</td>
</tr>
<tr>
<td>Powder X-Ray Diffraction (PXRD)</td>
<td>Atomic Force Microscopy</td>
</tr>
<tr>
<td></td>
<td>Magic Angle Spinning Techniques</td>
</tr>
<tr>
<td></td>
<td>Cross-Polarization Techniques</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nuclear Magnetic Resonance</th>
<th>Mechanical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magic Angle Spinning Techniques</td>
<td>Tensile Strength</td>
</tr>
<tr>
<td>Cross-Polarization Techniques</td>
<td>Elongation</td>
</tr>
<tr>
<td></td>
<td>Young's Modulus</td>
</tr>
</tbody>
</table>
Miscibility can be experimentally determined with DSC, hot stage microscopy and theoretically using solubility parameter calculations to give a prediction of the possibility of formation of solid molecular dispersions after HME (Forster et al., 2001a). HME of miscible components results in solid molecular dispersions formation, whereas extrusion of immiscible components led to an amorphous drug dispersed in the polymeric excipients. The presence of a single Tg between the Tg of the amorphous drug and carrier is evidence of miscible system (Lu and Zografi, 1998). The Gordon-Taylor equation states that the Tg of an ideally mixed solid molecular dispersions will be the sum of the weight fraction, thermal expansion and Tg of the individual components (Schneider, 1989). Partial miscibility is evident when the Tg of the drug is shifted towards the Tg of the polymer, or vice-versa whereas if both the Tg values remains practically unchanged at all mass ratios it is strong evidence of an immiscible system (Yu et al., 1998). The drug solubility in the polymeric carrier may increase during HME as a result of the elevated temperatures, high pressure and intense mixing.

Thermoanalytical analytical methods include those that examine the system as a function of temperature. DSC has been widely used to study the thermal properties of materials used in HME. DSC can be used for the quantitative detection of transitions (melting point, glass transition) in which energy is required or liberated (i.e., endothermic and exothermic phase transformations). Generally, the hot melt extrudate is scanned and compared to a corresponding physical mixture of the drug, polymeric carrier and other excipients.

Thermogravimetric analysis (TGA) is a measure of thermally induced mass loss of a material as a function of applied temperature. TGA can be used as a screening tool for the thermal stability of materials used in HME provided that volatile degradants are produced (Bruce et al., 2005, Schilling et al., 2008, Zhu et al., 2006a).
Microthermal analysis can be used to identify phase separation based on the differences in the thermal topography of hot-melt extrudates. Phase separation in hot-melt extrudates containing itraconazole and Eudragit E100 has been identified using microthermal analysis (Six et al., 2003). Hülsmann et al. (2001) used both the isothermal microcalorimetry and moisture adsorption gravimetry to investigate whether the stability of the melt extruded solid dispersions was influenced by water vapour.

Powder X-ray diffraction (PXRD) is one of the most commonly used experimental tools to characterize the crystalline properties within the melt extrudates and the solid state miscibility of API within the polymeric matrix. Characterizing the crystallinity of a material using PXRD is based on Bragg’s law, in which parallel incident X-rays strike the crystal planes and are then diffracted at angles related to the spacing between the planes of molecules in the lattice which can result in a characteristic fingerprint region in the diffraction pattern for the crystalline material. If there is no overlay in the fingerprints of the drug and carrier, the crystallinity of the drug and polymer within the melt extrudates can be determined. Thus, PXRD can be used to differentiate between amorphous solid dispersions and solid dispersions in which the drug is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. PXRD was efficient in studying the extent of drug re-crystallization qualititatively and quantitively during storage of hot-melt extrudates at stress conditions of temperature and humidity (Forster et al., 2001b; Ghebremeskel et al., 2006).

In addition to the use of the spectroscopic techniques (FT-IR, Raman) in characterizing the drug/polymer interactions, they can be used to examine solid state properties within the melt extrudates. These spectroscopic techniques can be used to differentiate between peaks that are sensitive to changes in crystallinity from those that are not (Taylor and Zografi, 1997).
Solid-state nuclear magnetic resonance (NMR) has been used to probe the crystallinity of materials. Solid state NMR (ssNMR), powder X-ray diffraction (PXRD), and transmission electron microscopy (TEM) have been used to characterize solid state properties and miscibility between PEO and ketoprofen (Schachter et al., 2004). In this study, ssNMR detected molecular interactions (hydrogen bonds) between the carboxylic group of ketoprofen and the ether oxygen of PEO which may be attributed to the high drug/polymer miscibility that promotes dispersion of ketoprofen in the amorphous domain of PEO.

Microscopy e.g. light microscopy, scanning electron microscopy (SEM) is considered as one of the best methods to study the crystalline properties and the surface morphology of hot-melt extrudates. Moreover, reliable particle size information can be obtained using these microscopic techniques (Crowley et al., 2007).

Fourier transform near-infrared (FT-NIR) spectrophotometer was a powerful method for the quantitation of clotrimazole contained in films produced by HME using polyethylene oxide as polymeric matrix when compared to a reference HPLC method (Venkata et al., 2004).
1.3.9 Applications of HME in the pharmaceutical industry

1.3.9.1 Hot-melt extruded dosage forms

HME originates from the polymer and food industry, but several research teams have explored the possibilities of HME as an alternative method to develop pharmaceutical dosage forms such as granules, sustained-release pellets, granules, matrix tablets, matrix-in-cylinder systems, capsules and implants. HME also has applications in topical drug delivery. The growing interest of the pharmaceutical industry in HME is evident from the increasing number of patents and publications available in the literature (Breitenbach, 2002, Crowley et al., 2007). HME has been evaluated to improve the dissolution rate of poorly water-soluble drugs and hence their oral bioavailability by forming solid dispersions and solid solutions (Breitenbach and Mägerlein, 2003; Forster et al., 2001a; Chokshi et al, 2008), to control or modify drug release and to mask the bitter taste of the drug (McGinity and Zhang, 2002). Tables 1.5 and 1.6 give an overview about the pharmaceutical applications of HME in designing different pharmaceutical dosage forms for oral drug delivery.
<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Drug</th>
<th>Carrier</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granules</td>
<td>diclofenac sodium</td>
<td>carnauba wax</td>
<td>(Miyagawa et al., 1996; 1999; Sato and Miyagawa, 1997)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>agar, microcrystalline cellulose, polyethylene oxide,</td>
<td>(Lyons et al., 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eudragit® L100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>phenylpropanolamine HCl</td>
<td>wax (Precirol® ATO 5, Sterotex® K)</td>
<td>(Liu et al., 2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eudragit® RS PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hydrochlorothiazide</td>
<td>α-lactose monohydrate</td>
<td>(Keleb et al., 2002; 2004; Van Melkebeke et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>sodium guaiiazulene sulfonate</td>
<td>lactose, corn starch, hydroxypropylcellulose, polyvinyl</td>
<td>(Nakamichi et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>riboflavin (sodium phosphate)</td>
<td>alcohol, α-lactose monohydrate</td>
<td>(Van Melkebeke et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>dicalcium phosphate anhydrate</td>
<td>α-lactose monohydrate</td>
<td>(Djuric et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>itraconazole</td>
<td>polyvinylpyrrolidone, hydroxypropylmethylcellulose,</td>
<td>(Miller et al., 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>poloxamer 407, polyethylene oxide</td>
<td></td>
</tr>
<tr>
<td>Pellets</td>
<td>Dilitiazem HCl</td>
<td>ethylcellulose, cellulose acetate butyrate, Eudragit®</td>
<td>(Follonier et al., 1994; 1995)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RS PM, poly(ethylene-co-vinyl acetate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>theophylline</td>
<td>microcrystalline cellulose, Eudragit® 4135 F</td>
<td>(Young et al., 2002; 2003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acryl-EZE®, carbopol® 974P, Methocel® K4M</td>
<td>(Young et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>guaifenesin</td>
<td>ethylcellulose, polyethylene oxide</td>
<td>(Young et al., 2007)</td>
</tr>
</tbody>
</table>
Table 1.6. Overview of different hot-melt extruded dosage forms (tablets and capsules)

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Drug</th>
<th>Carrier</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>Chlorpheniramine maleate</td>
<td>polyethylene oxide</td>
<td>(Zhang and McGinity, 1999; Crowley et al., 2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eudragit® RS PO, Eudragit® RD 100</td>
<td>(Zhu et al., 2002a; 2002b; 2004; 2006a; Fukuka et al., 2006a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eudragit® E PO</td>
<td>(Fukuka et al., 2006a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chitosan, xanthan gum, polyethylene oxide, microcrystalline cellulose</td>
<td>(Fukuka et al., 2006b)</td>
</tr>
<tr>
<td></td>
<td>acetohydroxamic acid</td>
<td>Eudragit® RS PO, Eudragit® E PO</td>
<td>(Fukuka et al., 2006a)</td>
</tr>
<tr>
<td></td>
<td>diltiazem HCl</td>
<td>Eudragit® RD 100, Eudragit® RS PO</td>
<td>(Zhu et al., 2006a)</td>
</tr>
<tr>
<td></td>
<td>indomethacin</td>
<td>Eudragit® RD 100, Eudragit® L 100, Eudragit® S 100, Eudragit® RL PO</td>
<td>(Zhu et al., 2006b)</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>Ethylcellulose, hydroxypropylmethylcellulose, xanthan gum</td>
<td>(De Brabander et al., 2003; 2004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eudragit® RS PO, microcrystalline cellulose</td>
<td>(Kidokoro et al., 2001)</td>
</tr>
<tr>
<td></td>
<td>theophylline (monohydrate)</td>
<td>polyethylene, cellulose acetate butyrate, polyvinyl acetate, polycaprolactone</td>
<td>(Sprockel et al., 1997; Zhang and McGinity, 2000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acryl-EZE®, carbopol® 974P, Methocel® K4M</td>
<td>(Young et al., 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glycercyl palmitostearate, glyceryl trimyristate</td>
<td>(Reitz and Kleinebudde, 2007; Reitz et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>guaifenesin</td>
<td>ethylcellulose</td>
<td>(Crowley et al., 2004b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acryl-EZE®, Eudragit® L 100-55</td>
<td>(Bruce et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>5-aminosalicylic acid</td>
<td>Eudragit® S100, Eudragit® L 100</td>
<td>(Bruce et al., 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eudragit® L 100-55, polyvinylpyrrolidone, Carbopol® 971P</td>
<td>(Andrews et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>ketoprofen</td>
<td>Eudragit® L 100</td>
<td>(Yang et al., 2008)</td>
</tr>
<tr>
<td>Capsules</td>
<td>Hydralazine</td>
<td>Hydroxypropylmethylcellulose acetate succinate, polyvinyl acetate phthalate</td>
<td>(Mehuys et al., 2005)</td>
</tr>
</tbody>
</table>
1.3.9.2 Hot-melt extruded solid dispersions

As the main topic of this thesis is focused on the application of the HME technology to prepare solid dispersions in order to enhance the dissolution properties of poorly soluble drugs, the remaining section of this introduction describes the use of HME for this pharmaceutical application. Table 1.7 gives an overview about the solid dispersions that have been manufactured using HME technology.

Solid dispersions of 17β-estradiol hemihydrate (17β-E2) have been prepared at an extrusion temperature of 60 °C, below the API melting point (175 °C) to enhance dissolution. Polyethylene glycol (PEG 6000), polyvinylpyrrolidone (Kollidon®) and vinylpyrrolidone-vinylacetate copolymers (Kollidon® VA64) were used as polymeric carriers and Sucroester® WE15 or Gelucire® 44/14 as additives during melt extrusion. A significant increase in dissolution rate was observed for HME solid dispersions in comparison to pure API or to a physical mixture. PVP and Gelucire® 44/14 were more efficient in enhancing the dissolution of 17β-E2 than other polymers or additives. A 30-fold increase in dissolution rate was observed for a formulation containing 10% 17β-E2, 50% PVP and 40% Gelucire® 44/14 when compared to the pure API. The observed dissolution enhancement was attributed to the improved wettability of the drug by the hydrophilic polymer and amphiphilic additive and the intimate mixing of the API and excipient (Hülsmann et al., 2000).
Table 1.7. Overview of the hot-melt extruded solid dispersions.

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Drug</th>
<th>Carrier</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliddispersions</td>
<td>indomethacin</td>
<td>polyvinylpyrrolidone, polyvinylpyrrolidone-co-vinyl acetate, Eudragit EPO</td>
<td>(Forster et al., 2001a, 2001b; Chokshi et al., 2005; Patterson et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>lacidipine</td>
<td>Eudragit® RL PO, Eudragit® RD 100, Eudragit® S100, Eudragit® L 100</td>
<td>(Zhu et al., 2006b)</td>
</tr>
<tr>
<td></td>
<td>nifedipine</td>
<td>Polyvinylpyrrolidone</td>
<td>(Forster et al., 2001a, 2001b, 2001c)</td>
</tr>
<tr>
<td></td>
<td>piroxicam</td>
<td>hydroxypropylmethylcellulose phthalate / acetate succinate</td>
<td>(Nakamichi et al., 2002, 2004)</td>
</tr>
<tr>
<td></td>
<td>tolvaptamidine</td>
<td>Polyvinylpyrrolidone</td>
<td>(Forster et al., 2001a)</td>
</tr>
<tr>
<td></td>
<td>dipyridamole</td>
<td>Polyvinylpyrrolidone, polyvinylpyrrolidone-co-vinyl acetate</td>
<td>(Patterson et al., 2007, 2008)</td>
</tr>
<tr>
<td></td>
<td>carbamazepine</td>
<td>Polyvinylpyrrolidone, polyvinylpyrrolidone-co-vinyl acetate Polyethylene glycol</td>
<td>(Patterson et al., 2007, 2008)</td>
</tr>
<tr>
<td></td>
<td>ibuprofen</td>
<td>Ethylcellulose</td>
<td>(De Brabander et al., 2002)</td>
</tr>
<tr>
<td></td>
<td>itraconazole</td>
<td>hydroxypropylmethylcellulose, polyvinylpyrrolidone-co-vinyl acetate, Eudragit® E100</td>
<td>(Verreck et al., 2005; Six et al., 2004, 2005)</td>
</tr>
<tr>
<td></td>
<td>nimodipine</td>
<td>hydroxypropylmethylcellulose, polyvinylpyrrolidone-co-vinyl acetate, Eudragit® E PO</td>
<td>(Zheng et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>Eudragit® E100, Eudragit® NE 30D</td>
<td>(Nollenberger et al., 2009)</td>
</tr>
</tbody>
</table>
The stability of 17β-E2 solid dispersions containing PVP and Sucroester® WE15 manufactured at different extrusion temperatures (60, 100, 160 and 180°C) was investigated in another study (Hülsmann et al., 2001). These excipients were chosen as it was shown by DSC that PVP and Sucroester® WE15 increased the Tg of amorphous 17β-E2 which can enhance the physical stability of amorphous 17β-E2. After six months storage at ambient conditions, there was no significant change in the drug release profiles for solid dispersions prepared at 60 and 180 °C while there was a decrease in the drug release for the solid dispersions prepared at 100 and 160 °C. The authors justified the results based on the solid state properties of the drug within the melt extrudates. PXRD analysis showed that only amorphous drug was present within the solid dispersions prepared at 180 °C before and after storage of solid dispersions and the drug was only in crystalline form in the solid dispersion prepared at 60 °C, after storage there was no change in the physical state of the solid dispersions and hence no significant change in the drug release profiles before and after storage. Solid dispersions prepared at 100 and 160 °C showed a significant decrease in drug release mostly due to the presence of the drug in two different states, amorphous and crystalline forms. During storage, the crystals probably acted as re-crystallization nuclei, resulting in re-crystallization and hence a decrease in drug release on storage (Hülsmann et al., 2001).

Forster et al. (2001a) studied the miscibility of indomethacin and lacidipine with 11 polymeric or nonpolymeric excipients theoretically by calculating the Hanson solubility parameters of these drugs and comparing them with the solubility parameters of the excipients. Differences in the drug/excipient solubility parameters of <7.0 MPa$^{1/2}$ were predicted to indicate miscible systems (glass solution) formation on HME, while differences of >10 MPa$^{1/2}$ were expected to indicate a lack of miscibility and thus not form glass solutions when melt extruded. Experimentally, miscibility was shown by changes in drug/excipient melting endotherms during DSC heat scans by determining the onset temperature of melting and the heat of fusion which have limitations in assessing miscibility when both the drug and the excipient occur at similar temperatures. Tg analysis from DSC prepared from quench cooled melts of drug and excipient provided an alternative means for predicting drug/excipient miscibility. Additionally, the presence of a single glass transition (Tg) at an intermediate temperature between the Tg of the API and the excipient is
indicative of the formation of single miscible system (glass solution). Drug/excipient miscibility was experimentally confirmed by hot stage microscopy (HSM). The results obtained experimentally were in agreement with solubility parameter predictions. In addition, drug/excipient systems predicted to be largely immiscible often exhibited more than one Tg. HME of miscible systems resulted in amorphous solid solution formation, whereas extrusion of an immiscible component led to amorphous drug dispersed in a crystalline excipient. Therefore, combining calculations from Hanson solubility parameters with thermal analysis has shown to be useful to predict formation of glass solutions with melt extrusion. Using these methods to determine drug/excipient miscibility, a prediction of the formation of solid solutions was possible using small quantities of materials before performing HME that required considerably higher quantities of drug and excipient (Forster et al., 2001a).

In another study, Forster et al. (2001b) characterized the physicochemical properties of glass solutions of indomethacin, lacidipine, nifedipine and tolbutamide prepared by HME using PVP or PVP/VA at a 1:1 drug/polymer ratio. The dissolution rates of the glass solutions were markedly improved compared to the crystalline drug or the corresponding physical mixtures. For example, approximately a 22-fold increase in the dissolution rate was achieved after 10 minutes in lacidipine/PVP/VA melt extrudates compared to crystalline lacidipine. Infrared spectroscopy confirmed the presence of hydrogen bonding between the carbonyl group of the polymer and the hydrogen donor group of the APIs (the carboxylic acid group of indomethacin, the amide group of tolbutamide, and the secondary amine group of lacidipine and nifedipine) within the melt extrudates whereas only indomethacin showed interaction with PVP in physical mixtures containing the amorphous form of the drug. All melt extrudates retained the amorphous form of drug when stored at 25°C/<10% RH for 8 weeks, whereas only indomethacin extrudates remained amorphous after 8 weeks storage at 25°C/75% RH. Lacidipine, nifedipine and tolbutamide melt extrudates showed a more substantial decrease in Tg and increased moisture content compared to indomethacin extrudates. Differences in the physical stability of drug/polymer extrudates were attributed to differences in drug/polymer hydrogen bonding, which affected the moisture content of the melt extrudates and consequently the glass transition of the melt extrudates during storage.
In a study conducted by Chokshi et al. (2005), the physico-mechanical properties of indomethacin with different polymer binary mixtures were characterized to assess drug/polymer miscibility prior to HME to select the most suitable polymers to produce solid solutions. Based on the physico-mechanical characterization, PVP, PVP/VA and Eudragit EPO were chosen to manufacture solid solutions of indomethacin (Chokshi et al., 2005). The physico-mechanical properties of the drug/polymer binary mixtures characterized, the solubility parameter (determined by the group contribution method), DSC and rheological analysis (torque rheology), were successful as predictive tools for solid solution formation of indomethacin with the aforementioned polymers after HME. Torque rheometry was used to assess the zero-rate viscosity ($\eta^*$) and activation energy ($E_a$, i.e. energy required to initiate the flow) of drug/polymer blends. The decrease in ($\eta^*$) for drug/polymer binary mixtures suggests miscibility of drug and polymer whereas the decrease in $E_a$ for drug/polymer binary mixtures suggests plasticization of the polymer by the drug.

In another study by Chokshi et al. (2008), glass solutions were prepared by HME of indomethacin with PVP, PVP/VA or Eudragit EPO which were selected based upon miscibility predictive tools used in a previous study (Chokshi et al., 2005). The purpose of this study in addition to enhance the dissolution properties of indomethacin was to stabilize the amorphous form of indomethacin both in the solid state, and during dissolution. The melt extrudates produced, showed higher intrinsic dissolution rates and solubility compared to indomethacin. The amorphous drug in glass solutions showed a tendency to revert back to the crystalline form with the rate of reversion depending upon on the nature and concentration of the polymer. Glass solutions with a high ratio of EPO provided superior stabilization of amorphous indomethacin. This stabilization was attributed to molecular interactions between indomethacin and Eudragit EPO rather than the glass transition temperature. The melt extrudates with EPO showed increased solubility in simulated gastric fluid (SGF), which was highly dependent on EPO concentration. The higher the concentration of EPO in the melt extrudates, the greater the solubility in the SGF. Melt extrudates with a drug to EPO ratio of 30:70 showed a 320-fold increase in solubility compared to corresponding physical mixture after 72 h with no change in the solubility when compared with the solubility after 24h, indicating the stability of the amorphous drug at higher polymer concentration. Conversely, the melt extrudates with lower EPO
Concentrations lower solubility after 72 h as compared to 24 h which may be attributed to the partial conversion of amorphous drug to crystalline form in SGF at 72h. In simulated intestinal fluid (SIF), the improvement of drug solubility was significantly lower compared to SGF and the increase in solubility was inversely related to polymer concentration. This may be attributed to the poor solubility of EPO and good solubility of the drug in SIF rather than the instability of the amorphous form which was further confirmed by PXRD. The melt extrudates formed using PVP and PVP/VA did not show any significant improvement in solubility in SGF indicating the instability of amorphous form and its conversion to the crystalline form confirmed by PXRD. Conversely, PVP and PVP/VA formulations showed improved solubility in SIF at 24 h which decreased after 72 h however remained higher than the pure drug or the corresponding physical mixtures. This suggests re-crystallization of the amorphous form of the drug. The observed increase in solubility was inversely related to polymer concentration at 24 h, which may be attributed to the high viscosity at high polymer concentrations (Chokshi et al., 2008).

The dissolution properties of nifedipine have been significantly enhanced using PEO as a carrier. In a study by Li et al. (2006), hot stage microscopy was used to test miscibility of drug in PEO with increasing temperature. Raman spectroscopy showed molecular interactions between nifedipine and PEO. Solid state properties within melt extrudates were sensitive to the extrusion temperature, with complete loss of crystallinity (amorphous form) being confirmed by PXRD and SEM at extrusion temperatures above 120°C. Dissolution rate was enhanced significantly compared to pure drug or corresponding physical mixtures (Li et al., 2006).

Solid dispersions of nimodipine, a dihydropyridine calcium channel blocker, were produced by HME using Eudragit® EPO, PVP/VA and HPMC. Eudragit® EPO and PVP/VA showed greater miscibility with nimodipine than HPMC as confirmed by XRPD, DSC and SEM. All melt extrudates showed a significant increase in the dissolution rate of nimodipine compared to the pure drug except for 10% drug loading level which showed slower dissolution rate compared to pure drug. This decrease in the dissolution rate is mostly attributed to the low solubility of EPO in pH 4.5. Based on the miscibility and drug dissolution enhancement, the authors concluded that NMD-PVP/VA system was the most appropriate system (Zheng et al., 2007a).
another study, the oral bioavailability of the solid dispersions compared to pure nimodipine in beagle dogs, their physical mixtures and the marketed drug product Nimotop® were assessed. Both the Cmax and the AUC(0-12) of nimodipine was comparable after administration of the Eudragit® EPO solid dispersion and Nimotop®, but the HPMC and PVP/VA dispersions exhibited much lower bioavailability, although the in vitro dissolution at pH 4.5 showed higher dissolution rate for PVP/VA. Based on these results the authors suggested that pH 4.5 acetate buffer containing 0.05% w/v SDS did not accurately represent in vivo behavior. In vitro dissolution study performed using 0.1M HCl containing 0.05% w/v SDS showed significantly higher dissolution rate for EPO solid dispersions compared to PVP/VA and HPMC solid dispersions providing more representative in vivo dissolution medium. However, both the Cmax and the AUC0-12 hr of all three solid dispersions were significantly higher than the corresponding physical mixtures and pure nimodipine powder (Zheng et al., 2007b).

Patterson et al. (2007) studied the effect of the manufacturing process on the physicochemical properties of PVP glass solutions of carbamazepine, dipyridamole and indomethacin. HME, spray drying and ball milling techniques were used to prepare the glass solutions. There was no effect on the physical stability of the glass solutions by the manufacturing technique, whereas it did affect the dissolution rate. The dissolution of the spray-dried glass solutions was generally poor, compared to HME and ball milled products. This was attributed to rapid dissolution of PVP from the small particles of the spray dried products leaving the poorly soluble drug without intimate contact during dissolution. In another study Patterson et al. (2008) investigated the physicochemical properties of carbamazepine and dipyrimadole solid dispersions prepared by spray drying or HME techniques using two grades of PVP/VA (64 and 37). The dissolution rate was significantly higher for solid dispersions prepared by HME compared to spray drying. In addition, the dissolution rate was slower from PVP/VA 37 than PVP/VA 64 prepared by HME. The drug release of HME PVP/VA 37 were slower than corresponding physical mixtures. This effect was attributed to a loss of matrix hydrophilicity due to intimate mixing with the drug (Patterson et al., 2008).
Itraconazole is a potent broad spectrum triazole antifungal drug. Itraconazole is a class II compound meaning its oral bioavailability is determined by dissolution in the GI tract. It is insoluble in water (1 ng/mL) and its solubility increases in pH 1 (6µg/ml) with an ionization constant of 4.0 and a very high octanol-water partition coefficient (log P > 5) (Peeters et al., 2002). A solid dispersion formulation containing itraconazole and HPMC at a ratio of (40/60 % w/w) was prepared using HME. The drug/polymer ratio selected was based on dose, miscibility and dissolution results of solid dispersions containing different ratios of itraconazole and HPMC prepared by solvent casting. A very significant increase in dissolution rate was obtained from the amorphous solid dispersion prepared by HME compared to the physical mixture. The prepared solid dispersion (40/60 %w/w) of Itraconazole/HPMC showed superior stability under accelerated stability conditions without any evidence of recrystallization or degradation for up to 6 months (Verreck et al., 2003). In another study, hydroxypropyl-β-cyclodextrin (HP-β-CD) was incorporated in ITZ-HPMC solid dispersions resulted in increasing the apparent solubility of ITZ (Rambali et al., 2003).

Itraconazole solid dispersions have been prepared using Eudragit EPO or PVP/VA alone or in combination using HME (Six et al., 2004). Itraconazole and Eudragit® EPO were miscible up to 13% w/w drug loading whereas itraconazole and PVP/VA were completely miscible. Itraconazole/EPO melt extrudates at 40% w/w achieved 80% of drug release after 30 min in SGF with re-crystallization after 2 h, whereas at same drug loading level, extrudates of itraconazole/PVP/VA showed only 45% release after 3 h. Combination of both polymers in different ratios, with a drug loading of 40% w/w was evaluated. DSC results showed clearly that a two phase system consisting of Itraconazole-Eudragit® EPO and Itraconazole-PVP/VA phases. Dissolution testing for different polymer ratios showed that Eudragit® EPO/PVPVA64 ratios of 50/50 and 60/40 showed significant increases in dissolution rate and level while ratios of 70/30 and 80/20 had a release of 85% after 30 min without any drug precipitation during the dissolution. The combination of two polymers resulted in solid dispersions with good dissolution properties and improved physical stability compared with the binary solid dispersion of itraconazole (Six et al., 2004). In a clinical study performed in human volunteers, itraconazole hot melt
extruded solid dispersion formulations of 40% w/w itraconazole and HPMC 2910, Eudragit E100 or a mixture of Eudragit® E100-PVP/VA were assessed in comparison with Sporanox®, the marketed form of itraconazole. The mean bioavailability (AUC, Cmax and Tmax) of itraconazole after administration of a HPMC solid dispersion was comparable to Sporanox®, whereas it was lower after administration of Itraconazole-Eudragit E100 or Eudragit E100-PVP/VA 64 dispersions (Six et al., 2005).

The efficiency of HME to overcome the limitations associated with drug particle engineering techniques such as particle aggregation, morphological instability and poor wettability has been examined (Miller et al., 2006). In this study, micronized particles of amorphous itraconazole stabilized with PVP or HPMC were produced by freeze drying. These solid dispersions were subsequently melt extruded with poloxamer 407 and PEO 200 M to deaggregate and disperse the micronized particles into the hydrophilic polymer matrix. HME did not alter the properties of the micronized particles as confirmed by DSC, XRD and SEM. Additionally, the dissolution rate of the micronized particles under sink conditions (0.1 M HCl) was improved by HME due to particle deaggregation and enhanced wetting. Under supersaturation dissolution testing (0.1 M HCl), the ITZ-HPMC micronized particle extrudates provided superior supersaturation of itraconazole compared to the ITZ-PVP micronized particle extrudates. Neither micronized particle extrudate formulation significantly reduced the rate of itraconazole precipitation from supersaturated solution once pH was increased (from pH 1.2 to 6.8 at 2 h). In vivo testing by oral dosing of rats showed statistically equivalent AUC values for the two extrudate formulations. By correlating the results of dissolution under supersaturated conditions with pH change to the in vivo AUC values, it appears that the rapid precipitation of itraconazole occurs upon entrance into the more neutral pH environment of the small intestine resulting in a brief opportunity for absorption. Therefore, it was concluded that optimizing the formulation of itraconazole to control the drug release so as to retard precipitation as pH increased may be highly beneficial to extend the absorption window in the small intestine. To achieve this objective, Miller et al., (2008) in another study used Carbopol® 974P as a stabilizing agent for supersaturated levels of itraconazole in neutral pH aqueous media. Hot-melt extruded solid dispersions was prepared using Eudragit® L100-55 as an enteric carrier. DSC and qualitative energy dispersive X-ray spectroscopy showed that the extruded compositions were entirely
amorphous and homogeneous with respect to drug distribution in the polymer matrix. Dissolution analysis revealed that the addition of carbopol to the Eudragit® L100-55 carrier system prolonged the release of supersaturated levels of itraconazole from the Eudragit® L100-500 matrix following an acidic-to-neutral pH transition. In vivo evaluation of itraconazole absorption in rats showed that the addition of carbopol substantially reduced the absorption variability seen with Eudragit® L100-55 carrier system. A five-fold increase in itraconazole absorption was achieved by the formulation containing 20% carbopol. In conclusion, substantial improvements in oral antifungal therapy with itraconazole can be achieved via intestinal targeting and polymeric stabilization of supersaturation.

Fukuda et al. (2008) studied the influence of sulfobutyl ether β-cyclodextrin (SBE7-β-CD; Captisol®) on the dissolution properties of ketoprofen from extrudates prepared by HME compared to extrudates containing the parent β-cyclodextrin(β-CD). The dissolution rate of ketoprofen from the prepared extrudates samples with SBE7-β-CD was significantly faster than physical mixtures and the extrudates prepared with the parent β-CD. All prepared samples were highly affected by exposure to elevated humidity due to the hygroscopic nature of SBE7-βCD.

Solid dispersions of compound A (anonymous) were manufactured by solvent co-precipitation (CP) and HME methods using HPMC-AS as a polymeric carrier. Both CP and HME produced amorphous solid dispersions and a single Tg was produced in the DSC thermograms indicating the formation of a miscible system (glass solutions). Both products had similar spectroscopic (FT-IR and Raman), hygroscopic properties and true densities; however, the CP product was more porous and had a larger specific surface area than the HME product as indicated by the BET and SEM. The CP product had a faster dissolution profile than the HME product mostly due to the larger specific surface area. The HME product was more stable than the CP product when the two products were supersaturated in aqueous solutions and the dried samples were characterized using PXRD after certain time intervals, which may be attributed to the surface area difference. The two products did not show any sign of re-crystallization after three months storage at 40°C/75%RH. (Dong et al., 2008).
Felodipine solid dispersions were prepared by HME technology using Eudragit® E100. A significant increase in dissolution (360-fold) was achieved using 90% Eudragit® E100 in SGF pH 1.2. Eudragit® E100 dissolves rapidly at low pH (<4) forming a polymer rich phase in which the drug molecules can dissolve. Due to the rapid dissolution a highly supersaturated solution of felodipine was generated, resulting in fast re-crystallization of the drug and subsequent decrease in concentration. For a physically mixed sample, dissolution was slightly improved due to the wetting properties of the polymer, however dissolution of physical mixtures were considerably lower than that observed for the glassy extrudates. To inhibit rapid re-crystallization of felodipine, a water insoluble polymer, Eudragit® NE was added and an efficient inhibition was achieved at 5% (w/w) concentration while above this concentration a decrease in dissolution was observed. DSC and PXRD confirmed amorphous felodipine within the melt extrudates. The significant increase in the dissolution was mostly related to presence of drug in the amorphous form with contribution additionally from the wetting properties of Eudragit® E100. The ability of Eudragit® NE to inhibit re-crystallization was attributed to the change in the local structure of Eudragit® E 100 in a nonadditive way by the minor amounts of Eudragit® NE added. This was confirmed using pair distribution function x-ray analysis (Nollenberger et al., 2008).
Chapter 2

MISCIBILITY AND INTERACTIONS BETWEEN BICALUTAMIDE AND POLYETHYLENE OXIDE IN HOT-MELT EXTRUDED SOLID DISPERSIONS
2.1 **INTRODUCTION**
Improving the dissolution rate, and hence oral bioavailability, is the most significant challenge encountered in the formulation of poorly soluble, BCS class II drugs in the pharmaceutical industry. There are a number of techniques that may be used to address this challenge including the use of drug salts, drug particle size reduction, solid dispersion formation, self emulsifying lipid formulations and the use of inclusion compounds based on cyclodextrin (Leuner and Dressman, 2000; Brewster et al., 2008). Of these methods, solid dispersions have been extensively studied for improving the aqueous solubility of poorly water-soluble drugs (Serajuddin, 1999).

Solid dispersions may be defined as pharmaceutical dosage forms in which the drug is dispersed in a biologically inert matrix, usually in order to enhance the drug oral bioavailability through improvement of its dissolution rate in aqueous media (Craig, 2002). Water-soluble or water-miscible carriers are usually used for this purpose e.g polyethylene glycols (Gines et al., 1996; Trapani et al., 1999), polyvinylpyrrolidone (Tantishayakul et al., 1999; Torrado et al., 1996), polyvinylpyrrolidone-polyvinylacetate copolymer (PVP/VA) (Forster et al., 2001b, Petterson et al., 2008), cellulose derivatives (Okimoto et al., 1997; Konno and Taylor, 2006), polyacrylates and polymethacrylates (Chokshi et al, 2005; Six et al., 2004), and sugars (Okonogi, 1997a; 1997b).

Solid dispersion technology research is highly active and provides an efficient way to increase the dissolution rate of many poorly soluble drugs (Vippagunta et al., 2007). In solid dispersions, the drug may present in a microcrystalline state (simple eutectic mixture), or amorphous embeddings in amorphous or crystalline carrier or as solutes in true glass or solid solution where the drug is molecularly solubilized in the carrier or a mixture of all (Breitenbach, 2002). The exact mechanism of the dissolution rate enhancement using solid dispersions is not fully understood although a number of theories suggest either carrier or drug controlled release. However, the solubility of the drug in concentrated solutions of the carrier mostly determines the mechanism of the drug release (Craig, 2002). Upon dissolution of the solid dispersion in an aqueous medium, the carrier will dissolve rapidly, releasing fine colloidal drug particles of very high surface area resulting in dissolution rate enhancement (Serajuddin, 1999). In such systems, drug-polymer intermolecular interactions (Taylor
and Zografi, 1997), the viscosity of the polymeric carrier (Breitenbach, 2002) and the glass transition temperature (Tg) of the solid dispersion (Van den Mooter et al., 2001) have been shown to significantly influence drug re-crystallization kinetics during storage and dissolution.

Traditional methods for preparing solid dispersions including spray drying, co-evaporation, co-precipitation and freeze-drying, are associated with several disadvantages including the need for specialized expensive equipment, difficulty in process scale-up and in the case of solvent methods long processing and drying times making processing cycles sub-optimal and highly expensive (Leuner and Dressman, 2000).

HME is an emerging non-ambient drug delivery technology that has been shown to be a viable method to produce a number of different pharmaceutical drug delivery systems including solid dispersions (Crowley et al., 2007). This technology is highly advantageous in that it is a continuous rather than a batch process (Chokshi et al., 2005), solvents are not required and the process may also be used for thermally labile drug compounds even though the process is non-ambient (Verreck et al., 2006a).

Solid molecular dispersions are amorphous solid dispersions in which the drug is dissolved at a molecular level in the polymer matrix forming a one phase system with the polymer (Chiou and Reigelman, 1971). Formulating the drug as solid molecular dispersions can result in significant enhancement in solubility and hence bioavailability because an amorphous drug has a lower thermodynamic barrier to dissolution and the particle size of the drug has been reduced to an absolute minimum i.e. to molecular dimensions (Goldberg et al., 1965; Hancock and Zografi, 1997). To form solid molecular dispersions (single phase) by hot melt methods, the drug and the polymer must be miscible in the molten form. Thus the miscibility between the drug and polymer is very important to be characterized in solid dispersions (Leuner and Dressman, 2000). It has been shown that melt extrusion of miscible components results in solid solution formation (single phase), whereas extrusion of an‘immiscible’ component leads to the formation of an amorphous drug dispersed within the polymeric matrix (Forster et al., 2001a). Achieving miscibility is important for the physical stability of the drug. Molecular level miscibility (single phase) between
polymer and drug is desirable as it can alter the local environment of the drug (Marsac et al., 2006b). Within an immiscible system the effect of the polymer on the physical stability of the amorphous drug will be limited and the properties of the pure amorphous solid will largely dominate crystallization behaviour within the mixture (Law et al., 2001; Six et al., 2002).

DSC has been used extensively to characterize drug/polymer miscibility both qualitatively and quantitatively. Quantitative measurement of the solubility of solid drugs dispersed in polymeric matrices was first described by Theeuwes et al. (1974). DSC was used to measure the solubility of propranol (Bodmeier and Paeratakal, 1989), salicylic acid and chlorpheniramine (Jenquin and McGinity, 1994), penciclovir (Ahmad et al., 2004), and oxybutynin (Malcolm et al., 2002) in a range of polymer systems.

Bicalutamide (BL) is a nonsteroidal antiandrogen (NSAA) with no androgenic, progestational or endocrine activity. BL binds to androgen receptors in the prostate cells preventing the growth-stimulating effects of 5α-dihydrotestosterone (DHT) on prostate tumours. In comparison to steroidal antiandrogens (SAA), cyproterone acetate being an example, NSAAAs are less often associated with adverse drug effects such as thromboembolism, fluid retention and loss of libido (Furr and Tucker, 1996). BL has a plasma elimination half-life ($t_{0.5}$) of approximately one week, and is administered orally as 50mg tablets once daily in maximum androgenic blockage regimens (Goa and Spencer, 1998). The lower incidence rate of diarrhea compared to flutamide, the once daily dosing and the lack of interstitial pneumonitis or light/dark adaptation problems associated with nilutamide makes BL one of the more patient acceptable NSAAAs (Furr and Tucker, 1996).
BL is a lipophilic drug (log $\text{P}_{\text{octanol/water}}$ is 2.92, ) that is well absorbed after an oral dose (Goa and Spencer, 1998). Data obtained from rat studies in an in situ intestinal loop model showed a rapid rate of absorption throughout the small intestine (Cockshott, 2004). BL has an extremely low aqueous solubility (<5 mg/L) and exhibits dissolution rate-limited absorption (Cockshott, 2004, Amidon et al., 1995). Consequently significant investment in terms of formulation development is required to improve the oral bioavailability and hence the clinical efficacy of BL pharmaceutical products. In a previous study it has been demonstrated that dispersion of BL within amorphous PVP (prepared via solvent evaporation methods) significantly improved the dissolution rate (Ren et al., 2006). The chemical structure of BL is shown in Figure 2.1

![Chemical structure of bicalutamide (BL)](image)

Figure 2.1 Chemical structure of bicalutamide (BL)

BL may exist in one of two crystalline conformational polymorphs (form I and II). Both polymorphs have similar chemical structures, but they have different internal crystal structures due to variation in the molecular conformation of the molecules that results in different internal molecular packing, and consequently different physico-chemical interactions (Le et al., 2009). These differences in molecular packing are mainly a result of the differences in the hydrogen bonding interactions between BL molecules in each polymorph (Figure 2.2). Both BL polymorphs (form I and form II) are considered monotropic, in which form I is more stable than form II because of the stronger hydrogen bonding interactions (Vega et al., 2007)
Crystalline BL (form I)

Crystalline BL (form II)

Figure 2.2. Molecular conformation of bicalutamide form I and form II showing the intermolecular hydrogen bonds represented as dashed lines. (Only H atoms involved in these intermolecular interactions are drawn.) (Vega et al., 2007).
Solid dispersions manufactured by the HME technology require a pharmaceutical grade thermoplastic carrier. Polyethylene oxide (PEO), a well known thermoplastic polymer, was selected as a hydrophilic carrier in this study due to its physicochemical properties. PEO is a free flowing non-ionic homopolymer synthesized by the heterogeneous catalytic polymerization of ethylene oxide monomer (Crowley et al., 2002; Li et al., 2006). It is miscible with water at all ratios as a result of hydration of the ether oxygen. PEO is a semicrystalline polymer with a melting range of 57-73 °C (Prodduturi et al., 2005). The low melting point enables extrusion at moderate temperatures without the need for a plasticizer. In addition, PEO contains a proton acceptor group, ethylene oxide, that enables it to form miscible blends through interactions with drugs or polymers that contain proton donor groups (Robeson et al., 1981). Interestingly, Schachter et al., (2004) have previously shown using solid state NMR spectroscopy that PEO was capable of forming highly miscible solid dispersions with ketoprofen. PEO is commercially available in a wide range of molecular weights (100,000 to 8,000,000). Low molecular weight PEO, which gel to a lower extent (Prodduturi et al., 2005), have been widely studied for use as carriers for hot melt extruded solid dispersions to improve the solubility of poorly soluble drugs (BCS class II drugs). Nifedipine dissolution rate and solubility were improved significantly using hot melt extruded PEO solid dispersions (Mwt 200,000 Daltons) (Li et al., 2006). Sustained release tablets of chlorpheniramine maleate have also been prepared using HME utilizing a high molecular weight PEO (Mwt 1,000,000 Daltons) (Crowley et al., 2002; Zhang and McGinity, 1999). PEO was efficient in manufacturing hot-melt extruded mucoadhesive transmucosal films with different drugs e.g. guaifenasin, ketoprofen, clotrimazole, ketoconazole (Crowley et al., 2004a; Mididoddi et al., 2006; Prodduturi et al., 2005). Figure 2.3 shows the chemical structure of PEO.

![Chemical structure of polyethylene oxide (PEO)](image-url)
2.1.1 Aims and objectives

The objective of this study was to characterize the physicochemical properties of BL-PEO hot melt extruded solid dispersions for enhancing the dissolution properties of BL using PEO as a hydrophilic polymer. Whilst PEO has been studied extensively for HME, there are a limited number of articles that report the formulation of solid dispersions for solubility enhancement and there are currently no reports of BL with PEO.

The principle aims and objectives of this study are summarized as follows:

- Study the feasibility of manufacturing BL-PEO solid dispersions using HME.
- Physicochemical characterization of the manufactured solid dispersions in terms of drug/polymer miscibility, solid-state properties, drug/polymer interactions, surface morphology and drug release properties using different characterization techniques.
- Investigate the solubility of BL in PEO experimentally using high speed differential scanning calorimetry (hyper-DSC).
- Study the effect of drug loading level on the solid state and drug release properties from solid dispersions.
- Examine the stability of the manufactured solid dispersions in terms of drug crystallinity and *in vitro* drug release properties.
- Determine the factors that affect the stability of the solid dispersions.
2.2 MATERIALS AND METHODS
2.2.1 Materials
BL was purchased from Taresh Chemicals Ltd. (Banbridge, UK), Polyethylene oxide (molecular weight 100,000 Daltons) (PEO 100,000) and sodium dodecyl sulfate (SDS) were purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). All other chemicals used were purchased from BDH Laboratory supplies (Poole, Dorset, England) and were of Analar grade or equivalent quality.

2.2.2 Preparation of BL-PEO melt extrudates
BL was mixed with PEO at BL-PEO weight ratios of 1:10, 2:10, and 3:10 using a mortar and pestle for 2 minutes. The physical mixtures were extruded using a co-rotating twin-screw extruder (Minilab, Thermo Electron Corporation, Germany) at a temperature of 100 °C and a screw speed of 80, 60, and 40 rpm for 1:10, 2:10, and 3:10 weight ratios, respectively. Melt extrudates were milled and passed through a 355 μm sieve and stored within glass vials in a dessicator over silica gel at 20 °C. A suitable quantity of the physical mixture from each drug loading was kept for analysis to compare to corresponding extrudates.

2.2.3 Preparation of an amorphous BL-PEO physical mixture
Amorphous BL was prepared by heating BL up to 200 °C for 2 minutes using a stainless steel beaker then rapidly quench cooling in an ice bath. The generation of amorphous BL was confirmed using DSC. Amorphous BL was subsequently mixed with PEO at a drug/polymer weight ratio of 2:10 for 2 minutes using a mortar and pestle.

2.2.4 Thermogravimetric Analysis (TGA)
The thermal stability of BL and PEO was assessed using a Thermal Advantage Model Q500 thermogravimetric analyzer from TA Instruments (New Castle, DE, USA). Samples were heated at 10 °C/min from 20 to 400 °C and the % of mass remaining was plotted as a function of temperature. An isothermal test for BL and PEO was conducted by heating the samples to 160 °C and holding at this temperature for 60 minutes. The % of mass remaining was plotted as a function of time. In all experiments nitrogen was used as a purge gas for the furnace chamber at a flow rate of 40 mL/min for the balance and 60 mL/min for the sample.
2.2.5 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of BL, PEO, melt extrudates and their corresponding physical mixtures and to investigate the miscibility of BL and PEO in binary mixtures at different drug/polymer weight ratios. The depression in the onset of melting for BL with increasing PEO content was used to calculate an interaction parameter ($\chi$) using the Flory-Huggins equation. DSC analyses were conducted on a Thermal Advantage Model Q100 DSC from TA Instruments (New Castle, DE, USA) equipped with a refrigerated cooling system (RCS, TA Instruments). Data analysis was performed using Universal Analysis 2000 software. Samples between 5.0 and 10.0 mg were accurately weighed in aluminum pans, which were crimped before testing, with an empty crimped aluminum pan being used as a reference pan. The DSC was calibrated for baseline with empty pans, and for temperature and enthalpy using indium. All samples were heated under a nitrogen atmosphere at a flow rate of 50 mL/min. At least three replicates were performed. Plots of heat flow (W/g) versus temperature were recorded. For thermal analysis of BL, BL-PEO melt extrudates and the corresponding physical mixtures, samples were heated at 10 °C/min from 25 to 220 °C and the melting point and enthalpy of fusion ($\Delta H$) (J/g) of crystalline BL were determined. Samples of amorphous BL, prepared according to the method described in section 2.2.3, were heated at 10 °C/min from 0 to 200 °C to determine the glass transition (Tg), re-crystallization temperature (°C) of amorphous BL and the melting temperature (°C) and enthalpy ($\Delta H$) (J/g) of re-crystallized BL.

2.2.5.1 Solid state plasticization of BL by PEO

Samples of BL-PEO physical mixtures over the concentration range from 10 to 90 % (w/w) BL were prepared by geometric mixing and heated at a rate of 10 °C/min from 0 to 220 °C, quench cooled to -90 °C and re-heated at 10° C/min to 220 °C. The onset of melting was taken as the extrapolated onset of the BL melting endotherm that appeared during the first heat cycle. The glass transition temperature (Tg) of the BL-PEO binary system was recorded in the second heat cycle as the midpoint of the step transition in the plot of heat flow versus temperature. At least three replicates were performed and the average was calculated for the onset of melting and enthalpy of fusion $\Delta H$ (J/g) for crystalline BL and for the Tg of BL-PEO binary systems.
2.2.5.2 Flory-Huggins Modeling

The Flory-Huggins interaction parameter ($\chi$) was estimated from melting point depression data (section 2.2.5.1). The Flory-Huggins interaction parameter ($\chi$) was calculated using equation (2.1)

$$\left( \frac{1}{T_{\text{mix}}} - \frac{1}{T_{\text{mpure}}} \right) = -\frac{R}{\Delta H_f} \left[ \ln \Phi_{\text{drug}} + \left(1 - \frac{1}{r}\right)\Phi_{\text{polymer}} + x\Phi_{\text{polymer}}^2 \right]$$  

Equation 2.1

Where $T_{\text{mix}}$ is the melting temperature of the drug in the presence of the polymer, $T_{\text{mpure}}$ is the melting temperature of the drug in the absence of the polymer, $\Delta H_f$ is the heat of fusion of the pure drug, and $r$ is the ratio of the molecular volume of the polymer to that of the lattice site, defined as being equal to the molecular volume of drug, $\Phi_{\text{drug}}$ and $\Phi_{\text{polymer}}$ are the volume fractions of the drug and the polymer, respectively and may be calculated from equations 2.2 and 2.3, respectively.

$$\Phi_{\text{drug}} = \frac{n_{\text{drug}}}{n_{\text{drug}} + n_{\text{polymer}} * r}$$  

Equation 2.2

$$\Phi_{\text{polymer}} = \frac{n_{\text{polymer}}}{n_{\text{drug}} + n_{\text{polymer}} * r}$$  

Equation 2.3

Where $n_{\text{drug}}$ is the number of drug molecules and $n_{\text{polymer}}$ is the number of polymer molecules. The number of molecules of a material can be calculated by multiplying the number of moles of the material with Avogadro's number ($6.022 \times 10^{23}$), which can be defined as the number of molecules in one mole of a material.

True densities were experimentally determined using an Accupyc 1330 helium pycnometer (Micrometritics, Norcross, GA). Table 2.1 shows the input values of BL and PEO that were used for calculating the drug polymer interaction parameter ($\chi$).
### Table 2.1 Properties used in Flory-Huggins Modeling

<table>
<thead>
<tr>
<th></th>
<th>MW (g/mol)</th>
<th>Density (g/cm³)*</th>
<th>Molecular Volume (cm³/mol)</th>
<th>ΔH_fus (J/g)</th>
<th>T_M (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicalutamide</td>
<td>430.37</td>
<td>1.42</td>
<td>303.08</td>
<td>124.97</td>
<td>466.46</td>
</tr>
<tr>
<td>PEO</td>
<td>100,000</td>
<td>1.21</td>
<td>82644.63</td>
<td>198.43</td>
<td>340.33</td>
</tr>
</tbody>
</table>

* As measured by helium pycnometry

#### 2.2.5.3 Solubility of BL in PEO matrix

DSC measurements of BL and BL-PEO physically mixed samples at weight ratios of 1:9, 2:8, 3:7, 4:6 and 5:5 were conducted on a Perkin-Elmer Diamond Differential Scanning Calorimetry (Pyris Series 5) system (Perkin-Elmer Ltd, USA). Samples between 4.0 and 6.0 mg were accurately weighed and placed in crimped aluminium pans. Thermal scans were performed over a temperature range from -50°C to 250°C under a dry nitrogen gas purge (20 mL/min), using a heating rate of 500°C/min.

#### 2.2.6 Powder X-ray Diffractometry (PXRD)

Powder X-ray diffraction (PXRD) patterns for BL, PEO, BL-PEO physical mixtures and melt extrudates were obtained using a Philips X'Pert PRO diffractometer with a PW3040 generator (Philips, Almelo, The Netherlands) with X'Pert Data Viewer Version 1.0 Software. The instrument was equipped with a Cu LFF DK137623 X-ray tube (PW3373/10). Samples were placed on a zero background sample holder and incorporated onto a spinner stage. Cu Kα1 radiation was used as a X-ray source. Soller slits (0.04 rad) were used for the incident and diffracted beam path. The angular range (3-60°) was scanned in continuous mode with a step size of 0.0167° and time per step of 50 s and a scan speed 0.024 (°/min). The diffraction pattern was measured with a voltage of 40 kV and a current of 40 mA.
2.2.7 Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) was used to examine the shape/structure of crystalline BL and the surface morphology of BL-PEO melt extrudates immediately after manufacture and after 6 months storage at (20 °C, 65% RH). Samples were mounted on aluminum discs using double-sided adhesive copper mounting tape and placed in a dry atmosphere, under vacuum, overnight prior to coating and analysis. Samples were then coated with a thin film of gold to a thickness of 15 nm using an Agar® Auto Gold Sputter Coater. Scanning electron microscopy was performed using a JEOL 6500F field emission microscope operating at an accelerating voltage of either 2 or 5 kV with a 4 μA beam current emission. Images were captured using Jeol® software.

2.2.8 Fourier-Transform Infrared (FT-IR) Spectroscopy

FT-IR analyses were performed on samples of crystalline and amorphous BL, PEO, melt extrudates and corresponding physical mixtures using a Fourier Transform Infrared Spectrophotometer model 4100 (FT/IR-4100) (Jasco, Japan) incorporating version 2 of the Jasco Spectra Manager Software. The samples were mixed with dry potassium bromide (KBr) using a mortar and pestle and compressed to prepare a KBr disk. A scanning range of 4000–400 cm⁻¹ was used for all samples with a resolution of 4 cm⁻¹.

2.2.9 Fourier-Transform Raman (FT-Raman) Spectroscopy

Raman spectra for crystalline and amorphous BL, PEO, melt extrudates, and their physical mixtures were obtained using an Avalon Raman station R3 Model AVRS003A spectrometer from Avalon Instruments Ltd. (Belfast, NI, UK) using a resolution of 2 cm⁻¹. Grams/AI version 7.02 spectral data processing software from Thermo Galactic™, a product of Thermo Fischer Scientific Inc., was used to process the collected data. The scanning range investigated was 3200–250 cm⁻¹.
2.2.10 In vitro drug release studies

The in vitro drug dissolution properties of BL powder, physical mixtures and milled extrudates were examined according to the USP paddle method (USP 30, 2007). Samples equivalent to 50 mg of BL were added to 1000 mL of de-ionized water containing 1% w/v sodium dodecyl sulfate (SDS) at a temperature of 37 ± 0.2°C. The solution was stirred with a rotating paddle at 50 rpm. Samples of 5 ml were withdrawn from each vessel at predetermined time intervals (2, 5, 10, 15, 20, 30, 45, 60 min), filtered over through cellulose acetate filter (0.45 µm, Nalgene Labware, Rochester, USA). At each time point the same volume of fresh medium was replaced. The concentration of BL in each sampled aliquot was determined using a UV-VIS spectrophotometer at 275 nm and a standard calibration curve that was linear over the concentration range 2.0-12.0 µg/mL. The percent of BL dissolved for each formulation (n=3) was plotted versus time. No interference from the PEO or SDS was observed at 275 nm. BL content uniformity was determined by dissolving extrudates in de-ionized water containing 2% SDS to obtain a theoretical BL concentration of 50 mg/L. The drug concentration was then analyzed using a UV-VIS spectrophotometer at 275 nm and a standard calibration curve that was linear over the concentration range 2.0-12.0 µg/mL.

2.2.11 Stability study

Stability studies were conducted at 20 ºC and 65% RH. Melt extrudates were placed in open glass vials stored in a controlled temperature environment (20ºC) inside a dessicator containing a saturated solution of sodium nitrite to generate the appropriate relative humidity (65% RH). Relative humidity inside the dessicator was recorded using a thermohygrometer. Melt extrudates stored at 20 ºC and 65% RH were tested for crystalline content using PXRD after 1, 3 and 6 months. Drug release studies and SEM images were also conducted on the melt extrudates stored for 6 months and compared to the melt extrudates examined immediately following manufacture.
2.2.12 Statistical analysis

The effect of formulation and storage of the melt extrudates at 20°C, 65% RH up to six months on drug dissolution were statistically analyzed using a repeated measures one-way ANOVA. Individual differences in drug dissolution between formulations were statistically identified using Fischer's PSDL test. In all cases \( p<0.05 \) denoted significance.
2.3 RESULTS AND DISCUSSION
2.3.1 Thermal analysis

Thermal stability of the materials used in HME is one of the most important properties required for materials to be eligible for this process. These ingredients must not degrade at or below the extrusion temperature used. The short residence time of the materials inside the heating barrel of the extruder (~1 minute) permits HME to be more feasible for some thermally labile compounds than other hot methods (Repka et al., 1999; Verreck et al., 2006a; Rothen-Weinhold et al., 1999).

Thermogravimetric analysis (TGA) is used to determine the degradation temperatures of materials, so it can be useful in assessing the thermal stability of materials prior to HME. TGA may be used to determine mass loss as a function of temperature. This is a very rapid technique that has often been used to identify volatile degradants. Bruce et al. (2005) used TGA to predict the thermal stability of 5-aminosalicylic acid and other ingredients prior to HME. As shown in Figure 2.4, the TGA ramp test showed that BL was thermally stable up to 250 °C after which there was a significant loss in its mass mostly due to volatile degradation, whereas the TGA ramp test showed that PEG was thermally stable up to 350 °C. These high degradation temperatures for BL and PEG suggest that these compounds may be suitable for HME at temperatures below 250 °C.

![Figure 2.4. Thermogravimetric analysis of bicalutamide (BL) and polyethyleneoxide (PEO).](image-url)
BL has two conformational polymorphs (form I and II) that have similar chemical structures but different internal crystal structure (Vega et al., 2007). DSC was used to investigate the thermal properties of BL. Figure 2.4 shows the DSC thermograms of crystalline BL (form I) and amorphous BL. DSC studies of BL showed a sharp endotherm at 196 ± 0.8 °C (ΔH=125.0± 0.7 J/g), corresponding to melting of crystalline BL (form I). Amorphous BL, exhibited a Tg at 56.4 ± 0.4 °C, a re-crystallization exotherm at 125.8 ± 0.5 °C, and a sharp endotherm at 193.5 ± 0.1 °C, corresponding to melting of re-crystallized BL (Figure 2.5). It has been previously reported that the exothermic peak observed following the glass transition represents conversion of amorphous BL to form II. The subsequent endotherm at 193.5 ± 0.1 °C represents melting of form II (Vega et al., 2007). Similar results were observed in the current study whereby amorphous BL undergoes a cold crystallization at 125.8 °C to form II. This was shown to subsequently melt at 193.5 °C.
Figure 2.5. A representative DSC thermograms of crystalline (form I) and amorphous bicalutamide (BL). The glass transition of amorphous BL has been expanded for clarity.
Forster et al. (2001a) showed that DSC can be used as an efficient predictive tool for drug/polymer miscibility prior to HME using small quantities of drug/polymer binary mixtures (Forster et al., 2001a). In this study, BL-PEO binary mixtures containing drug : polymer weight ratios of 1:10, 2:10 and 3:10 were prepared and analyzed using DSC. The endotherm corresponding to fusion of crystalline BL (form I) could not be detected in the DSC heating scans of physical mixtures (Figure 2.6), indicating that BL was solubilized in the melted PEO. This is often a significant drawback of standard DSC in systems that have a polymer melting point below the drug melting point. These findings indicate that PEO acts as a good solvent for BL and forms a miscible binary matrix. To form solid molecular dispersions (solid solution) by hot methods, the drug and polymer must be miscible at the processing temperatures (Leuner and Dressman, 2000). Based on the observed DSC results, there is strong evidence of miscibility between BL and PEO.

BL-PEO physical mixtures at drug/polymer weight ratios of 1:10, 2:10 and 3:10 were extruded at a temperature of 100 °C. This extrusion temperature was selected based on the melting point of PEO (67.33 ± 0.75 °C) (Table 2.2). Usually 15–60 °C above the melting point of semi-crystalline polymers or the glass transition temperature of amorphous polymers is required to obtain a polymer melt viscosity suitable for HME (Crowley et al., 2007). Trials were conducted to extrude the BL-PEO physical mixtures at a temperature of 85 °C and a screw speed of 100 rpm, but problems of low flow rate of the melt through the die opening were encountered. To try to resolve these problems the extrusion temperature was increased up to 100 °C, resulting in significant improvement in the flow rate of the melt through the die opening and hence a more efficient HME. During exit from the die, the drug/polymer mixtures at all weight ratios were transparent indicating drug/polymer miscibility at these processing conditions. Following cooling, the melt extrudates at a drug/polymer ratio of 3:10 turned white indicating significant re-crystallization of BL, whereas the melt extrudates of 1:10 and 2:10 ratios were opaque. Even pure PEO samples extruded without BL were opaque after cooling. This opacity of PEO melt extrudates may be attributed to the fact that PEO is a semicrystalline polymer that contains crystalline regions which are usually dense and impart opacity in the extruded PEO samples (Produtturi et al., 2005).
To confirm the thermal stability of BL and PEO at the extrusion temperature used (100 °C), TGA isothermal tests were conducted on pure BL and PEO samples. Negligible mass loss, 0.5 % of BL and 1.3 % of PEO, was observed during the isothermal test (60 minutes at 160 °C). These TGA results confirmed that both BL and PEO have acceptable thermal stability at a temperature of 160 °C, which was well above the extrusion temperature. Based on these TGA isothermal tests results and the high degradation temperatures, which are significantly higher than the extrusion temperature, BL and PEO can be considered to be thermally stable and suitable for HME. Furthermore, the short residence time of the materials within the extruder (~1 minute) also facilitates drug and polymer stability.

DSC thermograms for freshly manufactured melt extrudates were generated and showed similar results as the DSC thermograms of the physically mixed samples in terms of the absence of a melting endotherm for BL (Figure 2.6). A lack of drug melting endotherm in the extrudates usually suggests the presence of the drug in an amorphous form within the dispersions, but this may not be confirmed using DSC especially when PEO melts before the drug. BL dissolved in the molten PEO during DSC heating scan in the physically mixed samples containing crystalline BL (Form I). These findings were in agreement with previous research on solid dispersions containing flurbiprofen, clotrimazole and PEO (Prodduturi et al., 2005, Ozeki et al., 1997). Although DSC was efficient in detecting miscibility between BL and PEO, it was not useful in providing information about the solid state properties of BL within the melt extrudates, so other techniques (PXRD and SEM) were used to define such properties.

Table (2.2) provides the average ± standard deviation of melting point (°C) of PEO and BL-PEO pre- and post-extruded samples. The DSC trace of PEO powder (Figure 2.6) had an endothermic peak at (67.33 ± 0.75 °C) corresponding to melting of the crystalline polymer. There was no significant change in the melting point of PEO as a function of processing (Table 2.2). In a previous study, it was reported that the melting point of PEO decreased significantly after HME with nifedipine as a result of drug/polymer molecular interactions (Li et al., 2006). In this context, it may be argued that in this study the lack of an observed melting point depression in PEO as a function of drug loading and processing (pre and post extrusion) (Figure 2.6) may
be attributed to weak interactions of BL with PEO. Interestingly, it was observed that extruded PEO had a much broader endotherm than the corresponding physically mixed samples. The broadening following extrusion may be attributed to the wider distribution of crystallites within the hot melt extruded samples (Figure 2.6) (Crowley et al., 2004a).

### Table 2.2. Melting points and enthalpies of PEO in pre and post extrusion samples

<table>
<thead>
<tr>
<th>Drug/Polymer ratio</th>
<th>Melting Point (°C)</th>
<th>Enthalpy (J/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-extrusion</td>
<td>Post-extrusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observed</td>
</tr>
<tr>
<td>PEO</td>
<td>67.33 ± 0.75</td>
<td>67.73 ± 1.02</td>
</tr>
<tr>
<td>1:10</td>
<td>66.76 ± 0.21</td>
<td>66.08 ± 1.25</td>
</tr>
<tr>
<td>2:10</td>
<td>66.78 ± 0.14</td>
<td>65.83 ± 1.04</td>
</tr>
<tr>
<td>3:10</td>
<td>66.81 ± 0.2</td>
<td>65.73 ± 0.72</td>
</tr>
</tbody>
</table>

The values presented in the table are the average ± standard deviation of three replicates (n=3)

*a calculated PEO enthalpy (J/g) obtained by multiplying the melting enthalpy (J/g) in pure PEO extruded samples by the ratio of PEO in BL-PEO melt extrudates samples. For example, calculated PEO enthalpy for melt extrudates at BL:PEO (1:10) = 166.6 * 10/11 = 151.45 g/J.

b values represent the difference between the calculated melting enthalpy of PEO and the experimentally observed PEO melting enthalpy i.e. the decrease in the calculated PEO melting enthalpy as a result of HME with BL.
The melting enthalpy (ΔH) (J/g) of PEO in pure PEO samples decreased significantly after HME (166 ± 4.96 J/g) comparing to the corresponding enthalpy of pre-extruded PEO samples (198.43 ± 8.60 J/g). This significant decrease in the enthalpy of PEO was mostly related to the significant decrease in the PEO crystallinity after HME. Similar findings have been reported previously within the literature (Prodduturi et al., 2005, Li et al., 2006, Crowley et al., 2004a). PEO, when cooled from the melt, does not usually re-crystallize in the same manner or to the same extent as the initial state. This may be attributed to the fact that semi-crystalline polymers commonly re-crystallize as lamellae allowing folded chain molecules to re-enter the crystallite at any time but some molecules may link or tie separate lamellae across the amorphous regions (Prodduturi et al., 2005).
All melt extrudates showed a slight decrease (5.78 - 6.08 J/g) in the observed enthalpy of PEO in comparison to the theoretical calculated values derived from pure PEO extruded samples (Table 2.2). This slight decrease in the theoretical calculated melting enthalpy of PEO after HME may be attributed to the effect of BL miscibility with PEO. These results suggest that the crystallinity of PEO after HME has not been affected significantly by the dissolved BL molecules and the decrease in the melting enthalpy of PEO in the extruded samples compared to the pre-extruded samples was attributed mainly to the loss of polymer crystallinity due to HME rather than due to BL solubilization.

2.3.2 Solid state plasticization of BL by PEO

Figure 2.7 shows DSC thermograms of BL-PEO physical mixtures over the concentration range from 10 to 90 % (w/w) BL (first heating cycle). DSC thermograms of BL-PEO physically mixed samples up to 20% (w/w) BL showed complete absence of a melting endotherm for crystalline BL (form I), whereas above this polymer level a BL melting endotherm was detected with significant broadness in comparison to the sharp melting endotherm observed for crystalline BL (form I). The BL melting endotherm area increased with increasing BL content in the binary mixtures. In addition, DSC thermograms of BL-PEO binary mixtures showed a decrease in the onset of melting temperature of crystalline BL (form I) with increasing PEO level in the binary mixtures (Figures 2.7 and 2.8).
Figure 2.7. DSC thermograms of BL:PEO binary mixtures at heating rate of 10 °C/min (first heating cycle).

Figure 2.8. Extrapolated onset of melting point for bicalutamide as a function of the volume fraction of PEO measured at a heating rate of 10 °C/min. The data shown is the average of three replicates and in all cases the COV was ≤ 1%.
In the second heat cycle, after quench cooling of the melt, a significant plasticization effect on amorphous BL was detected with increasing PEO level in the binary mixtures. This plasticization effect on amorphous BL was characterized by the significant decrease in the glass transition (Tg) of amorphous BL (Table 2.3 and Figure 2.9). For example, a significant decrease in the Tg of amorphous BL (56.4±0.3 °C) was observed when a binary mixture containing 60% was examined (-31.3±2.7 °C). It was not possible to detect the Tg of BL in the binary mixtures containing 10, 20 and 30 % (w/w) BL level which might be due to the low concentration of BL at these physical mixtures. Additionally, it was not possible to detect the Tg of PEO using DSC which may be due to the small proportion of the amorphous domain within semi-crystalline PEO. PEO is an easy-to recrystalize polymer with over 85% crystallinity present in the pure powder (Li et al., 2006). The glass transition temperature (Tg) of PEO has been reported to be -67 °C (Mishra and Dubey, 2000).

Because of the difficulty in detecting the Tg of PEO, it was not possible to make a definite conclusion about the type of miscibility between BL and PEO. If the Tg detected in the DSC thermograms was the only Tg of the binary system that means a single phase system has been formed; whereas if there was another Tg in the system that could not be detected for the amorphous domain of PEO that means a two phase system had been formed. Partial miscibility is evident when the Tg of the drug is shifted towards the Tg of the excipient, or vice-versa while if both the Tg values remains practically unchanged at all mass ratios, there is strong evidence of an immiscible system (Yu et al., 1998). Thus based on the solid state plasticization effect by PEO on amorphous BL, a partial miscibility between BL and PEO at least can be assumed.
Table 2.3. The glass transition (Tg) of BL in pure and binary mixtures with PEO.

<table>
<thead>
<tr>
<th></th>
<th>Tg (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amorphous BL</td>
<td>56.4 ± 0.3</td>
</tr>
<tr>
<td>BL:PEO (w/w)</td>
<td></td>
</tr>
<tr>
<td>9:1</td>
<td>38.0 ± 0.3</td>
</tr>
<tr>
<td>8:2</td>
<td>22.1 ± 1.3</td>
</tr>
<tr>
<td>7:3</td>
<td>5.7 ± 0.7</td>
</tr>
<tr>
<td>6:4</td>
<td>-8.9 ± 1.2</td>
</tr>
<tr>
<td>5:5</td>
<td>-21.9 ± 1.1</td>
</tr>
<tr>
<td>4:6</td>
<td>-31.3 ± 2.7</td>
</tr>
</tbody>
</table>

Tg = glass transition temperature determined experimentally by DSC.
The values presented in the table are the average ± standard deviation of three replicates (n=3).

Figure 2.9. Plasticization of bicalutamide (BL) by PEO.
2.3.3 *Flory-Huggins Modeling*

To calculate the Flory Huggins interaction parameter (\(\chi\)) equation (2.1) was rearranged. A plot of \((1/T_{M_{mix}}-1/T_{M_{pure}})*((\Delta H_{fus}/-R)-\ln(\Phi_{drug})-(1-1/m)\Phi_{polymer})\) vs. \(\Phi_{polymer}^2\), as shown in Figure 2.10, yielded a linear relationship \((r^2 > 0.99)\) with a slope \((\chi)\) equal to 1.076. Negative Flory-Huggins interaction parameters describe systems which exhibit strong and numerous adhesive interactions which favor miscibility, whereas positive interaction parameters characterize systems exhibiting stronger cohesive interactions (Marsac *et al.*, 2006b). The positive Flory-Huggins interaction parameter \((\chi)\) suggests that the cohesive interactions among the PEO monomers and the BL molecules are much stronger than the adhesive forces between BL and PEO.

![Figure 2.10. Plot used to calculate the interaction parameter \((\chi)\) (for the bicalutamide-PEO system based on equation (2.1)).](image-url)

\[
y = 1.0757x + 0.0188 \\
R^2 = 0.9868
\]
2.3.4 Solubility of BL in PEO polymeric matrix

The solubility of solid drugs dispersed in polymeric matrices was determined quantitatively using DSC for first time by Theeuwes *et al.* (1974). In essence this method is based on the fraction of drug solubilised within the matrix not contributing to the melting endotherm associated with the dispersed drug fraction. By plotting the measured $\Delta H_f$ values versus drug concentration for a range of loadings and extrapolating to zero $\Delta H_f$, the solubility of the drug in the polymer may be estimated. Hyper DSC overcomes the disadvantages associated with conventional DSC for determining solubility of drugs in polymer systems whereby solubility can only be measured at the drug melting temperature. The heating rates may inhibit further solubilisation due to the increase in solubility profile caused by increasing the temperature that may otherwise occur during slower scans, so faster heating rates can reduce further dissolution of drug into the matrix and thus a more realistic estimation of drug solubility in a polymer matrix may be achieved. The solubility of metronidazole in silicone elastomer (0.216 % w/w) was predicted efficiently using hyper DSC illustrating the simplicity and efficacy of this technique. Furthermore, the faster the scan rate the better the prediction of solubility as kinetic events are minimized (Gramaglia *et al.*, 2005).

The DSC scan for pure BL at heating rate 500 °C/min showed a melting endotherm at 200 °C, and an enthalpy of fusion equal to 119.7 (J/g). BL-PEO (10, 20, 30, 40 and 50 % w/w) were investigated at scan rates of 500 °C/min. Figure 2.11 shows the effect of increasing drug concentration on the melting endotherm, with higher concentrations causing the size of the melting endotherm to increase, as it relates to the concentration of undissolved drug present in the formulation at the melting temperature. By plotting $\Delta H_f$ against the drug loading concentration and extrapolating to zero $\Delta H_f$, as in Figure 2.12, the solubility of BL in PEO can be determined. Linear trend lines were fitted to the data with regression values exceeding 0.99. The solubility values, calculated as the x-intercept was 6.2 % (w/w).
Figure 2.11. DSC thermograms of BL (% w/w) in BL-PEO binary physical mixtures at heating rate of 500 °C/min.

Figure 2.12. A plot of bicalutamide (BL) concentration (%w/w) against the enthalpy of fusion at heating rate of 500 °C/min.
2.3.5 Crystalline properties of hot-melt extrudates

Figure 2.13 shows X-ray patterns for pure BL, pure PEO and a typical physical mixture at BL-PEO weight ratio of 1:10, whereas Figure 2.14 shows the X-ray patterns of the melt extrudates immediately following the manufacture and after storage at 20 °C and 65% RH up to 6 months. PEO is a semicrystalline polymer with over 85% crystallinity (Li et al., 2006), so its X-ray diffraction pattern showed distinct characteristic peaks at 2θ values 19.1, 23.0, 26.0, 26.9, 35.3, 36.0 and 39.5°. Crystalline BL has two polymorphs that have significantly different molecular conformations. Such conformational differences arise from differences in the torsion angles within the molecule that result in form I adopting an open structure whereas form II is more extensively folded and is thus more closed in conformation (Vega et al., 2007). These conformational variations give rise to PXRD patterns with subtle differences. The most distinct crystal peaks for pure crystalline BL (form I) were observed at 2θ 12.1, 16.7, 18.8, 19.2, 23.5, 24, 6, 29.2, 29.5, 31.1°. Most of the characteristic BL peaks overlapped the PEO crystal bands. X-ray patterns of the 1:10 and 2:10 melt extrudates showed a significant decrease in the intensity of the characteristic BL peak at 2θ 12.1° (peak #1) which was recorded as a very small peak (Figures 2.14). Additionally, there was a complete absence of the characteristic BL peaks that were recorded clearly in PXRD pattern of the physical mixture samples at 2θ 17.0, 29.5° assigned as peak #2 and #3, respectively, in Figures 2.13 and 2.14. These results indicate the significant loss in BL crystallinity within 1:10 and 2:10 melt extrudates and the presence of BL mainly as an amorphous state within these melt extrudates. The limit of crystallinity detection in PXRD was shown to be between 1 and 10 % (Brittain, 1995; Andrews et al., 2009a). The X-ray pattern of the 3:10 melt extrudates, showed distinct sharp crystal bands of BL especially at 2θ 12.35° and 31.60° indicating that crystalline BL was present significantly within these melt extrudates (Figure 2.14).
Figure 2.13. Powder X-ray diffraction patterns for crystalline BL (form I), a representative physical mixture of BL and PEO. Peaks #1, #2 and #3 were assigned for BL peaks.
PXRD patterns of melt extrudates samples at 1:10 and 2:10 weight ratios stored at 20 °C and 65% RH showed distinct BL crystal peaks after 1 month storage which increased in intensity after 3 and 6 months storage. The BL crystal peaks detected in PXRD pattern of melt extrudates of 3:10 weight ratio increased in intensity upon storage (Figure 2.14). It was difficult to get a definite conclusion about the polymorph type that was generated upon BL re-crystallization from the melt extrudates especially that with the broadness of the re-crystallized BL peaks and given that PEO bands overlapped most of the BL characteristic peaks.

The rapid recrystallization of amorphous BL within PEO melt extrudates may be attributed to the plasticization of BL by PEO which resulted in lower Tg values in comparison to amorphous BL and hence higher molecular mobility and less physical stability. Another factor that might affect the stability of amorphous BL within PEO melt extrudates is the solubility of BL within the PEO polymeric matrix. The lowest BL concentration manufactured in this study was 9.1% (w/w) within the melt extrudates at drug/polymer ratio of 1:10, which was higher than the solubility of BL within PEO matrix determined by hyper-DSC (6.2% w/w). The presence of the very small peak of BL at 20 12.1° (peak #1) (Figure 2.14) in the PXRD pattern of freshly prepared melt extrudates at 1:10 ratio suggests that BL at this level exceeded its saturation solubility in PEO matrix resulting in an unstable binary system and hence increased tendency for amorphous BL to re-crystallize especially that these very small crystals can act as nuclei that may accelerate crystals growth within the melt extrudates.
Figure 2.14 Powder X-ray diffraction patterns for BL-PEO hot-melt extruded samples (a) 1:10 (b) 2:10 and (c) 3:10 immediately after manufacture and after storage for 6 months at 20 °C, 65% RH. Peaks #1, #2 and #3 were assigned for BL peaks.

SEM is one of the best methods to study the crystalline properties of hot-melt extrudates. By examining the surface morphology of melt extrudates using SEM, the presence of crystalline particles or amorphous domains can be probed and reliable particle size information also can be obtained using this technique (Crowley et al., 2007). SEM studies were conducted to investigate the surface morphology of the melt extrudates in comparison with pure drug (Figure 2.15). After HME of BL-PEO binary systems, the freshly prepared melt extrudates had a smooth surface and were free from any crystalline BL (needles) at drug/polymer weight ratios of 1:10 and 2:10 suggesting that the amorphous form of BL was dominated within these freshly prepared melt extrudates. Conversely, some BL crystals were detected in the melt extrudates at a drug/polymer ratio of 3:10. It was not possible to detect any BL crystals in the 1:10 and 2:10 melt extrudates using SEM although PXRD patterns of these melt extrudates showed very small peak at 2θ 12.1°. These results may be attributed to that these BL crystals may present in very small number and size that could not be detected easily using SEM. However, SEM results were in agreement with PXRD suggesting the presence of drug crystallinity in the melt extrudates containing BL at 30 % w/w of polymer.
After storage of the melt extrudates for six months (65% RH, 20°C), drug/polymer ratios at 1:10 and 2:10 showed distinct BL crystals. The crystals were larger in size and quantity within melt extrudates at a drug/polymer ratio of 2:10 in comparison to 1:10. The BL crystals in the melt extrudates at a drug/polymer ratio of 3:10 become significantly larger in size and number after six months storage (65% RH, 20°C) (Figure 2.15).

Figure 2.15 Scanning electron microscope images of (a) crystalline bicalutamide (BL) (at 100X magnification); (b) PEO HME (at 5,000X magnification); (c) BL-PEO HME (2:10) immediately following manufacture (at 5,000X magnification); (d) BL-PEO HME (1:10), (e) (2:10), (f) (3:10) after 6 months storage at 20°C, 65% RH (at 5,000X magnification).
2.3.6 Drug/polymer interactions

FTIR and Raman spectroscopic studies were conducted in order to characterize the nature of the intra- and intermolecular interactions within BL in the crystalline and amorphous state and to investigate the interaction between BL and PEO within the melt extrudates. The chemical structures of BL and PEO are shown in Figures 2.1 and 2.3, respectively.

BL has two functional groups that can act as proton donors, the amide (N-H) and the hydroxyl (O-H) group, whereas there are many functional groups that can act as proton acceptors (oxygen atoms of the carbonyl (C=O), the hydroxyl (O-H) and the sulfonyl (O=S=O) groups). Furthermore, the nitrogen atom of the amide (N-H) and nitrile (C≡N) groups can act as proton acceptors (Jeffrey, 1997). The presence of proton donor and acceptor functional groups within BL increases the potential sites for hydrogen bonding, both intra- and intermolecular. In this respect, both forms of BL possess intramolecular hydrogen bonds between the amide (donor) and the hydroxyl (acceptor) however due to conformational differences, form I is stabilized by hydrogen bonding between C19-H19...O16 whereas form II shows significant hydrogen bonding between C23-H23...O16. In addition, both forms possess significantly different intermolecular hydrogen bonding (Vega et al., 2007).

The chemical structure of PEO consists of repeating units of polyethylene oxide monomers. PEO can act as a proton acceptor through the oxygen atom of ethylene oxide monomer (–CH2-CH2-O-) (Robeson et al., 1981), which may interact with the proton donor groups of BL, either the hydroxyl or/and amide groups during HME. The FTIR spectrum of PEO showed a characteristic absorption band at 1097 cm⁻¹ which is related to the bending vibration of C-O, while the two bands located at 1344 and 2890 cm⁻¹ are due to the bending and stretching vibrations of C-H bonds, respectively. The broad absorption band around 3434 cm⁻¹ is due to the stretching vibration of the O-H bonded to C-H (Figure 2.16).
In this study we have utilized FTIR and Raman spectroscopy in an attempt to identify the differences in the interactions at the molecular level between the crystalline and amorphous forms of BL. In previous studies it has been clearly demonstrated that there are significant differences between the spectra of the amorphous and crystalline forms of a drug (Smrecki et al., 1997). In brief, peak width, shape, intensity and position are known to differ between the amorphous/crystalline forms of a drug compound. Figure 3.16 shows the most interesting peaks of the FTIR spectra for BL in the crystalline form I and amorphous state. The most important characteristic peaks for crystalline form I BL in the FTIR are the stretching vibrational bands of the N-H group (3339 cm\(^{-1}\)), the carbonyl group (1688 cm\(^{-1}\)) and the nitrile group (2228 cm\(^{-1}\)). As expected, the crystalline form of BL had peaks that were sharper and of greater intensity in comparison to amorphous BL. The decrease of peak intensity observed within the amorphous form of BL may be attributed to lack of long-range order and the resultant increase in the distribution of bond lengths and vibrational energies in comparison to the crystalline form (Smrecki et al., 1997). The FTIR spectrum for crystalline BL (form I) also showed a small peak in the region 3400-3650 cm\(^{-1}\) for the stretching vibration of the hydroxyl group (O-H). This sharp peak may be attributed to intramolecular interaction of the hydroxyl group with the adjacent carbonyl (Ren et al., 2006). Interestingly these peaks were not present in the FTIR spectrum of amorphous BL.
Figure 2.16. FTIR spectra of crystalline (form I) and amorphous BL showing (a) the carbonyl; (b) the nitrile (c) the amide vibration modes.
Raman spectroscopy being complementary to FTIR showed similar trends when comparing the crystalline to amorphous form of BL. Figures 2.17 and 2.18 show the most interesting peaks of the Raman spectra collected for BL in the crystalline and amorphous state. As shown in Figures 2.17 and 2.18, there were distinct differences between the crystalline (form I) and amorphous form of BL. There were also significant differences between form I and form II of BL. In particular, the peaks attributed to the nitrile (2230 cm⁻¹) and carbonyl (1686 cm⁻¹) groups were significantly broader in the amorphous form however there was no lowering of intensity. The Raman spectra of crystalline BL (form I) had a distinct peak at 1516 cm⁻¹, that may be attributed to N-H in-plane bending (Smrecki et al., 1997). This peak also showed broadening in the amorphous form. The Raman spectra of crystalline form I and form II also displayed considerable differences. As previously reported by Vega et al, (2007) there are characteristic maxima at 600, 1430 and 1496 cm⁻¹ for form II.

![Raman spectra showing the nitrile vibration mode of crystalline form I and II) and amorphous BL.](image)

Figure 2.17. Raman spectra showing the nitrile vibration mode of crystalline form I and II) and amorphous BL.
Figure 2.18. Raman spectra showing the carbonyl and amide vibration modes of crystalline (form I and II) and amorphous BL.

In relation to peak position, both the FT-IR and Raman spectra confirmed that the amorphous form of BL had the carbonyl, nitrile and N-H peaks at higher wavenumbers. FTIR (Figure 2.16) confirmed a shift in the carbonyl group from 1688 cm\(^{-1}\) (crystalline BL) to 1703 cm\(^{-1}\), the N-H stretch from 3339 cm\(^{-1}\) to 3373 cm\(^{-1}\) whereas no shift has been occurred for the nitrile (CN) group (2228 cm\(^{-1}\)). Additionally, Raman spectra (Figures 2.17 and 2.18) showed a shift in the carbonyl from 1686 cm\(^{-1}\) to 1706 cm\(^{-1}\), the N-H in-plane bend from 1516 cm\(^{-1}\) (form I) to 1526 cm\(^{-1}\) and a very small shift in the nitrile group from 2230 cm\(^{-1}\) to 2232 cm\(^{-1}\). Moreover, the carbonyl band of form II was observed at a higher wavenumber than form I (1712 cm\(^{-1}\) in comparison to 1688 cm\(^{-1}\)). Both crystalline (forms I and II) and amorphous forms of BL contained an intense band at approximately 1616 cm\(^{-1}\) (amorphous form and form II) or 1614 cm\(^{-1}\) (form I). This band may be attributed to C-C ring stretching modes of vibration (Brittain, 2009). The subtle difference observed may be due to the difference in the hydrogen bonding character within the amorphous and crystalline forms. Interestingly, form II has a smaller, second band of much lower intensity just below 1600 cm\(^{-1}\). This band is also present in the amorphous form of BL but is not as well resolved.
Typically, the formation of hydrogen bonds within a given system may be readily identified through either a red shift in the absorption band (movement to lower wavenumber), band broadening and/or peak intensification. Whilst the latter two spectroscopic characteristics (peak broadness and intensity) of hydrogen bond formation may be utilized when comparing crystalline compounds, it is extremely difficult to use such indicators when drawing a comparison between crystalline and amorphous drug forms. This is due to the fact that amorphous drug forms as a result of the high level of disorder, exhibit non-specific broadening and intensity reduction (Kaushal et al., 2008). Therefore a red-shift in the position of a characteristic absorption band has become the most useful marker for hydrogen bond formation, particularly when characterizing solid dispersions that often consist of an amorphous drug form embedded in a polymeric matrix (Lu and Zografi, 1998). The significant shift to a higher wavenumber for the carbonyl and N-H bands in the amorphous form of BL in comparison to form I would suggest that there is a weakening of the hydrogen bonds upon disruption of the highly ordered crystal lattice. In both crystalline forms (I and II), molecular conformation is stabilized by intramolecular hydrogen bonding whereas crystal cohesion is strongly facilitated by intermolecular hydrogen bond interactions. Generation of the amorphous form would disrupt the crystal lattice of form I and would therefore be expected to reduce/weaken these interactions since they are a function of the regular packing within the crystal. Interestingly the Raman spectra of form II was similar to that obtained for amorphous BL. This would suggest that the molecular environment within the higher energy crystal form (form II) is similar to the amorphous system resulting in a similar energy requirement to cause vibration of characteristic functional groups of BL.

Figure 2.19 shows the FTIR spectra recorded for the melt extrudates and for physical mixtures of form I BL and amorphous BL with PEO. The FTIR spectrum of the physical mixture containing form I BL showed the stretching vibration band of the amide (N-H) group of BL which was observed in the FTIR spectra of form I (3339 cm\(^{-1}\)). Similar to the FTIR spectrum of physically mixed samples of amorphous BL with PEO, the stretching vibration band of (N-H) group was absent from the FTIR spectra of 1:10 and 2:10 melt extrudates (Figure 2.19). On the other hand, this band was observed clearly in the FTIR spectra of the 3:10 melt extrudates. The absence of the N-H stretching vibration band from the spectra of 1:10 and 2:10 melt extrudates
may be attributed to peak broadening due to presence of amorphous BL, which has been confirmed by PXRD and SEM. The very broad stretching vibration band of the O-H of PEO may overlap the broad stretching vibration band of N-H group of amorphous BL.

Figure 2.19 FT-IR spectra of PEO, BL-PEO hot melt extrudates (HME) and physical mixtures (PM).
Figure 2.20 a and b illustrates the Raman shift region from 1500 to 1750 cm\(^{-1}\) and from 2200 to 2260 cm\(^{-1}\), respectively, for the melt extrudates, a typical physical mixture of form I BL and PEO at drug/polymer weight ratio of 3:10. The Raman spectra of melt extrudates at 1:10 and 2:10 ratios were similar to the spectrum of amorphous form of BL particularly in terms of peak broadness. On the other hand, the 3:10 melt extrudates and the physically mixed samples of form I BL showed similar spectra to form I BL. Similar to the Raman spectrum of the amorphous form of BL, broadness and shifting to higher frequency were observed for the stretching vibration bands of the carbonyl group and the bending vibration band of the N-H group in the Raman spectra of 1:10 and 2:10 melt extrudates (Figure 2.20a). These shifts in the carbonyl stretch and the N-H bend vibration bands of BL were not observed in the 3:10 melt extrudates. The stretching vibration band of the nitrile group (CN) in the spectra of 1:10 and 2:10 melt extrudates showed broadness similar to the spectrum of amorphous BL (Figure 2.20b). These FTIR and Raman results suggest that BL existed mainly as an amorphous form within the 1:10 and 2:10 extrudates, whereas form I was present within the 3:10 melt extrudates.
To investigate any intermolecular interactions between BL and PEO, the FTIR and Raman spectra of the melt extrudates were compared to the spectra of a physically mixed sample of amorphous BL and PEO. As shown in Figure 2.19, the peak which was attributed to the stretching vibration band of the carbonyl group (C=O) of amorphous BL (1703 cm⁻¹) was shifted significantly to higher frequency 1735 and 1741 cm⁻¹ in the FTIR spectra of 1:10 and 2:10 melt extrudates, respectively, whereas it occurred at 1701 cm⁻¹ in the FT-IR spectrum of physically mixed sample of amorphous BL and PEO. The stretching vibration band of the carbonyl group was detected sharply at 1688 cm⁻¹ in the 3:10 melt extrudates without any shifting compared to FTIR spectra of crystalline BL (form I) and the physically mixed sample of form I BL and PEO. The significant shift in the stretching vibration band of the carbonyl group in the melt extrudates containing amorphous BL in comparison to the physically mixed sample of amorphous BL and PEO suggests the presence of weak interactions (not hydrogen bonding) between the carbonyl group of amorphous BL and the oxygen atom of the polyethylene oxide monomer of PEO. These weak interactions may occur between the partial negatively charged oxygen atoms of polyethylene oxide and the partial positively charged carbon atoms of the carbonyl groups of BL during HME. These attractive forces between the positively
charged carbon atoms of amorphous BL and the negatively charged oxygen atoms might be weakened by the repulsive forces offered by the negatively charged oxygen atoms of the carbonyl group of BL leading to the presence of weak interactions between PEO and BL. It was shown that miscible blends of PEO with poly (methyl methacrylate) (PMMA) or poly (phenyl methacrylate) polymers were formed based on the presence of very weak interactions between the polymers (Rao et al., 1985; Woo et al., 2000). Rao et al. (1985) suggested that the attractive forces between the negatively charged oxygen atoms of PEO and positively charged carbonyl carbon atoms of a PMMA are weakened by the repulsive forces offered by the negatively charged oxygen atoms of the carbonyl group of PMMA. Similarly this may explain the shift to a higher wavenumber for the carbonyl of BL. In essence, the newly formed interaction between BL and PEO is weaker than interaction between BL molecules.

Both FTIR and Raman spectra of the melt extrudates did not show any significant changes in the position of the bands that were related to the polyethylene oxide group of PEO which may be attributed to the weakness of drug/polymer interactions with BL and the presence of PEO in much larger quantities within the melt extrudates in comparison to BL. These results indicate the absence of any specific strong intermolecular interactions between BL and PEO. In comparison to amorphous form, the Raman spectra of 1:10 and 2:10 melt extrudates showed a red shift for the stretching vibration band of the nitrile (CN) group (2232-2228 cm\(^{-1}\)) (Figure 2.20b). This red shift for the nitrile (CN) group may be attributed to nonhydrogen-bonded weak interactions with PEO. It has been previously reported that the nitrile (CN) group frequency shift is sensitive to the existence of interaction. Hydrogen bonding causes a blue shift of the CN stretching mode frequency, whereas distorted or non-hydrogen-bonded interactions would exhibit red shifting (Choi et al., 2008). This red shift for the nitrile (CN) group has not been observed in the spectrum of 3:10 melt extrudates, which was located at same position as in the spectra of physically mixed samples of BL form I and PEO (2230 cm\(^{-1}\)). Additionally, there were not any significant changes in the position of the N-H bend vibration and C-C ring stretching modes of vibration in the Raman spectra of 1:10 and 2:10 melt extrudates comparing to the Raman spectrum of amorphous BL. Even the significant shift occurring in the stretching vibration band of the carbonyl group of BL in the FT-
IR spectra of the melt extrudates at 1:10 and 2:10 ratios could not be detected using Raman spectroscopy which might be related to the weakness of such interactions especially given that carbonyl group (>C=O) is considered as a weak Raman scattering group because of its asymmetric nature which typically has a strong band in infrared spectra (Smith and Dent, 2006).

2.3.7 In vitro drug release studies

Figure (2.21) shows the dissolution profiles of BL-PEO extrudates at ratios of 1:10, 2:10 and 3:10. In addition, the dissolution profile of pure BL and a typical physical mixture BL:PEO (1:10) are shown. The significant decrease ($p < 0.0001$) in the percent drug release from the physically mixed sample after 10 minutes dissolution in comparison to the percent drug release from pure BL samples may be attributed to the viscosity of PEO and its ability to form a viscous gel upon its contact with the dissolution medium (Prodduturi et al., 2005). However, after 60 minutes, no significant difference ($p = 0.1918$) in percent drug release was achieved from the physical mixture samples comparing to the pure drug (Table 2.4).

There was a significant increase ($p < 0.0001$) in the percent release of BL from all melt extrudates after 60 minutes in comparison to the physical mixture and pure BL samples. The increase in percent release of BL from the melt extrudates was highly dependent on the PEO concentration. Increasing the ratio of PEO in the melt extrudates resulted in higher percent BL release. The greatest increase in BL release was achieved from the dissolution of melt extrudates at drug:polymer ratio of 1:10 that showed a 6.22-fold increase in the percent drug release after 60 min compared to the pure drug (Table 2.4). Moreover, there was a significant improvement in the percent of BL dissolved from the melt extrudates at drug:polymer ratio of 2:10 and 3:10 ratios, which showed 4.36-fold and 2.55-fold increases after 60 min, respectively. The presence of amorphous BL as an amorphous form in the 1:10 and 2:10 melt extrudates or as significantly smaller crystals in the 3:10 melt extrudates compared to BL crystals in the pure drug samples (Figure 2.15), may significantly affect BL dissolution. Furthermore, once the solid dispersions were exposed to aqueous media and PEO dissolved, BL was released as very fine, colloidal particles with an enhanced surface area resulting in significant dissolution enhancement.
(Serajuddin, 1999). The hydrophilicity of PEO and the subsequent effect during dissolution and the fact that drug molecules embedded within the polymeric matrix are released simultaneously with the dissolved polymer results in a higher percent of drug release because of the improved wetting properties of BL. Dissolution rate and extent was improved significantly from hot melt extruded nifedipine-PEO solid dispersions as a result of the effect of dissolving polymer and the presence of amorphous drug (Li et al., 2006). The release rate of flurbiprofen from solid dispersions prepared by solvent evaporation was greatly affected by the dissolution characteristic of the carrier. Flurbiprofen solid dispersions, using PEO as a carrier, showed improved dissolution in comparison with hydroxypropyl cellulose (HPC) solid dispersions, and the % drug release increased with increasing PEO content (Ozeki et al., 1997).

It has been previously reported that solid dispersions are highly efficient in enhancing the dissolution properties of poorly soluble drugs (BCS class II drugs), and hence improving their oral bioavailability (Chiou and Reigelman, 1971, Leuner and Dressman, 2000, Serajuddin, 1999). The significant improvement in the BL dissolution properties from the melt extrudates indicate the importance of HME in manufacturing solid dispersions for this purpose (BCS class II drugs) (Breitenbach, 2002). The significant enhancement in BL dissolution from PEO hot melt extruded solid dispersions may have a significant improvement in BL oral bioavailability, particularly given that BL has a dissolution rate limited absorption due to its low aqueous solubility (Cockshott, 2004).
Table 2.4. Percent release of BL from extruded samples tested immediately following manufacture and after storage for six months at 20°, 65% RH. The dissolution properties of an exemplar physical mixture (1:10) are also shown for comparison purposes. The values presented in the table are the average ± standard deviation of three replicates.

<table>
<thead>
<tr>
<th>Ratio of BL:PEO</th>
<th>Form</th>
<th>Q10</th>
<th>Q60</th>
<th>Increase in % drug release*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mins</td>
<td>60 mins</td>
<td></td>
</tr>
<tr>
<td>1:10</td>
<td>Physical mix</td>
<td>1.96 ± 0.58</td>
<td>10.17 ± 1.32</td>
<td>0.24</td>
</tr>
<tr>
<td>1:10</td>
<td>Extrudate</td>
<td>26.02 ± 0.73</td>
<td>70.84 ± 1.45</td>
<td>3.16</td>
</tr>
<tr>
<td>1:10</td>
<td>Stability</td>
<td>21.41 ± 0.65</td>
<td>62.66 ± 1.11</td>
<td>2.60</td>
</tr>
<tr>
<td>2:10</td>
<td>Extrudate</td>
<td>17.32 ± 0.64</td>
<td>38.44 ± 0.99</td>
<td>2.10</td>
</tr>
<tr>
<td>2:10</td>
<td>Stability</td>
<td>15.09 ± 0.31</td>
<td>33.70 ± 0.69</td>
<td>1.83</td>
</tr>
<tr>
<td>3:10</td>
<td>Extrudate</td>
<td>8.25 ± 0.07</td>
<td>29.1 ± 1.42</td>
<td>1.0</td>
</tr>
<tr>
<td>3:10</td>
<td>Stability</td>
<td>5.47 ± 0.72</td>
<td>21.3 ± 0.34</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Q10 and Q60 are percentage drug release after 10 min and 60 min, respectively. Q10 and Q60 for BL = 8.23 and 11.21 % respectively. * Increase compared to pure BL, which was calculated by dividing Q10 of the samples by Q10 of pure BL (10 min) and by dividing Q60 of the samples by Q60 of pure BL (60 min).
To confirm that these differences in drug dissolution were related to the dissolution properties of the samples and there was no significant differences in the drug content, the content uniformity of the melt extrudates was determined. All formulations contained 100 ± 5% of the BL label claim. The range observed for the extrudates was from 96.7 to 101.4 % with an average ± s.d of 98.5 ± 1.8 % for (1:10), 98.6 ± 1.3 % for (2:10) and 99.6 ± 1.8 for (3:10).

The dissolution profiles of the melt extrudates (HMEs) stored at 20 °C and 65% RH up to 6 months showed a significant decrease in the percent drug release comparing to the corresponding freshly prepared extrudates, as shown in Table 2.4 and Figure 2.22 (p = 0.0015, 0.0023 and 0.0008 for 1:10, 2:10 and 3:10, respectively). This significant decrease in drug release was mostly due to the significant BL recrystallization within the melt extrudates during storage as confirmed by SEM and PXRD. This indicates the significance of the solid state properties of BL within the melt extrudates on drug dissolution. Even with the significant decrease in drug dissolution profiles after storage, the percent drug release was still significantly larger than the percent drug release achieved from pure drug (p< 0.0001 for all ratios) or
from the physical mixture samples \( (p < 0.0001 \text{ for } 1:10 \text{ and } 2:10 \text{ ratios}; \text{ whereas } p = 0.0002 \text{ for } 3:10 \text{ ratio}). \) Similar findings were reported for loperamide/PEG 6000 solid dispersions, prepared by spray drying, which showed significant decrease in drug release after 6 months storage at 25 °C and 52 % RH compared to freshly prepared samples, but still the drug concentrations achieved after storage were greater than those achieved from the dissolution of pure loperamide (Weuts et al., 2005). These results may be attributed to the ability of the polymer to create a better microenvironment for the dissolution of the drug from the solid dispersions in which the drug is in close contact with the polymer resulted in improving the drug wetting properties.

![Dissolution profiles of BL-PEO HME immediately after manufacture (1:10) (▲), (2:10) (■), (3:10) (♦) and after 6 months storage at (20°C, 65% RH) (1:10) (△), (2:10) (□), (3:10) (◊). The data shown is the average of three replicates and in all cases the COV was < 10%.](image)

Figure 2.22 Dissolution profiles of BL-PEO HME immediately after manufacture (1:10) (▲), (2:10) (■), (3:10) (♦) and after 6 months storage at (20°C, 65% RH) (1:10) (△), (2:10) (□), (3:10) (◊). The data shown is the average of three replicates and in all cases the COV was < 10%.
2.4 CONCLUSIONS
HME was used to manufacture solid dispersions of BL using PEO as a hydrophilic carrier without the use of any plasticizer. DSC was inefficient in characterizing the solid state properties of BL in the melt extrudates. PXRD and SEM confirmed that amorphous form of BL was dominated within the melt extrudates at BL : PEO ratios of 1:10 and 2:10, whereas crystalline BL was present significantly in the 3:10 melt extrudates. FTIR and Raman spectroscopic studies confirmed the PXRD and SEM results of amorphous solid dispersions formation after HME up to drug loading of 20% (w/w) of PEO. These results suggest the efficiency of these spectroscopic techniques in characterizing the solid state properties of BL within PEO melt extrudates.

FT-IR spectroscopy showed the presence of weak intermolecular interactions between the carbonyl group of BL and the oxygen atoms of PEO. The absence of any strong specific hydrogen bonding between BL and PEO enabled Flory solution theory to be applied to characterize the drug/polymer miscibility in BL-PEO binary system. Flory Huggins interaction parameter ($\chi$), calculated using melting point depression data from DSC, showed a positive value indicating that adhesive forces formed between BL and PEO during HME were weaker than the cohesive forces between BL or PEO chains. These results were in good agreement with FTIR and Raman results in terms of the weakness of such interactions between BL and PEO.

The melt extrudates showed significant improvement in drug dissolution compared to pure BL or physically mixed samples with PEO. The drug release from the melt extrudates was highly dependent on the drug : polymer ratio. Increasing the PEO content resulted in a significant improvement in drug dissolution. The highest increase in drug release was achieved from the melt extrudates using a drug : polymer ratio of 1:10 with a 6.22-fold increase in drug release being achieved after 1 h in comparison to pure drug. The significant enhancement in drug dissolution from the melt extrudates may be attributed to the solid state properties of the melt extrudates and the hydrophilicity of PEO that results in improved wetting properties for BL. These results indicate the efficiency of HME in manufacturing solid dispersions exhibiting improved dissolution properties that may have a significant effect in improving the oral bioavailability and thus to improve the therapeutic outcomes of the drug.
PXRD and SEM showed significant re-crystallization of amorphous BL in the melt extrudates after storage at 20 °C and 65% RH, which significantly decreased the dissolution properties of BL. Many factors may facilitate drug re-crystallization in BL-PEO amorphous systems. The solid state plasticization effect of PEO on amorphous BL resulted in a lowering of the Tg of amorphous BL and hence an increase in molecular mobility. Additionally, the presence of very small crystals, recorded by PXRD, within 1:10 and 2:10 may act as nuclei that accelerated re-crystallization of amorphous BL. The lack of any strong specific hydrogen bonding between BL and PEO confirmed by spectroscopic techniques (FTIR and Raman) may be a critical factor in that molecular mobility is not significantly reduced and thus BL may readily re-crystallize.
PHYSICOCHEMICAL CHARACTERIZATION OF HOT-MELT EXTRUDED BICALUTAMIDE-POLYVINYLPIRROLIDONE SOLID DISPERSIONS
3.1 INTRODUCTION
Amorphous solid dispersions are highly efficient systems used to improve the aqueous solubility of poorly soluble drugs (BCS class II drugs), which have low oral bioavailability due to their low aqueous solubility (Leuner and Dressman, 2000). Although highly advantageous in terms of improving aqueous solubility, the number of commercial pharmaceutical products containing amorphous drugs on the market is extremely low (Serajuddin, 1999). This low commercial productivity is mostly attributed to the physical instability of amorphous drug forms as a result of their high free energy (Hancock and Zografi, 1997). Amorphous systems are highly susceptible to spontaneous re-crystallization during storage, particularly in highly humid conditions or during dissolution (Hancock and Parks, 2000).

Consequently there is a necessity to stabilize amorphous drug forms in order to obtain maximum benefit. Physical stabilization of amorphous drug forms is a major area of research in the area of pharmaceuticals (Konno and Taylor, 2006, Aso et al., 2004, Miyazaki et al., 2004). Understanding the factors that can affect the stability of amorphous systems and prevent re-crystallization is necessary to establish efficient methods that can help in the physical stabilization of these systems. The absence of three-dimensional long range order in the amorphous drug forms results in systems with high molecular mobility (Hancock and Zografi, 1997). It has been reported that such systems even have significant molecular mobility at temperatures considerably lower than their glass transition temperature (Hancock et al., 1995). Furthermore, plasticization due to absorption of water (vapour moisture) can significantly reduce the Tg of amorphous drug forms and hence increase the probability for crystallization (Hancock and Zografi, 1994).

Amorphous solid dispersions using pharmaceutical polymers can enhance the physical stability of the amorphous forms. Miscibility between the drug and polymer in the solid state is a very critical factor that needs to be considered to achieve acceptable physical stabilization. Miscible drug/polymer systems result in solid molecular dispersions (single phase) in which the properties of the amorphous drugs can be changed significantly by the polymer, whereas this effect is minimal in amorphous solid dispersions where the amorphous drug is embedded within the polymeric matrix as clusters or aggregates (two phases). In the latter system,
crystallization is often controlled by the properties of the amorphous drug with limited effect from the polymeric carrier (Marsac et al., 2006b).

Manufacturing solid molecular dispersions using polymers with a high Tg can result in miscible systems (single phase) that have only one Tg, between the Tg of the amorphous drug and the Tg of the polymer. This miscible system often results in an increased Tg of amorphous drug form and hence a reduced molecular mobility as a result of anti-plasticization. Furthermore, significant increases in the viscosity of the binary system decrease the diffusion of amorphous drug molecules and hence prevent drug aggregation and crystallization (Van den Mooter et al., 2001).

Drug/polymer interactions within solid dispersions have a critical role in stabilization of amorphous drug forms. It has been shown that the formation of hydrogen bonding interactions between amorphous drug and polymer within solid molecular dispersions can significantly improve the physical stability of the amorphous form (Matsumoto and Zografi, 1999; Taylor and Zografi, 1997; Huang et al., 2008; Miyazaki et al., 2004).

Certain types of molecular association are needed to achieve crystallization, so disruption of the hydrogen bond patterns in amorphous compounds would be useful in the physical stabilization of amorphous phases. Thus by targeting the proton donor and/or acceptor groups in the amorphous drug to interact with the polymer can result in inhibition of cold crystallization of the amorphous form (Tang et al., 2002). At polymer levels where the anti-plasticization effect is minimal, PVP has been shown to inhibit crystallization of amorphous indomethacin by formation of hydrogen bond interactions. Subsequent disruption of amorphous indomethacin dimers and hence prevention of self association of indomethacin prevented re-crystallization (Taylor and Zografi, 1997).

Additionally, drug/polymer interactions can reduce the hygroscopicity of water-soluble polymers used in solid dispersions through the formation of interactions with the drug that reduce the affinity of the polymer toward moisture. This would therefore decrease the effect of moisture on the molecular mobility of the amorphous drug (Thypo et al., 2007; Forster et al., 2001b).
Polyvinylpyrrolidone (PVP) is an amorphous hydrophilic polymer with a high glass transition temperature (Tg) that has been used to manufacture solid dispersions using HME technology. PVP for example, has been utilized in the dispersion of 17-Estradiol hemihydrate to enhance in vitro dissolution rate (Hülsmann et al., 2001). Moreover, PVP has been successfully formulated into HME drug delivery systems for indomethacin, nifedipine, lacidipine, tolbutamide (Forster et al., 2001a, 2001b, 2001c).

Very importantly, PVP has been shown to form stable solid dispersions by inhibition of drug re-crystallization and it has been reported that drug-PVP intermolecular interactions play a critical role in this stabilization process (Matsumoto and Zografi, 1999). Figure 3.1 shows the chemical structure of PVP. PVP has a carbonyl group that can act as a proton acceptor with drugs having proton donor groups e.g. carboxylic acids to form hydrogen bonds, that can result in physical stabilization of amorphous solid dispersions (Taylor and Zografi, 1997; Thypo et al., 2007). Furthermore, the high Tg of PVP limits molecular mobility of the amorphous drug and also improves amorphous stability (Van den Mooter et al., 2001).

The high Tg of PVP may limit its application in solid dispersion preparations using HME. To achieve a feasible HME process using PVP, a plasticizer may be required to reduce its Tg and its melt viscosity and hence facilitate the extrusion process. Furthermore, reducing the processing temperature using a plasticizer may also allow thermally labile drugs to be processed. Interestingly, drug/polymer binary systems have been melt extruded successfully without the use of conventional plasticizers. In several studies reported in the scientific literature, it has been shown that active pharmaceutical ingredients may act as solid state plasticizers and hence negate the use of conventional plasticizing systems (Forster et al., 2001b; and Chokshi et al., 2005).
It was shown in chapter 2 that hot melt extruded BL-PEO solid dispersions were efficient in enhancing the dissolution properties of BL, but amorphous BL was shown to re-crystallize upon storage under high humidity conditions. Consequently, this resulted in a significant decrease in drug dissolution. The physical instability of these solid dispersions may result in a significant decrease in oral drug bioavailability during the shelf life of the drug, and hence may result in a lack of clinical efficacy. The plasticization effect of PEO on amorphous BL and the lack of any specific strong hydrogen bonding between BL and PEO were considered the most important factors affecting BL re-crystallization from PEO solid dispersions. In this study, PVP was used as a carrier to manufacture BL solid dispersions using HME technology. PVP has a high Tg and can form strong hydrogen bonding interactions with drugs that have proton donor groups that can result in the physical stabilization of amorphous drugs (Van den Mooter et al., 2001, Forster et al., 2001b, Taylor and Zografi, 1997; Gupta and Bansal, 2005). Hence we aim to develop more stable solid dispersions using this rationale.

![Chemical structure of polyvinylpyrrolidone (PVP)](image)

**Figure 3.1. Chemical structure of polyvinylpyrrolidone (PVP)**
3.1.1 Aims and objectives

The potential of HME technology to produce stable solid dispersions of BL-PVP was examined in this study. Although there are a number of studies reporting the use of PVP to form solid dispersions using HME, there are currently no articles describing the use of BL and PVP. Therefore, the aim of this study is to address this deficit by manufacturing HME solid dispersions using PVP and BL.

The principle aims and objectives are as follows:

- To examine the feasibility of HME in producing solid dispersions containing BL and PVP as a hydrophilic polymer.
- Characterize the physicochemical properties of manufactured hot melt extruded solid dispersions in terms of drug/polymer miscibility, solid state properties, drug/polymer interactions, surface morphology and drug release properties.
- Define the differences in interactions at the molecular level between the crystalline and amorphous forms of BL using spectroscopic techniques.
- Investigate the storage stability of the prepared solid dispersions and the negative effect this may have on drug dissolution.
- Examine the stabilizing effect of PVP on the amorphous form of BL within the melt extrudates, and to study the fundamental properties affecting cold crystallization.
3.2. MATERIALS AND METHODS
3.2.1 Materials
BL was purchased from Taresh Chemicals Ltd. (Banbridge, UK), Polyvinylpyrrolidone K25 (molecular weight 24,000 Daltons) (PVP K25), sodium dodecyl sulfate (SDS), triacetin (TCN) and dibutyl sebacate (DBS) were all purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Triethyl citrate (TEC) was purchased from Morflex, Inc. (Greensboro, NC, USA). All other chemicals used were purchased from BDH Laboratory supplies (Poole, Dorset, England) and were of Analar grade or equivalent quality.

3.2.2 Preparation of BL-PVP melt extrudates
BL was mixed with PVP at BL-PVP weight ratios of 1:10, 2:10, and 3:10 using a mortar and pestle for 2 minutes. TEC (10% w/w of PVP content) was subsequently added and mixed, again using a mortar and pestle, for a further 2 minutes. The wet mass was then passed through a sieve (710 μm), collected and extruded using a co-rotating twin-screw extruder (Minilab, Thermo Electron Corporation, Germany) at a temperature of 155 °C and a screw speed of 100 rpm. Melt extrudates were milled and passed through a 355 μm sieve and stored within glass vials in a dessicator over silica gel at 20 °C. A suitable quantity of the physical mixture from each drug loading was kept for analysis to compare to corresponding extrudates.

3.2.3 Preparation of an amorphous BL-PVP binary mixture
Amorphous BL was prepared by heating BL up to 200 °C for 2 minutes using stainless steel beaker followed by quench cooling in an ice bath. The generation of amorphous BL was confirmed using DSC. Amorphous BL was subsequently mixed with PVP K25 at a weight ratio of 3:10 (BL:PVP) for 2 minutes using a mortar and pestle.

3.2.4 Thermogravimetric analysis (TGA)
TGA analyses were performed according to the method described in chapter 2, section 2.2.4.
3.2.5 Differential Scanning Calorimetry (DSC)

DSC was used to test the efficiency of different liquid plasticizers and solid BL in reducing the Tg of PVP; to characterize the thermal properties of BL, PVP, the prepared extrudates, their corresponding physical mixtures and; to investigate the miscibility of BL with PVP at different drug loading levels. DSC analyses were performed according to the method described in chapter 2, section 2.2.5. For glass transition (Tg) determination, the samples were subjected to heat-cool-heat cycle from 25 to 220 °C, to remove the thermal history. The Tg was calculated as the midpoint of the step transition in the plot of heat flow versus temperature in the second cycle.

3.2.5.1 Gordon-Taylor calculations

According to the Gordon–Taylor equation (equation 3.1), drug polymer miscibility can be predicted by the presence of a single Tg located between the Tg of amorphous drug and polymer, depending on the relative proportion of each component. The Tg of all mixtures was calculated using the Gordon–Taylor equation as shown in below.

\[
T_{g_{mix}} = \frac{w_1 T_{g_1} + k w_2 T_{g_2}}{w_1 + k w_2}
\]

Equation 3.1

\[
K \approx \frac{T_{g_1 \rho_1}}{T_{g_2 \rho_2}}
\]

Equation 3.2

\(T_g\) and \(T_{g_2}\) are the glass transition temperatures of two components, \(w_1\) and \(w_2\) are the weight fractions of components, and \(K\) is calculated from the density (\(\rho\)) and \(T_g\) of the amorphous form of BL and PVP. The true density (\(\rho\)) of amorphous BL and PVP were 1.4173±0.0003 and 1.1768±0.0008 g/cm³, respectively, measured using an AccPyc 1330 helium pycnometer (Micromeritics®) (Norcross, USA). The Tg values obtained from the Gordon-Taylor equation were subsequently compared to the Tg values observed experimentally.
3.2.6 Powder X-ray Diffractometry (PXRD)
PXRD analyses were performed according to the method described in chapter 2, section 2.2.6.

3.2.7 Scanning Electron Microscopy (SEM)
SEM analyses were performed according to the method described in chapter 2, section 2.2.7.

3.2.8 Fourier Transform Infrared (FTIR) Spectroscopy
FTIR analyses were performed according to the method described in chapter 2, section 2.2.8.

3.2.9 Fourier Transform Raman (FT-Raman) Spectroscopy
Raman spectroscopic analyses were performed according to the method described in chapter 2, section 2.2.9.

3.2.10 In vitro drug release studies
The in vitro drug dissolution properties of BL powder, physical mixtures and milled extrudates were examined according to the USP paddle method (USP 30, 2007). Samples equivalent to 50 mg of BL were added to 1000 ml of de-ionized water containing 1% (w/v) sodium dodecyl sulfate (SDS) at a temperature of 37 ± 0.2 °C. The solution was stirred with a rotating paddle at 50 rpm. Samples of 5 ml were withdrawn from each vessel at predetermined time intervals (every minute for the first 10 minutes then at 20, 30, 45 and 60 minutes) filtered through cellulose acetate filter (0.45 μm, Nalgene Labware, Rochester, USA). At each time point the same volume of fresh medium was replaced. The concentration of BL in each sampled aliquot was determined using a Cary 50 (Varian Ltd, Oxford, UK) UV-VIS spectrophotometer at 275 nm and a standard calibration curve that was linear over the concentration range (2.0-12.0 μg/mL). The average percent of BL dissolved for each sample (n=3) was plotted versus time. No interference from the PVP, TEC or SDS on the BL assay was found at 275 nm. The BL content uniformity was determined by dissolving extrudates in de-ionized water containing 2% SDS to obtain a theoretical BL concentration of 50 mg/L. The drug concentration was then analyzed using a UV-VIS spectrophotometer.
at 275 nm using a standard calibration curve that was linear over the concentration range (2.0-12.0 μg/mL).

3.2.11 Stability study
Stability studies were conducted at 20 °C at 45% and 65% RH. Melt extrudates and a physical mixture of amorphous BL with PVP were placed in open glass vials which were stored in a controlled temperature environment (20 °C) inside a dessicator containing saturated salt solutions (sodium nitrite) to generate the appropriate relative humidity. The relative humidity inside the dessicator was recorded using a thermohygrometer. Melt extrudates stored at 20 °C, 65% RH were removed after 1, 3 and 6 months and tested for crystalline content using PXRD. Drug dissolution studies and SEM images were also conducted on melt extrudates stored at 20 °C, 65% RH for 6 months and compared to those tested immediately following manufacture. Samples stored at 20 °C, 45% RH were tested for BL crystallinity using PXRD after 1, 3, 6 and 12 months. Samples of physical mixtures containing amorphous BL stored at 20 °C at 45% and 65% RH were tested for crystalline content by PXRD after 1 week.

3.2.12 Statistical analysis
Two-tailed one sample t-test was used to compare the experimental Tg values of BL-PVP system determined by DSC versus the theoretical values predicted by Gordon-Taylor equation (α = 0.05). The effect of the formulation and storage of the melt extrudates at 20°C and 65% RH up to six months on drug dissolution were statistically analyzed using a repeated measures one-way ANOVA. Individual differences in drug dissolution between formulations were statistically identified using Fischer’s PSLD test. In all cases p<0.05 denoted significance.
3.3 RESULTS AND DISCUSSION
3.3.1 Thermal analysis

Thermal properties of BL were characterized in chapter 2. It was shown based on TGA ramp test that BL was thermally stable up to 250°C. Table 3.1 summarizes the most important thermal events in the DSC thermograms of BL, PVP and BL-PVP physical mixtures (PM). Drug/polymer miscibility at processing temperature is a prerequisite for producing solid molecular dispersions by hot methods (Leuner and Dressman, 2000). In this study, DSC was used to examine the miscibility between BL and PVP using small quantities of drug/polymer binary mixtures prior to HME (Forster et al., 2001a).

BL-PVP binary mixtures over a concentration range of 10 to 100% (w/w) of PVP content were prepared and investigated using DSC. DSC traces from the first heat ramp of PVP and BL-PVP physical mixtures exhibited a broad endotherm associated with free water (due to hygroscopic nature of PVP) close to 100 °C and a second, subtle endotherm corresponding to the fusion of crystalline BL (form I) in the BL-PVP binary mixture samples. As expected the enthalpy of this transition increased in proportion to increasing BL concentration within the physical mixture. The second heat ramp of all physical mixtures displayed a single $T_g$ that was positioned between the $T_g$ of PVP and amorphous BL.

The miscibility of two amorphous substances can be investigated by comparison of the theoretical (calculated using the Gordon Taylor equation) and experimentally observed glass transition values. Interaction between unlike components typically results in a lower free volume, less flexibility for molecular rearrangement and experimental $T_g$ values that exceed those predicted by the Gordon Taylor equation (Gupta and Bansal, 2005). The experimental and theoretical $T_g$ values are shown in Table 3.1 and Figure 3.2. A positive deviation from ideal behaviour was observed for all physical mixtures (experimental $T_g$ values exceeded the theoretical values) suggesting that intermolecular forces between BL and PVP were much stronger than the intermolecular forces between individual BL or PVP molecules. The interaction (Taylor and Zografi, 1997) and reduction in molecular mobility of the drug (increased $T_g$ of miscible system relative to $T_g$ of amorphous
BL) may account for the crystallization inhibition observed in the solid dispersions (Van den Mooter et al., 2001).

It was shown that heating form I above the $T_m$ followed by crash cooling results in the formation of the amorphous form of BL. Within the physically mixed samples, heating beyond $T_m$ followed by cooling at (10 °C/min) resulted in formation of binary systems that exhibited a single glass transition temperature, that exceeded the $T_g$ of the amorphous form of BL. Single phase systems in which the drug and polymer are highly miscible have been previously reported to exhibit a single $T_g$ (Lu and Zografi, 1998). The DSC results observed are clearly indicative of the formation of miscible, amorphous solid dispersions of PVP and BL upon exceeding the $T_m$ of BL. Moreover, a significant decrease in the glass transition temperature of PVP was observed upon increasing the BL concentration over a concentration range of 10 to 100% (w/w) of PVP content. Therefore, the miscibility of PVP and BL, facilitated through molecular interactions has resulted in solid-state plasticization of PVP.

From the data presented in Table 3.1, it is apparent that some of the physical mixtures had a $T_g$ below the cold crystallization temperature of amorphous BL. Therefore we should expect cold crystallization to occur if molecular mobility associated with glass/rubber transition was the limiting factor in stabilization once the $T_g$ of the solid dispersion had been exceeded (in some cases the $T_g$ of the physical mixtures was as low as 96.8 °C). None of the physical mixtures exhibited cold crystallization upon heating to 220 °C suggesting that molecular interactions between PVP and BL and the ability of PVP to inhibit molecular aggregation of BL are fundamental to crystallization inhibition.
### Table 3.1. Thermal properties of BL and physical mixtures (PMs) of BL and PVP.

<table>
<thead>
<tr>
<th></th>
<th>Tm (°C)</th>
<th>Tg exp (°C)</th>
<th>Tg theory (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>196.4 ± 0.6</td>
<td>56.4 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>PVPK25</td>
<td></td>
<td>154.6 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>BL:PVP PM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:10</td>
<td>158.0 ± 1.6</td>
<td></td>
<td>122</td>
</tr>
<tr>
<td>2:10</td>
<td>116.9 ± 1.4</td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>3:10</td>
<td>112.8 ± 2.0</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>4:10</td>
<td>109.1 ± 1.0</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>5:10</td>
<td>98.9 ± 0.2</td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>10:10</td>
<td>96.8 ± 0.6</td>
<td></td>
<td>64</td>
</tr>
</tbody>
</table>

Tm = melting endotherm temperature  
Tg exp = experimentally observed glass transition temperature.  
Tg theory = calculated using the Gordon-Taylor equation  
The experimentally observed values presented in the table are the average ± standard deviation of three replicates (n=3).

---

**Figure 3.2** Phase diagram of bicalutamide (BL) and PVP K25 binary mixtures.  
Tg by GT equation (○), Tg by experiment (■). Each datum point is the average of three replicates. The coefficient of variance (COV) was less than 2% in all cases.
These findings of the miscibility of BL with PVP, the ability of PVP to stabilize the amorphous BL by its antiplasticization effect and the strong intermolecular interactions formed were encouraging to proceed with HME of BL-PVP binary system in order to manufacture stable solid molecular dispersions.

A binary mixture of BL-PVP at a drug/polymer weight ratio of 1:1 was prepared and trials were conducted on this formulation for HME without using any plasticizer based on the solid state plasticization effect by BL. HME was only possible at a temperature of 180 °C and a screw speed of 100 rpm. Although the extrusion temperature (180 °C) was more than 80 °C above the Tg of this formulation (Table 3.1), the flow rate of the produced melt extrudates during their exit through the die opening was extremely slow. These unsuccessful trials indicated that solid state plasticization was not sufficient to allow efficient extrusion of solid dispersions, so a liquid plasticizer was incorporated within the formulations.

Three different liquid plasticizers, triacetin (TCN), dibutylsebecate (DBS) and triethylcitrate (TEC) were assessed in terms of their thermal stability (volatility) and their efficiency to plasticize PVP. TGA analysis was used to assess plasticizer volatility (Figure 3.3). The TGA standard heat ramp results at 10 °C/min showed that DBS had the lowest volatility among the three liquid plasticizers while TCN had the highest volatility. At this early stage of screening it was decided that TCN mass loss was too high to warrant further investigation. After initial plasticizer volatility screening, the efficiency of the plasticizer to reduce the Tg of PVP (155 °C) was assessed through examination of the thermal properties of several polymer/plasticizer physical mixtures (prepared using a mortar and pestle). The addition of 10% (w/w) TEC or 10% (w/w) DBS to PVP significantly reduced the Tg. TEC reduced the Tg of PVP by approximately 50 °C to 107.5 ± 0.5 °C. In comparison to DBS (10% w/w loading decreased the glass transition of PVP to 128.7 ± 3.2°C), TEC was more efficient at reducing the glass transition temperature of PVP and resulted in less variability around the glass transition temperature. To further examine the suitability of TEC, a 15% (w/w) loading was investigated and shown to reduce the Tg to 99.2 ± 0.7° °C. Given the small decrease in Tg upon increasing the TEC concentration to 15% w/w it was decided to use TEC at a concentration of 10% (w/w) for all hot melt extruded formulations.
Figure 3.3 Thermogravimetric analysis of triacetin (TCN); triethyl citrate (TEC); and dibutyl sebacate (DBS).

Three physical mix formulations of BL-PVP at weight ratios 1:10, 2:10 and 3:10 were prepared using TEC at a concentration of 10% (w/w) of PVP content. The DSC thermograms of these physical mixtures showed a small broad endotherm for BL in the first heat ramp with an increase in the enthalpy of this transition in proportion to increasing BL concentration within the physical mixture (Figure 3.5). The second heat ramp of all physical mixtures displayed a single $T_g$ that was positioned between the $T_g$ of PVP and amorphous BL (Figure 3.6) at 110, 96 and 97 °C for BL:PVP:TEC (1:10:1, 2:10:1 and 3:10:1) ratios, respectively. Generally a temperature of 15–60 °C above the $T_g$ of the amorphous polymer is required to facilitate HME (Crowley et al., 2007). HME trials on the prepared (BL:PVP:TEC) formulations were conducted at a temperature of 145 °C and at a screw speed of 100 rpm. The produced melt extrudates were opaque (non-transparent) in their appearance indicating that these processing conditions were not sufficient to produce a miscible BL-PVP system (glass solution). It was reported that the generation of transparent melt extrudates is a strong indicator of glass solutions (miscible system), whereas a cloudy or an opaque extrudate is indicative of a crystalline material (Forster et al., 2001b). Additionally, the flow rate of the melt extrudates through the die exit was too slow due to the relatively high melt
viscosity of the drug/polymer matrix within the extruder. Based on these unsuccessful trials, the extrusion temperature was raised up to 155 °C using the same screw speed (100 rpm), and all produced melt extrudates at these processing conditions were transparent giving an initial indication of the formation of a miscible system.

Thermal stability for BL using TGA ramp and isothermal tests was characterized in chapter 2, and it can be deduced from these results that BL is thermally stable at a temperature of 155 °C based on the negligible mass loss at this temperature during both the heat ramp and isothermal (160 °C for 60 minutes) tests. Additionally, TGA tests conducted using a standard heat ramp and an isothermal test (160 °C for 60 minutes) confirmed the thermal stability of PVP. PVP did lose a small percentage of total mass (~6%), which was attributed to water loss (Figure 3.4). Water content within PVP was confirmed using Karl Fischer titration (x=5.3±0.13%, n=3). TEC showed a mass loss of 4% at a temperature of 155 °C (ramp test at 10 °C/min) indicating its acceptable volatility at the extrusion temperature used.

![Figure 3.4 Thermogravimetric analysis of bicalutamide (BL) and polyvinyl pyrrolidone (PVP K25)](image-url)
Based on the negligible mass loss during the ramp and isothermal TGA tests for BL and PVP and the acceptable volatility of TEC during the TGA ramp test at the extrusion temperature used (155°C), it can be assumed that the formulation components were thermally stable during the HME process and if any degradation occurred, it was negligible especially given the short residence time of these materials inside the extruder (~ 1 minute).

Immediately following HME, melt extrudates were scanned using DSC. Interestingly the DSC thermograms of all melt extrudates showed a complete absence of the melting endotherm of BL in the first heat ramp, although a small broad melting endotherm for crystalline BL (form I) was present in all physically mixed samples (Figure 3.5). A single glass transition was recorded in the second heat ramp of all melt extrudates tested at 105, 96 and 96 °C for BL:PVP:TEC (1:10:1, 2:10,1 and 3:10:1) formulations, respectively. These DSC results are indicative of formation of a miscible amorphous solid dispersion (glass solution) even though the extrusion temperature was below \( T_m \) for BL (Figure 3.6). The formation of miscible amorphous solid dispersions at temperatures below the \( T_m \) of BL may be explained by the intense mixing (high shear forces), high pressures and the non-ambient conditions inside the extruder barrel which all facilitate intimate mixing at a molecular level. Furthermore, neither the melt extrudates nor the cooled physical mixtures showed evidence of re-crystallization of amorphous BL to form II (shown to occur at 125.8 ± 0.5°C in Figure 2.5) indicating the ability of PVP to act as re-crystallization inhibitor for amorphous BL.

PVP has been shown to inhibit re-crystallization of many different drugs entrapped within solid dispersions in the amorphous state (Matsumoto and Zografi, 1999; Van den Mooter et al., 2001). Often this effect is attributed to molecular miscibility and thus the presence of a single glass transition at a temperature higher than the \( T_g \) of the amorphous drug. The \( T_g \) of BL was observed at 56.4 ± 0.4 °C whereas all melt extrudates and physical mixtures had a single \( T_g \) that was considerably higher than this value. In addition, intermolecular interactions, particularly hydrogen-bonding between amorphous drugs and polymeric carriers have been shown to further reduce molecular mobility and hence significantly retard recrystallization during storage (Taylor and Zografi, 1997).
Figure 3.5. DSC thermograms of PVP K25, physical mixtures (PM) and hot melt extrudates (HME) for the first heating run of a heat-cool-heat cycle.

Figure 3.6. DSC thermograms of PVP K25, physical mixtures (PM) and hot melt extrudates (HME) for the second heat ramp of a heat-cool-heat cycle.
3.3.2 Crystalline properties of hot-melt extrudates

The PXRD patterns for crystalline BL (form I), a typical drug-PVP physical mixture (drug to polymer ratio of 1:10) and all hot melt extrudates (drug to polymer ratios of 1:10, 2:10 and 3:10) immediately following manufacture are shown in Figure 3.7. PXRD data collected shows crystalline BL (form I) had characteristic peaks at 2θ angles of 12.1, 18.8, 23.5, 24.6, 29.2, 29.5, 31.1 and 36.7 °, that are characteristic of form I. The X-ray pattern of the 1:10 physical mixture, which was typical of all physical mixtures, clearly showed characteristic peaks of crystalline BL (form I) albeit with lower intensities. Conversely, all melt extruded samples were devoid of characteristic BL peaks and were similar in shape to the XRD pattern observed for amorphous PVP.

The PXRD results, coupled with the information gathered from DSC (single Tg) suggests the formation of molecular dispersions in all extruded samples. Although the formation of high-energy solid solutions is favourable in terms of improving solubility in the gastrointestinal (GI) fluids and hence oral bioavailability, the physical instability of the amorphous state and the tendency for re-crystallization during storage is a major issue (Wang et al., 2005).

![Figure 3.7. Powder X-ray diffraction patterns for crystalline BL, a representative physical mixture of BL and PVP and hot-melt extruded samples immediately following manufacture.](image-url)
It was shown using DSC that the glass solutions formed during the HME process are stable to cold crystallization at temperatures above the Tg during thermal studies, the stability of melt extrudates under different storage conditions (20 °C, 45% RH and 20 °C, 65% RH) were also considered. Figure 3.8 shows the PXRD data recorded for the melt extrudates stored for twelve months at 20 °C, 45% RH and a physical mixture of PVP with amorphous BL stored under the same conditions for 1 week. There were no characteristic bands of crystalline BL in the PXRD patterns of extruded samples however the physical mixture of PVP with amorphous BL stored under the same conditions for one week had bands that were characteristic of crystalline BL. The broadness of the amorphous halo upon which low intensity bands are superimposed make it very difficult to define whether form I or form II is present in the recrystallized amorphous physical blend.

Figure 3.8. Powder X-ray diffraction patterns for hot-melt extruded samples stored for one, three and six months at 20 °C, 45% RH.
Melt extrudates and an amorphous physical mixture were also stored under higher humidity conditions (65% RH, 20 °C) for one, three and six month periods. Figure 3.9 shows the PXRD patterns obtained for these samples. A physical mixture of amorphous BL with PVP showed re-crystallization after one-week storage. Again, the lack of peak intensity makes it difficult to define which polymorph has formed under these conditions. The re-crystallization of amorphous BL may be attributed to the low glass transition temperature of the amorphous form of BL (~56°C), which would be further reduced upon ingress of moisture at elevated relative humidity. The increased mobility as a result of moisture ingress in the high humidity environment (65% RH) and the inability of PVP to suppress molecular mobility due to lack of intimate mixing on a molecular level are significant factors that attribute to the reduced stability of the physically mixed form. Furthermore the lack of significant secondary interactions between PVP-BL within the physically mixed samples may also account for the observed rapid re-crystallization. Significant enhancement in the physical stability of amorphous BL was observed in the extruded samples providing a clear indication of restriction of molecular movement within this environment possibly facilitated through molecular interaction between PVP and BL (Taylor and Zografi, 1997). All of the extrudates retained the amorphous form of BL for one month under these storage conditions however after 3 months there was evidence of re-crystallization within all HME samples. A small peak at 12.1° and 23.5° was evident in the 1:10 and 2:10 samples however only the peak at 12.1° was evident in the 3:10 sample. The intensity of the peaks increased in the following order, 1:10>2:10>3:10. Moreover, after six months storage the intensity of these peaks increased significantly suggesting a higher level of crystalline material within the samples. The improved physical stability of hot melt extrudates compared to the amorphous BL-PVP physical mixture (1 week) identifies the importance of the HME in stabilizing amorphous BL as a result of formation of solid molecular dispersions exhibiting a single $T_g$, that is higher than the $T_g$ of amorphous BL. Moreover, the formation of intermolecular interactions within the prepared melt extrudates which are stronger than the intermolecular interactions between the individual BL amorphous molecules, concluded by comparison of experimental and theoretical $T_g$ calculations (Gordon-Taylor equation), may also aid in stabilizing the molecular dispersion. The number and the intensity of peaks corresponding to crystalline BL after 3 and 6 months storage at 20°C, 65% RH were highly dependent upon the loading levels of
BL within the melt extrudates. Two small peaks characteristic of crystalline BL were evident at 12.1 and 23.5° at BL:PVP loadings of 1:10 and 2:10 after three months storage at 65% RH, 20 °C, whereas only the peak at 12.1° was evident within the 3:10 sample. Interestingly after six months storage, all extrudates showed clear evidence of re-crystallization.

In this study it has been shown that extrudates containing higher drug loadings are more stable during storage. Given that the $T_g$ value of the extrudate decreased as the drug loading increased, i.e., 3:10 had the lowest $T_g$, the improved storage stability may be attributed to the decreased affinity to absorb moisture due to a lower ratio of PVP within the extruded matrix. In previously published work by Konno and Taylor (2008) it has been shown that the nucleation rate of felodipine in amorphous solid dispersions did not vary with the type of polymer in the absence of moisture. However in the presence of moisture, nucleation rates were dependent upon the type and level of polymer in the solid dispersion. Therefore in solid dispersions containing higher polymer levels, the greater level of moisture within the matrix will result in greater plasticization of the HME solid dispersion and significantly disrupt BL/PVP intermolecular interactions facilitating re-crystallization.
Figure 3.9. Powder X-ray diffraction patterns for hot-melt extruded samples stored for twelve months at 20 °C, 65% RH.
SEM was used to examine the surface of the extrudates after storage for six months (65% RH, 20°C) to determine if BL crystals could be observed. Melt extrudates that were examined immediately following manufacture were smooth and devoid of any crystalline BL 'needles' whereas extrudates stored for 6 months at 20°C and 65% RH showed distinct BL crystals (Figure 3.10). The results obtained using SEM correlated well with PXRD data that also suggested a small level of recrystallization under these conditions for the extrudates.

Figure 3.10. Scanning electron microscope images of (a) crystalline bicalutamide; (b) BL-PVP HME (3:10) immediately following manufacture; (c) BL-PVP HME (2:10) after 6 months storage at (20°C, 65% RH) at 1,000X magnification; (d) BL-PVP HME (2:10) after 6 months storage at (20°C, 65% RH) at 5,000X magnification.
3.3.3 Drug/polymer interactions

The nature of interactions at the molecular level in amorphous and crystalline forms of BL was discussed in detail in chapter 2 (section 2.3.6). In this study, FTIR and Raman spectroscopic studies were conducted in order to characterize the interaction between BL and PVP within the melt extrudates that may be pertinent to stabilization of the high-energy amorphous form (Taylor and Zografi, 1997).

As mentioned in chapter 2, BL has two proton donors, the amide (N-H) and hydroxyl (O-H) groups, whereas the oxygen atom of the carbonyl (C=O), the hydroxyl (O-H) and the sulfonyl (O=S=O) groups and the nitrogen atom of the amide (N-H) and nitrile (C≡N) groups can act as proton acceptors (Jeffrey, 1997). In relation to the polymeric matrix into which BL was dispersed, PVP possesses two proton-accepting groups, the oxygen atom of the carbonyl group (C=O) and the nitrogen atom of the pyrrole ring. Due to the three dimensional structure of PVP, the C=O group is regarded as the more favorable site for potential interaction (Thypo et al., 2007).

Figure 3.11 and 3.12 show a representative FTIR spectrum for a melt extrudate (3:10) and allows for a comparison between extruded samples and physical mixtures of form I BL and amorphous BL with PVP. The stretching band of the amide (N-H) group of BL (3339 cm\(^{-1}\)) that was evident in the FTIR spectra of form I was present in the physical mixture of form I with PVP. As expected the N-H stretch was not present in the spectrum recorded for the physical mixture of amorphous BL with PVP or within the spectrum recorded for the melt extrudates (Figure 3.11). The most distinct peak of PVP was the stretching vibration of the carbonyl group (C=O) at 1655 cm\(^{-1}\) (Figure 3.12). This band, which was especially sharp because of the dipolar nature of the N-C-O group (Smrecki et al., 1997), makes it very difficult to resolve the band for the carbonyl of BL. The Raman spectra of the extrudates were similar in nature to the amorphous form of BL whereas the physically mixed samples were more characteristic of form I BL. This suggested BL existed in a highly disordered state within the extrudates.
Figure 3.11. FTIR spectra of extrudates (HME) and physical mixtures (PM) showing the amide stretch of BL.

Figure 3.12. FTIR spectra of extrudates (HME) and physical mixtures (PM) showing the carbonyl stretch of PVP.
In comparison to the amorphous form, all melt extrudates displayed a red shift in their Raman spectra for the C-N triple bond stretch (2232 to 2228 cm$^{-1}$), C-C ring stretching mode (1616 to 1612 cm$^{-1}$) and the N-H in-plane bending (1526 to 1522 cm$^{-1}$) (Figures 3.13 and 3.14). These subtle downward peaks shifts observed for extruded samples may be attributed to the presence of drug/polymer interactions within the melt extrudates (Tang et al., 2002). These interactions may reduce molecular mobility within the melt extrudates. This may explain the enhanced stability of the solid dispersion in comparison to amorphous BL. The formation of strong intermolecular interactions within the extrudates not only resulted in peak shifts in both Raman and FTIR but also resulted in positive deviation of the experimentally observed $T_g$ in comparison to the value predicated by the Gordon-Taylor equation. These secondary interactions undoubtedly improve the physical stability of amorphous BL within the melt extrudates. Hydrogen bonding interactions between PVP and tolbutamide via the amide group of the drug and the carbonyl pyrrole group of PVP has been reported previously after HME (Forster et al., 2000b). In the same study, it was reported that PVP as well formed new hydrogen bonding interactions via its carbonyl group with the secondary amine group of lacidipine and nifedipine and with the carboxylic acid group of indomethacin after HME. The physical stability at high relative humidity for indomethacin/PVP melt extrudates was greater than other drug/PVP melt extrudates. It was suggested that strength of the hydrogen bonding might have a significant effect in such results especially that only physical mixtures of amorphous indomethacin/PVP prepared by mortar and pestle showed hydrogen bonding interactions.
Chapter 3

Figure 3.13. Raman spectra of extrudates showing the nitrile vibrational mode of BL.

Figure 3.14 Raman spectra of extrudates showing the characteristic vibrational modes of BL (carbonyl and N-H in-plane bend).
3.3.4 In vitro drug release studies

The dissolution properties of BL-PVP extrudates, a representative physical mixture (1:10) and pure BL are shown in Figure 3.15. Dissolution of BL from the physical mixture was significantly higher than dissolution of pure BL ($p = 0.0001$), 2.31-fold increase in drug release after 60 min, Table 3.2 (Forster et al., 2001b). Moreover, all melt extrudates showed a significant increase in the percent release of BL in comparison to pure BL and the physical mixture (1:10) ($p<0.0001$ in all cases). The increase in maximum percent of BL dissolved was dependent on the drug : polymer ratio. Increasing the ratio of PVP resulted in a higher release rate of BL and also a greater percentage of dissolved BL (Table 3.2). The release rate was greatest for the 1:10 (BL:PVP) ratio. After 60 minutes the percentage of BL released from the 1:10 extrudate was 8.93-fold greater than that observed for pure BL, while for drug:polymer ratios of 2:10 and 3:10 increases of 8.05 and 7.53-fold were observed. It was reported previously that indomethacin dissolution properties from solid dispersions prepared by HME were highly dependent on the type and concentration of the polymer (Chokshi et al., 2008).

The improvement in BL release was significantly higher from all melt extrudates comparing to pure drug or physically mixed samples, indicating the importance of HME in achieving dosage forms with improved solubility and thus for BCS class II compounds, improved bioavailability. Dissolution rate and extent of lacidipine, nifedipine, tolbutamide and indomethacin have been increased significantly after HME with PVP compared with the physical mixtures and crystalline drug (Forster et al., 2001b).
Table 3.2. Percent release of BL from extruded samples tested immediately following manufacture and after storage for six months at 20°, 65% RH. The dissolution properties of an exemplar physical mixture (1:10) are also shown for comparison purposes. The values presented in the table are the average ± standard deviation of three replicates.

<table>
<thead>
<tr>
<th>Ratio of BL:PVP</th>
<th>Form</th>
<th>Q10</th>
<th>Q60</th>
<th>Dissolution rate increase*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mins</td>
<td>60 mins</td>
<td></td>
</tr>
<tr>
<td>1:10</td>
<td>Physical mix</td>
<td>15.45 ± 0.92</td>
<td>26.29 ± 1.69</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>Extrudate</td>
<td>95.93 ± 1.4</td>
<td>100.14 ± 1.1</td>
<td>11.66</td>
</tr>
<tr>
<td></td>
<td>Stability</td>
<td>93.61 ± 1.33</td>
<td>99.02 ± 0.74</td>
<td>10.37</td>
</tr>
<tr>
<td>2:10</td>
<td>Extrudate</td>
<td>81.24 ± 1.28</td>
<td>90.28 ± 1.36</td>
<td>9.87</td>
</tr>
<tr>
<td></td>
<td>Stability</td>
<td>79.50 ± 1.21</td>
<td>89.07 ± 2.09</td>
<td>9.66</td>
</tr>
<tr>
<td>3:10</td>
<td>Extrudate</td>
<td>69.79 ± 1.46</td>
<td>84.36 ± 2.44</td>
<td>8.48</td>
</tr>
<tr>
<td></td>
<td>Stability</td>
<td>69.51 ± 2.01</td>
<td>83.3 ± 2.34</td>
<td>8.45</td>
</tr>
</tbody>
</table>

* Increase compared to pure BL (n=3). Q10 and Q60 are percentage drug release after 10 min and 60 min, respectively. Q10 and Q60 for BL = 8.23 and 11.21 % respectively.
Figure 3.15 Dissolution profiles of BL crystalline (Δ), BL-PVP PM (1:10) (■), BL-PVP HME (1:10) (◊), (2:10) (▲), (3:10) (□) immediately after manufacture. The data shown is the average of three replicates and in all cases the COV was < 9%.

The solid dispersion method, by which a drug is molecularly dispersed, in a solid carrier, is one of the most commonly employed pharmaceutical approaches to increase solubility and bioavailability of poorly soluble drugs (Leuner and Dressman, 2000). In this study, formation of glass solutions by HME markedly improved the dissolution rate and extent of BL. This significant improvement in drug dissolution after HME was mostly attributed to the presence of BL in the amorphous form within the melt extrudates, decreased drug particle size to molecular dispersion and the intimacy of mixing with a hydrophilic polymer (Breitenbach, 2002). This intimate mixing of BL with PVP during dissolution improves wetting properties and hence greater drug dissolution concentrations may be achieved (Craig, 2002). Since BL has a dissolution rate limited absorption (Cockshott, 2004), the significant enhancement in aqueous solubility of BL by HME with PVP may result in improved oral bioavailability. In vivo studies in dog model showed that a melt extrudate of a model BCS class II drug using PVP-K30 provided a 7-fold greater bioavailability than a control formulation consisting of crystalline drug triturated with poloxamer 188 (Lakshman et al., 2008). In addition, PVP K30 solid dispersions were shown to have greater bioavailability than solid dispersions prepared using different methods (co-evaporation, spray drying and spray granulation). It was hypothesized that spray-dried
and spray-granulated formulations were not intimately or molecularly dispersed as well as melt extrudates that were subject to high shear mixing during processing.

To ensure the differences in drug dissolution were not attributed to heterogeneous dispersion of drug within the extrudates, BL uniformity within the extruded formulations was determined. All formulations contained 100 ± 5% of the BL label claim. The range observed for the extrudates was from 96.7 to 101.9 % with an average ± s.d of 99.1 ± 1.5% for (1:10), 99.1 ± 2.6% for (2:10) and 99.0 ± 1.9 for (3:10).

The dissolution properties of the extrudates tested immediately following manufacture and those tested after six months storage (20 °C, 65% RH) are shown in Figure 3.16. Interestingly there were no significant differences between the two sets of data (immediately tested and stored for six months with \( p = 0.2121, 0.4171, 0.6180 \) for 1:10, 2:10 and 3:10 melt extrudates, respectively) despite the presence of a small number of BL crystals on the surface of extrudates (confirmed using SEM). The BL crystals were very fine and in distinct/localized regions of the extrudate. Consequently the presence of these small, localized crystals do not significantly affect the drug release properties. Previously, it has been reported that the presence of a small amount of crystalline drug (due to storage) embedded in a melt extrudate did not have a significant effect on drug dissolution. This was attributed to drug dissolution being dominated by the amorphous drug fraction with limited contribution from the small crystals present (Li et al., 2006). In a separate study, the drug release rate and extent for solid dispersions using HPMC-E5 prepared by HME did not differ after 6 months storage (30°C/60%RH) conditions, although some drug re-crystallization has been observed by PXRD (Ghebremeskel et al., 2006). Furthermore, there was no noticeable effect of the presence of small amounts of crystalline drug on indomethacin dissolution from PVP melt extrudates which achieved a complete drug release in 60 minutes (Forster et al., 2001b).
Figure 3.16. Dissolution profiles of BL-PVP HME immediately after manufacture (1:10) (○), (2:10) (△), (3:10) (▲); and after 6 months storage at (20°C, 65% RH) (1:10) (■), (2:10) (●), (3:10) (□). The data shown is the average of three replicates and in all cases the COV was < 9%.
3.4 CONCLUSIONS
Solid molecular dispersions of BL with PVP were prepared by HME technology. The solid-state properties of BL, physical mixtures and hot melt extrudates were characterized using DSC, PXRD, FTIR and Raman spectroscopy. The glass transition values of physical mixtures determined by DSC were higher than those calculated using the Gordon Taylor equation suggesting the presence of intermolecular forces between BL and PVP that are stronger than the intermolecular interactions among the individual components. All hot melt extrudates had a single $T_g$ between the $T_g$ of amorphous BL and PVP indicating miscibility of BL with PVP and the formation of solid molecular dispersions. Further investigations using DSC confirmed solid-state plasticization of PVP by amorphous BL and hence antiplasticization of amorphous BL by PVP. PXRD and SEM confirmed the presence of amorphous BL within the hot melt extrudates immediately following manufacture. Further investigation using FT-IR and Raman spectroscopy confirmed the presence of the amorphous form of BL within the hot melt extrudates. In addition, FTIR and Raman spectroscopy strongly suggested the presence of strong intermolecular interactions mostly hydrogen bonding between BL and PVP within the hot-melt extrudates.

BL-PVP melt extrudates showed a significant enhancement in BL release compared to pure BL and BL-PVP physical mixtures. The percent BL release from melt extrudates was dependent on the BL to polymer ratio. This enhancement of BL release from the melt extrudates may be attributed to the generation of the amorphous form of BL during HME and improvement in the wettability of BL through molecular dispersion within hydrophilic PVP. The enhancement in BL dissolution may improve BL oral bioavailability since this is limited by the poor gastrointestinal solubility of the drug. This potential improvement in the BL bioavailability may improve the clinical outcomes of BL by achieving more consistent drug absorption and improving the drug safety profile.

Storage of the extrudates confirmed the stability of the amorphous form for twelve months at 20°C, 45% RH, whereas storage at 20 °C, 65% RH resulted in re-crystallization after 3 months. Interestingly the small level of BL re-crystallization after 6 months storage under these conditions had no effect on the dissolution properties of the extrudates.
THE DEVELOPMENT OF
FAST-ACTING SOLID DISPERSION
FOR THE IMPROVED DELIVERY OF
CELECOXIB
4.1 INTRODUCTION
HME solid dispersions prepared using hydrophilic polymers are one of the most attractive methods used to increase the solubility of poorly soluble drugs, BCS class II, that have low bioavailability because of their aqueous solubility. Tablet formulations for oral drug administration are considered to be the most preferred dosage form for drug administration in terms of the cost effectiveness and patient compliance. Melt extrudates produced by HME may be cut into tablets of desired size and shape containing the required drug loading. Several research groups have demonstrated that HME is a viable technology in producing tablets for pharmaceutical use (Fukuka et al., 2006a, 2006b; Bruce et al., 2005; Andrews et al., 2007).

In the pharmaceutical industry, HME offers many advantages over traditional tablet manufacturing methods like direct compression and wet granulation (chapter 1, section 1.3.3). Hot melt extruded tablets can be manufactured without specific powder requirements like particle size, compressibility and compactibility (Breitenbach, 2002; Crowley et al., 2007). Thus, HME can provide a robust solution for the materials that have poor powder characteristics to be formulated as tablet dosage forms. Conversely, hot-melt extruded tablets have a dense structure with low porosity that may cause retardation in the drug release from the polymeric matrix as a result of the slow penetration rate of aqueous solution into the matrix. This delay in drug release might consequently result in lowering drug bioavailability and hence its therapeutic response. Thermal treatment of amorphous polymers has also been shown to decrease polymer free volume (Follonier et al., 1995). It has been suggested that tablets prepared by HME have slower drug release rates than those prepared by traditional methods due to lower porosity and higher tortuosity (Crowley et al., 2004b). This problem may be solved by milling the melt extrudates to increase the surface area available for dissolution and hence increase the drug release rate. However, the increased surface area achieved by milling may result in increased aggregation and hence decreased drug dissolution rate (Miller et al., 2006). Additionally, milling of hot-melt extruded amorphous solid dispersions may increase moisture adsorption by hydrophilic polymers as a result of the increase in the surface area, which may affect the physical stability of the amorphous drug forms at high humidity conditions (Miller et al., 2006). Moreover, melt extrudates are typically very difficult to mill to obtain a suitable particle size distribution (Verreck et al., 2006b).
It was shown that pressurized carbon dioxide (CO$_2$), acted as a temporary plasticizer during HME, increased the milling efficiency of the melt extrudates (Verreck et al., 2005, 2006b, 2007). The resultant melt extrudates have a foam like structure as a result of the expansion of CO$_2$ at the extrusion die resulting in an increased specific surface area and porosity. A reduction in dissolution rate during the first 5 min was reported for itraconazole/PVP/VA solid dispersions milled samples treated with CO$_2$ during HME. This initial reduction in the drug release rate for the CO$_2$ treated samples was attributed to particle agglomeration (Verreck et al., 2005).

A supercritical fluid (SCF) is defined as a substance for which both pressure ($P$) and temperature ($T$) are above its critical $P$ and $T$ values (Pasquali et al., 2008). The macroscopic appearance of a SCF is homogeneous and opalescent without phase separation (single phase) since, at this point, a SCF has a density close to or higher than its critical density. At these conditions, the vapour and liquid phases become indistinguishable and the substance behaves as a single distinct phase, separate from the liquid and gas phases (Figure 4.1). The physico-chemical properties at supercritical conditions are intermediate between liquid and gas. Like a liquid, the SCF shows a density value appreciable for solvation, while the viscosity and diffusivity facilitate mass transfer. These properties can be easily tuned by merely changing temperatures and pressures. All gases can form SCF at specific critical conditions ($P$, $T$).

![Carbon dioxide pressure-temperature phase diagram](image)

Figure 4.1. Carbon dioxide pressure-temperature phase diagram (Nalawade et al., 2006).
Carbon dioxide (CO\textsubscript{2}) usually behaves as a gas in air under standard conditions (\(T\) and \(P\)) or as a solid called dry ice when frozen. If the temperature and pressure are both increased above a critical point, it can adopt properties midway between a gas and a liquid. It can diffuse through solids like a gas and dissolves materials like a liquid. For pharmaceutical applications, CO\textsubscript{2} is an ideal SCF because it has a relatively mild critical temperature. Supercritical conditions are easily attained (\(T = 304.15\) K, \(P = 7.38\) MPa) and it can be removed from the system by simple depressurization (Nalawade \textit{et al.}, 2006). It is non-toxic, chemically inert, non-flammable, relatively inexpensive and recyclable (Supramaniam \textit{et al.}, 1997). These attractive properties make CO\textsubscript{2} a promising alternative to noxious organic solvents for pharmaceutical use. Supercritical fluid technology using CO\textsubscript{2} has already proved its applicability in the preparation of pharmaceutical formulations e.g. particle micronization for producing drug powders of micron and submicron dimensions with controlled particle size and purity (Subramaniam \textit{et al.}, 1997) via antisolvent precipitation, aerosolisation and rapid expansion of supercritical fluid solutions (Chiou \textit{et al.}, 2007; Kerc \textit{et al.}, 1999; Benedetti \textit{et al.}, 1997; Alessi \textit{et al.}, 1996; Young \textit{et al.}, 2000; Yeo \textit{et al.}, 1993). Additionally, supercritical carbon dioxide (scCO\textsubscript{2}) has been used for preparation of liposomes encapsulating water-soluble compounds (Frederiksen \textit{et al.}, 1997).

It is well known that CO\textsubscript{2} can act as a plasticizer by reducing the glass transition temperature for a number of amorphous and semi-crystalline polymers either by being absorbed between the polymer chains causing an increase of free volume and a decrease of chain entanglement or by acting as a molecular lubricant that reduces melt viscosity (Chiou \textit{et al.}, 1985). For this reason, the combination of pressurized gases with HME has received increasing attention in the polymer industry in the last decade (Tomasko \textit{et al.}, 2003). It was shown that pressurized CO\textsubscript{2} acted as a temporary plasticizer for pharmaceutical polymers, PVP/VA 64, ethylcellulose (EC 20cps), Eudragit E100 and PEO, allowing for a reduction in processing temperature and melt viscosity during HME (Verreck \textit{et al.}, 2005, 2006a, 2006b, 2007; Lyons \textit{et al.}, 2007). The crystalline content of EC 20cps was altered as a function of pressure and temperature while no change in the thermal properties of PVP/VA 64 and Eudragit E100 extrudates occurred after CO\textsubscript{2} treatment (Verreck \textit{et al.}, 2006b). Combination of pressurized CO\textsubscript{2} with HME has been shown to be effective for
processing thermally labile drugs. As an example, Verreck et al. (2006a) extruded \( p \)-aminosalicylic acid with EC 20cps. The reduced viscosity achieved by using scCO\(_2\) allowed higher extrusion speeds to be achieved and hence resulted in improving the throughput and productivity of HME (Lyons et al., 2007).

Celecoxib (CX), a non-steroidal anti-inflammatory drug (NSAID), is chemically designated as \( 4\)-\( \left[ 5\)-(4-methylphenyl)-3-trifluoromethyl\)-1\( H \)-pyrazol-1-yl\]-benzene-sulfonamide (Figure 4.2). CX is the first specific inhibitor of cyclooxygenase-2 (COX-2) approved to treat patients with rheumatism and osteoarthritis with no inhibition of cyclooxygenase-1 at therapeutic doses. CX also has analgesic and anticancer properties. The selective inhibition of COX-2 is thought to lead to a reduction in the unwanted effects of NSAIDs with significantly lower upper gastrointestinal complication rates than for traditional nonselective NSAIDs (Davies et al., 2000).

![Figure 4.2. Chemical structure of celecoxib (CX)](image)

CX is a weakly acidic (pKa is 11.1) and hydrophobic drug (\( \log P = 3.5 \)) and has low aqueous solubility contributing to the high variability in absorption after oral administration (Paulson et al., 2001). According to the biopharmaceutical classification system (BCS) (Amidon et al., 1995), CX is classified as a class II drug as it has a low solubility and a high permeability (Paulson et al., 2001; Yazdanian et al., 2004). The peak plasma concentration occurs 2 to 4 hours after oral administration (Davies et al., 2000). Rapid onset of action is necessary to provide fast pain relief in the treatment of acute pain. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of CX to obtain faster onset of action, minimize the
variability in absorption, and improve the overall oral bioavailability. This may be achieved by formulating the drug as a fast release hot-melt extruded tablets containing solid molecular dispersions of CX with a hydrophilic polymer.

The formulation of CX into solid dosage forms using traditional tableting processes is extremely difficult due to the inherent CX powder physical properties (Leonard and Patricia, 2001).

- CX exists in three polymorphic forms.
- CX is isolated as agglomerates of long needle shaped crystals, which exhibit cohesiveness, low bulk density and compressibility, and poor flow properties.
- The particle size of CX influences the content uniformity, dissolution and bioavailability of the product.

The poor tabletability of CX and the poor dissolution performance and hence low bioavailability necessitate investigation of more feasible manufacturing processes. HME provides one of the most attractive methods to resolve these problems as no specific powder requirements are needed to manufacture fast release hot-melt extruded tablets.

PVP, a well known hydrophilic polymer, was used in this study as a polymeric matrix. It was shown in chapter 3 that PVP enhances the dissolution properties of bicalutamide (BL) and acted efficiently as a solid-state stabilizer for the amorphous form of BL (Andrews et al., 2009b). In the scientific literature, PVP has been used as a carrier to produce solid molecular dispersions of CX using different traditional methods e.g. solvent evaporation and melt methods (not HME) to enhance the aqueous solubility and stability of amorphous CX (Kakumanu and Bansal, 2002; Gupta et al., 2004).
4.1.1 Aims and objectives

In this study we aim to assess the suitability of HME to produce fast-acting solid dispersions with enhanced solubility for the improved delivery of CX.

The principle aims of this chapter are as follows:

- Study the feasibility of manufacturing fast-release hot-melt extruded solid dispersions of CX/PVP binary system.
- Physico-chemical characterization of the manufactured hot-melt extruded solid dispersions in terms of drug/polymer miscibility, solid state properties, drug/polymer interactions, surface morphology and drug release properties using different characterization techniques.
- Determine the effect of processing factors (milling, scCO₂) on the physico-chemical properties of the manufactured hot-melt extruded tablets in terms of thermal properties, crystallinity, drug/polymer interactions, surface morphology and drug release properties.
- Investigate the stability of the prepared solid dispersions in terms of crystallinity and drug release properties.
4.2 MATERIALS AND METHODS
4.2.1 Materials

Celecoxib (CX) was a kind gift from Hikma Pharmaceuticals Co. (Amman, Jordan), Polyvinylpyrrolidone K25 (molecular weight 24,000 Daltons) (PVP K25) and Triton® X-100 were purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). All other chemicals used were purchased from BDH Laboratory supplies (Poole, Dorset, England) and were of Analar grade or equivalent quality.

4.2.2 Preparation of CX-PVP melt extrudates

CX was mixed with PVP at CX-PVP weight ratios of 3:7, 1:1, and 7:3 using a mortar and pestle for 2 minutes. The physical mixtures were extruded using a co-rotating twin-screw extruder (Minilab Thermo Electron Corporation, Germany) at a screw speed of 100 rpm and a temperature of 150 °C for 1:1 and 7:3 ratios, whereas a temperature of 170 °C was used for the 3:7 ratio. The cylindrical melt extrudates, which were transparent in appearance, were milled and passed through a 355 μm sieve. Melt extrudates at a drug/polymer weight ratio of 3:7 were also cut into tablets having a weight equivalent to 50 mg CX (167±2 mg). Melt extrudates at a ratio of 7:3 were friable and the weight of 1:1 ratio equivalent to 50 mg CX was relatively small (100 mg), so 3:7 ratio were found to be the most convenient ratio to be cut into tablets for scCO₂ experiments. All samples were kept in glass vials in a dessicator over silica gel at 20 °C. A suitable quantity of the physical mixture from each drug loading was kept for analysis to compare to corresponding extruded formulations.

4.2.3 Exposure of melt extrudates to scCO₂

CX-PVP hot-melt extruded tablets at a drug/polymer weight ratio of 3:7 were transferred into a high pressure vessel (Figure 4.3) consisting of a CO₂ cylinder, a Thar Technologies P50 high pressure pump and a 250 mL high pressure vessel from Thar Technologies fitted with a safety rupture disk, a pressure transducer and thermocouple valves and tubing. Melt extruded tablets were exposed to CO₂ at a pressure of 100 bar and a temperature of 40 °C (above its critical T and P) to generate scCO₂. After 24 hours, the chamber was depressurized and the CO₂ evacuated over a period of 1 min. Samples were either kept as tablets (167±2 mg) or milled and sieved.
through a 355 μm sieve. All samples were kept in glass vials in a dessicator over silica gel at 20 °C.

Figure 4.3. (a) The pressure chamber set up featuring the pump with the cooling system, the pressure vessel and the controller box. (b) The off-line pressure chamber set up.
4.2.4 Preparation of an amorphous CX-PVP physical mixture
Amorphous CX was prepared by heating CX up to 170 °C for 2 minutes using a stainless steel beaker then rapidly quench cooled in an ice bath. The generation of amorphous CX was confirmed using DSC. The prepared amorphous CX was subsequently mixed with PVP at drug/polymer weight ratio of 3:7 using a mortar and pestle.

4.2.5 Thermogravimetric Analysis (TGA)
TGA analyses were performed according to the method described in chapter 2, section 2.2.4. The TGA ramp test was performed at 10 °C/min from 20 to 500 °C, whereas the isothermal test for CX and PVP was conducted by heating the samples to 170 °C and holding at this temperature for 60 minutes.

4.2.6 Differential Scanning Calorimetry (DSC)
Differential scanning calorimetry (DSC) was used to characterize the thermal properties of CX, PVP and melt extrudates (pre and post scCO₂ exposure). Additionally, DSC was used to investigate the miscibility of CX and PVP using the Gordon Taylor (GT) equation. DSC analyses were performed according to the method described in chapter 2, section 2.2.5. For thermal analyses of CX, crystalline CX samples were heated at a heating rate of 10 °C/min from 25 to 200 °C to determine the melting temperature (°C) and enthalpy (ΔH) (J/g) of crystalline CX, whereas samples of amorphous CX, prepared according to method described in section 4.2.4, were heated at 10 °C/min from 0 to 200 °C to define the glass transition (Tg), recrystallization temperatures (°C) of amorphous CX and the melting temperature (°C) and enthalpy (ΔH) (J/g) of re-crystallized CX. For determination of the glass transition (Tg) of PVP and melt extrudates, samples were subjected to heat-cool-heat cycle from 25 to 200 °C at 10 °C/min, to remove the thermal history, and the Tg was calculated as the midpoint of the step transition in the plot of heat flow versus temperature in the second heat cycle.
4.2.6.1 Gordon-Taylor calculations

The Tg values of CX-PVP binary systems were predicted using the Gordon–Taylor equation (equation 3.1). The true density (ρ) of amorphous CX and PVP were 1.3477±0.0003 and 1.1768±0.0008 g/cm³, respectively, measured using an AccPyc 1330 helium pycnometer (Micromeritics®) (Norcross, USA). The Tg values predicted from the Gordon-Taylor equation were subsequently compared to the Tg of the melt extrudates observed experimentally by DSC.

4.2.7 Powder X-ray Diffractometry (PXRD)

PXRD analyses were performed according to the method described in chapter 2, section 2.2.6.

4.2.8 Scanning Electron Microscopy (SEM)

SEM analyses were performed according to the method described in chapter 2, section 2.2.7.

4.2.9 Fourier Transform Infrared (FT-IR) Spectroscopy

FTIR analyses were performed according to the method described in chapter 2, section 2.2.8.

4.2.10 Fourier Transform Raman (FT-Raman) Spectroscopy

Raman spectroscopic analyses were performed according to the method described in chapter 2, section 2.2.9.

4.2.11 In vitro drug release studies

The in vitro drug dissolution profiles of CX powder, physical mixtures and melt extrudates (pre and post scCO₂ exposure) either as tablets or milled extrudates were examined according to the USP paddle method (USP 30, 2007). Samples equivalent to 50 mg of CX were added to the dissolution medium (500 mL) consisting of simulated gastric fluid (SGF) as described by USP but without pepsin and containing 0.1% (w/v) Triton®-X100 at a temperature of 37 ± 0.2°C. The solution was stirred with a rotating paddle at 100 rpm. Samples of 5 ml were withdrawn from each vessel
at predetermined time intervals (5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300 min), filtered through a cellulose acetate filter of 0.45 μm (Nalgene Labware, Rochester, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd, Oxford, UK) UV-VIS spectrophotometer at 250 nm and a standard calibration curve that was linear over the concentration range (2.5-20 μg/mL). The percent of CX dissolved for each sample (n=3) was plotted versus time. No interference from PVP, NaCl or Triton®-X100 on the CX assay was observed at 250 nm.

4.2.12 Accelerated stability study

Stability studies were conducted at 40°C and 75% RH. Samples of hot-melt extruded tablets (with and without scCO₂), milled melt extrudates and a physical mixture of amorphous CX with PVP were placed in open glass vials stored at 40 °C inside a dessicator containing a saturated sodium chloride solution to generate the appropriate relative humidity (75% RH). Relative humidity inside the dessicator was recorded using a thermohygrometer. PXRD was used to test the stored samples for crystalline content after 5 days storage for the physically mixed samples whereas milled extrudates were tested after 1, 2 and 3 months. Drug dissolution studies were also conducted on the hot-melt extruded tablets after 3 months storage and compared to the corresponding hot-melt extruded tablets tested immediately following manufacture.

4.2.13 Statistical analysis

Two-tailed one sample t-test was used to compare the experimental Tg values of CX-PVP system determined by DSC versus the theoretical values predicted by Gordon-Taylor equation (α = 0.05). The effect of the formulation, milling, exposure to scCO₂ and storage of the melt extrudates at 40°C, 75% RH up to three months on drug dissolution were statistically analyzed using a repeated measures one-way ANOVA. Individual differences in drug dissolution between formulations were statistically identified using Fischer's PLSD test. In all cases p<0.05 denoted significance.
4.3 RESULTS AND DISCUSSION
4.3.1 Thermal analysis

During HME, pharmaceutical materials are exposed to high temperatures that might lead to their degradation, so thermal stability especially at temperatures used for HME is a prerequisite for this process (Crowley et al., 2007). The advantage of the short residence time of the materials within the extruder makes HME more successful than other hot-melt methods for heat-labile drugs like hydrocortisone (Repka et al., 1999) and p-aminosalicylic acid (Verreck et al., 2006a) and for heat labile polymers like polylactic acid (PLA) (Rothen-Weinhold et al., 1999).

TGA is a highly efficient technique for detecting volatile degradants and has been used efficiently to test the thermal stability of materials prior to HME (Bruce et al., 2005, Schilling et al., 2008, Zhu et al., 2006a). In this study, TGA was used to determine the suitability of CX and PVP for HME in terms of thermal stability. The degradation temperatures of CX and PVP, determined using a TGA ramp test, were 250 and 310 °C, respectively (Figure 4.4). Based on these results, a decision was taken to proceed with the HME for CX-PVP binary system.

![Figure 4.4. Thermogravimetric analysis (TGA) of celecoxib (CX) and PVP](image-url)
Figure 4.5 shows the DSC thermograms of crystalline and amorphous CX forms. The DSC thermogram of crystalline CX showed a sharp endotherm at 163.2 ± 0.9 °C ($\Delta H = 84.0 \pm 4.9$ J/g), corresponding to melting of CX. Amorphous CX showed a glass transition (Tg) at $58.9 \pm 0.2$ °C, cold crystallization at $131.5 \pm 3.1$°C, and a sharp endotherm at $163.0 \pm 0.4$ °C for melting of re-crystallized CX.

Figure 4.5. A representative DSC thermogram of crystalline and amorphous celecoxib (CX). The glass transition of amorphous CX has been expanded for clarity.
Melt extrusion temperature is mostly determined based on the Tg of the polymer. Usually 15-60 °C above the Tg of amorphous polymers is needed for HME based on the melt viscosity produced inside the extruder (Crowley et al., 2007). PVP K25 had a Tg of 154.6±0.7 °C (chapter 3, section 3.3.1). Because of this high Tg, PVP K25 polymer could not be extruded alone at temperatures below 200 °C without using any plasticizer. Drug/polymer miscibility may result in a solid state plasticization effect due to molecular interaction between the drug and polymer. In this study, a physical mixture of crystalline CX with PVP was prepared at a drug/polymer weight ratio of 3:7 and analyzed using DSC. The second heat ramp of the DSC thermogram showed a single Tg between the Tg of amorphous CX and the Tg of PVP, at 120±1.23 °C (samples were heated above the melting temperature of CX and cooled at 10 °C/min). These results suggest miscibility of CX with PVP and a solid state plasticization effect by CX on PVP. Subsequently, HME trials were conducted to extrude this binary mixture (CX:PVP 3:7 ratio) at the lowest possible temperature above the Tg using a screw speed of 100 rpm. HME was only possible at a temperature of 170°C. Transparent melt extrudates were produced at these processing temperatures giving an initial indication of the formation of a miscible, single phase system (Forster et al., 2001b). Using this preliminary data, further ratios of CX/PVP physical mixtures (1:1 and 7:3) were prepared. HME for these formulations was possible at a temperature of 150 °C using a screw speed of 100 rpm. The resultant melt extrudates were again transparent indicating the formation of miscible systems at these drug loading levels.

The highest temperature used during the HME was 170 °C, based on that an isothermal test at this temperature using TGA was conducted to confirm the thermal stability of CX and PVP at this temperature. Negligible loss in mass was detected for CX (less than 1%) at a temperature of 170 °C during the ramp test and after 60 minutes maintaining the sample isothermally at 170 °C. PVP showed a small percentage of loss in mass (~6 %) at a temperature of 170 °C during the TGA ramp and isothermal tests. This significant loss is mostly due to the moisture content of PVP which is related to its very high hygroscopic nature as was confirmed by Karl Fischer titration (chapter 3, section 3.3.1), which showed a water content of (x=5.3±0.13%, n=3) in the PVP samples tested.
Based on the high degradation temperatures of CX and PVP, which were significantly higher than the extrusion temperatures, the negligible weight loss at these temperatures, and the short residence time of the materials within the extruder (~1 minute), it can be assumed that both CX and PVP were thermally stable during the HME process and if any degradation occurred, it was negligible.

The DSC traces of melt extrudates were devoid of a melting endotherm characteristic of crystalline CX in the first heating cycle, while a single Tg in between the Tg of amorphous CX and the Tg of PVP was observed in the second heating cycle suggesting drug-polymer molecular miscibility (Figure 4.6). It was not possible to observe the Tg of the melt extrudates in the first heating cycle as it was overlapped by the broad endotherm of the moisture content in the samples tested. The absence of a CX melting endotherm and the presence of single Tg situated between the Tg of amorphous drug and polymer suggests the formation of a single phase molecular dispersion between CX and PVP that is formed during HME (Lu and Zografi et al., 1998).

There was a significant decrease in the Tg of PVP in all melt extrudates upon increasing CX loading level (Table 4.1 and Figure 4.6) indicating the ability of CX to act as a solid state plasticizer for PVP and the presence of interactions at the molecular level between CX and PVP. The solid state plasticization effect of CX on PVP facilitated the melt extrusion process and allowed for processing without the use of any conventional plasticizers even at a temperature of 150 °C, below the glass transition (Tg) temperature of PVP (154.6 ± 0.7 °C). Table 4.1 provides a summary of the thermal events obtained from the DSC analysis of CX, PVP and melt extrudates.
Table 4.1. Thermal properties of celecoxib (CX), PVP and CX-PVP melt extrudates.

<table>
<thead>
<tr>
<th></th>
<th>Tm (°C)</th>
<th>Tg (°C) exp</th>
<th>Tg (°C) theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib (CX)</td>
<td>163.2 ± 0.9</td>
<td>58.9 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>PVPK25</td>
<td></td>
<td>154.6 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>CX:PVP HME</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:7 (pre scCO₂)</td>
<td>130.7 ± 1.7</td>
<td>95.6</td>
<td></td>
</tr>
<tr>
<td>3:7 (post scCO₂)</td>
<td>131.1 ± 0.3</td>
<td>95.6</td>
<td></td>
</tr>
<tr>
<td>1:1</td>
<td>112.3 ± 0.7</td>
<td>76.4</td>
<td></td>
</tr>
<tr>
<td>7:3</td>
<td>88.4 ± 0.9</td>
<td>65.6</td>
<td></td>
</tr>
</tbody>
</table>

Tm = melting endotherm temperature, Tgexp = experimentally observed glass transition temperature, Tgtheory = calculated using the Gordon-Taylor Equation, HME denotes hot melt extrudate. The values presented in the table are the average ± standard deviation of three replicates (n=3)

Figure 4.6. DSC thermograms of PVP, CX-PVP hot melt extrudates (HME) (the second heating run of a heat-cool-heat cycle).
DSC traces of melt extrudates at all drug/polymer ratios (Figure 4.6) showed complete absence of cold crystallization, typical for amorphous CX, indicating the ability of PVP to act as an efficient re-crystallization inhibitor for amorphous CX. Previously, it has been shown that PVP had a similar effect with various other drugs (Matsumoto and Zografi, 1999; Van den Mooter et al., 2001). The anti-plasticization effect of PVP on the Tg of amorphous CX had an important role in this solid stabilization of amorphous CX during the DSC heating scan. As shown in Table 4.1, the Tg of amorphous CX increased from 58.9 ± 0.2 °C in amorphous CX samples to 130.7±1.7, 112.3±0.7 and 88.4±0.9 °C in the melt extrudates samples at drug/polymer ratios of 3:7, 1:1 and 7:3, respectively. Furthermore the significant increase in the Tg of amorphous CX had an important role in reducing the molecular mobility of CX, and hence in reducing the probability for nucleation and crystallization.

The Gordon-Taylor equation was used to calculate the theoretical Tg values of CX-PVP binary systems at different drug/polymer weight ratios (3:7, 1:1 and 7:3), and compared to the observed Tg values of corresponding melt extrudates (Table 4.1). Experimentally determined Tg values for the melt extrudates were significantly higher than the corresponding theoretical values (Figure 4.7). The observed positive deviation is indicative of solid molecular dispersions possessing lower free volume than that expected from the ideal mixing of drug and polymer, suggesting the presence of drug/polymer intermolecular interactions, most probably secondary in nature, which were stronger than the intermolecular interactions between individual drug or polymer molecules (Gupta and Bansal, 2005). The inhibition of cold crystallization of amorphous CX during the DSC heat scan may be attributed to the reduction in molecular mobility as a result of both the anti-plastisization effect of PVP and the formation of strong intermolecular interactions between CX and PVP. The suitability of PVP in forming stable solid dispersions containing drug in a high energy amorphous form has been previously reported by many authors (Matsumoto and Zografi, 1999; Van den Mooter et al., 2001; Taylor and Zografi, 1997). Critically enhanced stability and improved aqueous solubility has been attributed to the capability of forming secondary interactions in addition to the elevation in Tg.
Figure 4.7. Glass transition temperatures of celecoxib-PVP binary systems as a function of celecoxib content. (■) Tg values of the melt extrudates determined experimentally using DSC, (◇) theoretical Tg values predicted using the Gordon-Taylor equation. The data shown is the average of three replicates and in all cases the COV was < 2%.

The primary aim of this study was to investigate the effect of scCO₂ on the solid state and the drug release properties of CX-PVP hot-melt extrudates. It is known that scCO₂ can act as a plasticizer for polymers by reducing their glass transition temperature or as a molecular lubricant by reducing their melt viscosity (Chiou et al., 1985). Supercritical CO₂ acted efficiently as a reversible plasticizer during HME of pharmaceutical polymers resulting in a reduction in the melt viscosity and the extrusion temperature (Verreck et al., 2005, 2006a, 2006b, 2007; Lyons et al., 2007). In an attempt to examine whether scCO₂ had an effect on the Tg of PVP, the treated samples were tested using DSC immediately after depressurizing the chamber. The Tg values of melt extrudates after scCO₂ exposure remained nearly unchanged (131.1 ± 0.3 °C), as shown in Table 4.1. These results suggest that if there was any effect on the Tg of the melt extrudates by scCO₂, this effect was mostly temporary or reversible. It was very difficult to make a definite conclusion about whether there was such reversible plasticizing effect by scCO₂ on CX-PVP melt extrudates during processing as once the chamber was depressurized and the melt extrudates were removed, CO₂ left the samples so rapidly. Moreover, any residual CO₂ would have been removed during the DSC heating cycle resulting in difficulty in detecting its effect on the Tg of the melt extrudates.
4.3.2 Crystalline properties of hot-melt extrudates

The PXRD patterns for crystalline CX, a typical drug-PVP physical mixture, and melt extrudates immediately following manufacture are shown in Figure 4.8. The most characteristic peaks in the PXRD pattern of crystalline CX are located at 2θ angles of 15.0, 16.0, 19.6, 21.5, 22.3, 23.4, 25.3, and 29.4°. The X-ray pattern of the CX crystalline-PVP physical mixture (3:7), which was typical of all physical mixtures, showed the characteristic peaks of crystalline CX albeit with lower intensities. These peaks were completely absent in PXRD patterns of all melt extrudates which were similar in shape to the PXRD pattern obtained for PVP in which there was an amorphous “halo” (Figure 3.7). The PXRD results were in agreement with the DSC results suggesting the formation of solid molecular dispersions.

Re-crystallization of drugs as powders of micron and submicron sizes has been previously reported using scCO₂ as a solvent or an anti-solvent for different drug substances (Alessi et al, 1996; Benedetti et al., 1997; Kerc et al., 1999; Chiou et al., 2007, Young et al, 2000). Therefore, following scCO₂ exposure, the CX-PVP melt extrudates were examined using PXRD to investigate whether there was any change in the solid state properties of the melt extrudates. PXRD results did not show any re-crystallization and CX remained in its amorphous form within PVP extrudates after scCO₂ exposure as shown in Figure 4.8. These PXRD results indicate that scCO₂ had no significant effect on drug crystallinity within the melt extrudates at the processing conditions used, which may be attributed to being CX is already miscible with PVP in the form of molecular dispersions and additionally due to the presence of strong intermolecular forces between the polymer and drug, as confirmed by the Gordon-Taylor calculations.
Figure 4.8. Powder X-ray diffraction (PXRD) patterns for crystalline CX, a representative physical mixture of crystalline CX and PVP and hot-melt extruded samples immediately following manufacture.

The PXRD patterns of melt extrudates stored for up to three months at 40 °C, 75% RH and a physical mixture of PVP with amorphous CX at drug/polymer weight ratio of 3:7 stored under the same conditions for five days are shown in Figure 4.9. PXRD patterns of the melt extrudates at drug/polymer weight ratios of 3:7 and 1:1 confirmed retention of CX in amorphous form, indicating the physical stability of these solid molecular dispersions for the whole period of the stability study (three months). The PXRD pattern obtained for the melt extrudate containing drug and polymer in the 7:3 ratio showed no re-crystallization after 1 month storage whereas very small peaks were observed in the PXRD pattern after two months storage which increased in intensity after three months storage.
Figure 4.9. Powder X-ray diffraction patterns (PXRD) for a physical mixture of amorphous CX and PVP and hot-melt extruded samples stored at (40 °C, 75 % RH) conditions.

These PXRD results indicate that PVP acted as a highly efficient stabilizer for the amorphous form of CX within the melt extrudates. Interestingly, the physical mixture of PVP and amorphous CX stored under the same conditions (40 °C, 75 % RH) for five days had distinct bands at 16.4, 19.9, 21.7, 22.6, 23.7, 25.6, and 29.7° indicative of the presence of crystalline CX. The instability of the amorphous CX-PVP physical mixture highlights the importance of HME for the formation of stable amorphous CX through the formation of solid molecular dispersions that had a single Tg that was significantly higher than the Tg of amorphous CX (anti-plasticization effect) (Table 4.1).
Scanning electron microscopy (SEM) was used to examine the surface morphology of the melt extrudates pre and post scCO$_2$ exposure. SEM images (Figure 4.10) showed that the melt extrudates prior to scCO$_2$ exposure had a smooth surface without the presence of CX crystals, whereas the SEM images of the melt extrudates post scCO$_2$ possessed a highly porous structure. These results indicate that scCO$_2$ acted efficiently as a foaming agent converting the dense structure of the melt extrudates into a porous-like structure. As shown in Figure 4.10, scCO$_2$ had no effect on the drug solid state properties within the melt extrudates, which in agreement with the PXRD results. The mechanism which scCO$_2$ may create this foamed structure can be explained by the high diffusivity of scCO$_2$ enabling it to penetrate efficiently through the melt extrudates. After depressurization in the chamber, CO$_2$ evaporated from samples rapidly creating pores within the structure of the extrudates.
Figure 4.10. SEM images of pre (a) and post (b) scCO$_2$ hot-melt extrudates at different magnifications (40X, 3,000X and 10,000X)
4.3.3 Drug/polymer interactions

The Gordon Taylor equation suggested the presence of drug/polymer intermolecular interactions between CX and PVP within the melt extrudates. These interactions were stronger than the intermolecular interactions between individual CX and PVP molecules. Drug/polymer interactions have been shown to have a significant role in the physical stabilization of amorphous drugs within solid dispersions (Taylor and Zografi, 1997, Matsumoto and Zografi, 1999). FTIR and Raman spectroscopic studies were conducted in order to characterize the nature of intermolecular interactions between CX and PVP during HME. As was discussed previously, PXRD and SEM confirmed the presence of CX in the amorphous form within the melt extrudates, so it was important to first characterize the significant differences in the spectra for crystalline and amorphous forms of CX, and then to use this information to define the form of CX after HME. In addition, we have used FTIR and Raman spectroscopy to identify key 'markers' of interaction such as band broadening and/or peak shifting.

CX has a sulfonamide group (SO2NH2) which can act as a proton donor through its amine group (NH2) and as a proton acceptor through its sulfonyl group (SO2). Other important proton accepting groups are the nitrogen atom of pyrazole group and the fluoride atom of (CF3) group in relation to the sulfonamide group. The electrons of the nitrogen atom are delocalized over the neighbouring oxygen atom as a result of the strong electron withdrawing nature of the SO2 group. This polarizes the nitrogen atom facilitating the release of protons (Adsmond et al., 2001). The presence of the proton acceptor and donor sites in CX increases the potential for inter and intramolecular interactions (Kaushal et al., 2008, Gupta and Bansal, 2005) which gives rise to a high crystal energy lattice (Tm CX 163.2 ± 0.9 °C).

As was mentioned in chapter 3, PVP possesses two proton-accepting groups, the oxygen atom of the carbonyl group (C=O) and the nitrogen atom of the pyrrole ring. The carbonyl (C=O) group is regarded as the more favorable site for potential interaction due to the three dimensional structure of PVP (Thypo et al., 2007).
FTIR and Raman spectroscopic studies were conducted in order to define key spectral differences between the amorphous and crystalline form of CX. It has been reported in previous studies that there were significant differences in the FTIR spectra of amorphous and crystalline forms of CX (Kaushal et al. 2008). In this study, FTIR and Raman spectra of amorphous and crystalline forms of CX were generated and compared. Figure 4.11 shows the changes in the position of the FTIR vibration modes of the most interesting groups of CX (NH, S=O and C-F) in amorphous and crystalline forms. The differences in the position of these bands indicate the change in the nature of intra and intermolecular interactions mostly hydrogen bonding between crystalline and amorphous CX molecules. In general, sulfonamides have a strong vibrational doublet due to NH\textsubscript{2} stretching in the region of 3390-3245 cm\textsuperscript{-1} (Socrates, 1994). The FTIR spectrum of crystalline CX showed a doublet for NH stretching vibrations of the sulfonamide group at 3342 cm\textsuperscript{-1} and 3232 cm\textsuperscript{-1} (Figure 4.11). The low band position of the doublet is indicative of strong hydrogen bonding within CX in the crystalline form (Kaushal et al., 2008). In amorphous CX, the doublet associated to the NH\textsubscript{2} group was shifted upward to values of 3388 and 3267 cm\textsuperscript{-1} which is indicative of a strengthening of the N-H bond due to weakening or a disruption of hydrogen bonding in the amorphous CX relative to the crystalline form (Kaushal et al., 2008). Shifting the N-H stretching vibration band to a lower frequency is indicative of strengthening of hydrogen bonding whereas shifting to higher frequencies is indicative of weakening of hydrogen bonding (Tang et al., 2002). The FTIR spectrum of crystalline CX showed stretching vibrations for the sulfonyl group (SO\textsubscript{2}) at 1347 cm\textsuperscript{-1} (asymmetric) and 1165 cm\textsuperscript{-1} (symmetric). In amorphous CX, the asymmetric stretch shifted downward to a value of 1341 cm\textsuperscript{-1} and the symmetric stretch exhibited an increase in intensity (Figure 4.11). These effects may be attributed to strong interactions of the oxygen atom of the sulfonamide group in the amorphous form (Kaushal et al., 2009). Strengthening of hydrogen bonds in the amorphous state compared to the crystalline form has been reported previously in felodipine, nicardipine and isradipine, although a weakening of hydrogen bonding in amorphous forms (disordered phase) of a drug is more typical (Tang et al., 2002). The symmetric stretching vibration of C-F which occurs at 1229 cm\textsuperscript{-1} was shifted significantly upward to 1238 cm\textsuperscript{-1} in the amorphous form (Figure 4.11). This suggests that CF\textsubscript{3}, in contrast to SO\textsubscript{2} and similar to the NH\textsubscript{2} group, interacts more strongly in the crystalline form than in the amorphous form (Kaushal et al., 2008).
Figure 4.11. FTIR stretching regions for CX (a) NH$_2$; (b) S=O and C-F.
Interestingly, Raman spectroscopy identified similar spectral differences between the crystalline and amorphous form of CX. Figure 4.12 shows the most interesting peaks of CX in the crystalline and amorphous states. There were distinct differences between the spectra of crystalline and amorphous forms of CX in terms of band shape, intensity and position. These differences indicate changes in the type of molecular level interactions between amorphous and crystalline CX molecules. In particular, the peaks attributed to N-H bending and the symmetric stretching vibrations of S=O and C-F groups were significantly broader and lower in intensity within amorphous CX compared to the crystalline form. Peak broadening and lowering of intensity in amorphous systems are mostly related to the high level of disorder and the lack of the long-range order (Smrecki et al., 1997, Kaushal et al., 2008). There was no significant shift in the N-H bend vibration of amorphous CX (1520 cm\(^{-1}\)), whereas it was located at 1522 cm\(^{-1}\) in the Raman spectra of crystalline CX. Additionally, the symmetric stretching vibration of SO\(_2\) which was located at 1160 cm\(^{-1}\) in the spectrum of crystalline CX was significantly shifted downward in the spectrum of amorphous CX to 1156 cm\(^{-1}\). Furthermore, there was a significant upward shifting in C-F group of amorphous CX to 1238 cm\(^{-1}\) from 1228 cm\(^{-1}\) in the spectrum of crystalline CX. The downward shift of S=O stretching vibrations and the upward shift in the stretching vibration of C-F were in good agreement with FTIR results that showed strengthening in hydrogen bonding interactions formed by S=O group whereas weakening in such interactions formed by C-F groups in amorphous CX compared to the crystalline form (Kaushal et al., 2008).
Figure 4.12. Raman spectra of crystalline (solid lines) and amorphous (dashed line) of CX (a) N-H bend; (b) S=O (stretch symmetric) and (c) C-F (stretch symmetric).
To investigate the intermolecular interactions between CX and PVP after HME, the FTIR spectra of melt extrudates were compared with a physically mixed sample of amorphous CX and PVP (Figure 4.13). The carbonyl stretching vibration of PVP was shifted downward from 1652 cm\(^{-1}\) in the physical mixture samples to 1644 cm\(^{-1}\) in the melt extrudates. The downward shift to lower frequency in the position of the stretching vibration band of the carbonyl group is mostly resulted from the formation of strong hydrogen bonding with the proton donor group of CX (NH\(_2\)). The small shift in the position of the carbonyl group in the physical mixture sample (1652 cm\(^{-1}\)) in comparison to PVP (1655 cm\(^{-1}\)) might be related to interaction between amorphous CX and PVP during the physical mixing in the mortar and pestle. A similar finding was reported by Forster et al. (2001b) as a result of interactions between amorphous indomethacin and PVP in physical mixture samples. Exposure of the melt extrudates to scCO\(_2\) had no significant effect on band position in comparison to melt extrudates pre scCO\(_2\).

Figure 4.13. FT-IR stretching regions of the carbonyl group in PVP, amorphous CX-PVP physical mixture (PM) and hot-melt extrudates (HME) (pre and post scCO\(_2\) exposure).
It was not possible to detect any change in the shape or position of the doublet peaks of \((\text{NH}_2)\) group of CX in the FT-IR spectra of the melt extrudates in comparison to the FT-IR spectrum of amorphous CX due to the broadness of these bands in an environment of high disorder (amorphous form) and due to overlapping of the broad hydroxyl band which may be attributed to adsorbed moisture by the hygroscopic PVP. These FTIR results give strong evidence of the presence of CX in an amorphous form within the melt extrudates especially that these doublet peaks were absent as well in the spectrum of the CX-PVP physical mixture samples containing amorphous CX while they were detected clearly in the FTIR spectrum of crystalline CX-PVP physical mixture samples (Figure 4.14). However, the red shift in the position of the carbonyl group of PVP in the FTIR spectra of the melt extrudates in comparison to its position in the spectrum of amorphous CX-PVP sample (as discussed earlier) was indicative of the presence of strong hydrogen bonding between the carbonyl group of PVP with CX, most probably with the N-H group of sulfonamide. A significant downward shifting in the position of the carbonyl group of \(N\)-methyl-2-pyrrolidone, a structural analogue to \(N\)-vinylpyrrolidone, was observed using FTIR in a CX-NMP binary system suggesting strong hydrogen bonding interactions with the N-H group of CX (Gupta and Bansal, 2005). Additionally in the same study, it was confirmed by molecular modelling studies that molecular interactions between CX and NMP were due to the hydrogen bonding between the carbonyl group of NMP and the N-H group of CX. Furthermore, it was reported previously that hydrogen bonding interactions exist between PVP and furosemide via the sulfonamide group of the drug with the carbonyl group of PVP (Doherty and York, 1987).
Figure 4.14. FT-IR spectra (3000-4000 cm\(^{-1}\)) of PVP, CX-PVP physical mixtures and hot-melt extrudates.

In general, Raman spectra of the physical mixtures containing crystalline CX were similar to the Raman spectrum of crystalline CX, whereas physically mixed samples containing amorphous CX and melt extrudates showed spectra that were similar to the Raman spectrum of amorphous CX. Figure 4.15 shows the Raman spectra (1100-1750 cm\(^{-1}\) region) of the melt extrudates versus the corresponding physical mixtures containing either crystalline or amorphous CX. These results confirmed the presence of CX as an amorphous form within the melt extrudates, suggesting the efficiency of Raman spectroscopy in characterizing the solid state properties of CX within the melt extrudates.
In order to get more information about drug/polymer interactions in CX-PVP binary system, Raman spectra of the melt extrudates were compared to the Raman spectrum of a physical mixture sample of amorphous CX and PVP. A significant upward shift in the position of the stretching vibration band of the S=O group was observed in all spectra of CX-PVP melt extrudates to 1164 cm\(^{-1}\). This peak was observed at 1155 cm\(^{-1}\) in the spectrum of the physically mixed sample containing amorphous CX (Figure 4.16). As was suggested earlier, the oxygen atom of the sulfonamide group interacts more strongly by hydrogen bonding with the proton donor group (N-H) in amorphous CX than in its crystalline form (Gupta and Bansal, 2005, Kaushal et al., 2008). The new strong hydrogen bonding interactions formed between the NH\(_2\) of CX and the carbonyl group of PVP by HME may result in disruption or weakening of the existing hydrogen bonding interactions between the sulfonyl group and the NH\(_2\) group in amorphous CX because the amide carbonyl group of PVP can act as a stronger proton acceptor than the sulfonyl group (Adsmond, 2001). This weakening in the hydrogen bonding with the sulfonyl group may cause the observed upward shifting in the stretching vibration band of the sulfonyl group in the melt extrudates. Gupta and Bansal (2005) suggested the
formation of stronger hydrogen bonding interactions between the NH$_2$ group of CX and the carbonyl group of N-methyl-2-pyrrolidone in CX-NMP binary system than the existing hydrogen bonding between the sulfonyl group and the NH$_2$ group which may be attributed to the stronger proton accepting capabilities of the carbonyl in comparison to the sulfonyl group. Raman spectroscopy was efficient to prove this hypothesis and to confirm FTIR results of the formation of strong hydrogen bonding between the NH$_2$ group of CX and the carbonyl group of PVP as a result of HME. This strong hydrogen bonding may have a critical role in the physical stabilization effect of the amorphous form of CX within the melt extrudates.

Figure 4.16. Raman spectra (1120-1260 cm$^{-1}$ region) of CX-PVP melt extrudates (solid line) in comparison to Raman spectra of CX-PVP physical mixtures containing amorphous CX (dashed line).
4.3.4 *In vitro drug release studies*

Generally, hot-melt extruded tablets have a dense structure with low porosity which may retard the drug release rate from the polymeric matrix. Consequently, this delay in drug release may result in lowering drug bioavailability and hence its therapeutic response. It was previously reported that hot-melt extruded tablets have slower drug release rates than those prepared by traditional methods due to their greater density and hence lower porosity (Crowley *et al.*, 2004b).

In vitro drug release studies were conducted using simulated gastric fluid (SGF) (pH 1.2) without pepsin but including 0.1% (w/v) Triton X-100, a surface active agent that can create a surface tension close to the surface tension of the in vivo gastric medium (Galia *et al.*, 1999). Figure 4.17 shows the *in vitro* drug dissolution profiles of the CX-PVP hot-melt extruded tablets and milled extrudates at drug/polymer weight ratio of 3:7 with and without exposure to scCO₂ in comparison to crystalline CX and the corresponding physical mixture. Crystalline CX powder showed 57.11±1.1 % dissolution after 1 h, whereas the physical mixture containing drug/polymer at a ratio of 3:7 had a significantly higher release (68.86±1.45 %) after 1 h (*p* = 0.0004). CX-PVP hot-melt extruded tablets at drug/polymer weight ratio of 3:7 without scCO₂ exposure showed only 20.87±0.09 % and 41.71±0.89 % drug release after 1 and 2 h, respectively. Complete drug release was achieved after 5 h. This slow release of drug from hot-melt extruded tablets without exposure to scCO₂ may be attributed to the dense structure of the melt extrudates (Crowley *et al.*, 2004b).

According to Noyes-Whitney equation (Noyes and Whitney, 1897), one of the most important factors that can accelerate the drug release rate is the increase in the surface area available for dissolution. To achieve this goal, CX-PVP hot-melt extruded tablets were further processed using two different processes milling and scCO₂ exposure. A significant enhancement in drug release rate was achieved from the hot-melt extruded tablets after exposure to scCO₂, 46.01±0.97 % and 92.22±0.95 % after 1 and 2 h, respectively, with complete drug release occurring after 2.5 h. This significant enhancement in the drug release rate (2.2-fold) (*p*<0.0001 in all cases) may be attributed to the foamed like structure of the melt extrudates after the exposure to scCO₂ as was shown in SEM images resulting in an increased surface area for dissolution and hence faster ingress of the dissolution medium through the polymeric
matrix. Conversely, more significant increase in drug release rate was achieved by milling the melt extrudates without scCO₂ exposure, particle size less than 355μm, achieving a complete drug release after 1h comparing to the non-treated and treated tablets with scCO₂ (p<0.0001 in all cases). This very rapid increase in drug release rate may be attributed to the massive increase in the surface area achieved by milling. To confirm that the significant enhancement in the drug release rate achieved from the hot-melt extruded tablets after scCO₂ exposure was related to the increase in the surface area of the melt extrudates, the melt extrudates after exposure to scCO₂ were milled and drug release studies were conducted on these milled samples, particle size less than 355μm, and similar dissolution profiles were obtained comparing to the milled extrudates without exposure to scCO₂ indicating that the enhancement in the dissolution rate of CX from the hot-melt extruded tablets after exposure to scCO₂ was related to the increase in the surface area available for dissolution.

The extent of CX absorption is limited by dissolution rate (Paulson et al., 2001). The time to reach peak plasma concentration (tmax) of CX is about three hours after oral administration, it is necessary to enhance the dissolution rate of CX to improve its overall oral bioavailability as rapid onset of action is desirable for CX to provide fast pain relief (Garti et al., 2006). Hence, a formulation with improved dissolution characteristics may significantly shorten the time to reach therapeutic levels in the systemic circulation and to achieve higher absorption extent. Therefore the significant increase in drug release rate from the melt extruded tablets after exposure to scCO₂ may significantly enhance the absorption rate of CX through the GI tract and hence produce faster therapeutic effects.
Figure 4.17. Dissolution profiles of crystalline CX (♦), CX crystalline-PVP (PM) (▲), CX-PVP hot-melt extruded (HME) tablets without scCO₂ exposure (▲), HME tablets after scCO₂ exposure (□), milled HME without scCO₂ exposure (●), milled HME after scCO₂ exposure (+), immediately after manufacture. The data shown is the average of three replicates and in all cases the COV was < 6%.

Drug release properties of the hot-melt extruded tablets with and without scCO₂ exposure were conducted after three months storage at 40°C, 75% RH. There was no significant difference in the dissolution rate of the stored tablets compared to the dissolution rate of the corresponding freshly prepared samples (Figure 4.18) ($p = 0.2128$ and $0.1552$ after 1 and 2 h, respectively, for the samples without scCO₂ treatment; whereas $p = 0.1015$ and $0.3686$ after 1 and 2 h, respectively, for the samples with scCO₂ treatment). These results may be attributed to the highly stable solid state properties of CX within the melt extrudates. The physical solid state stability of these tablets can be deduced from the high physical stability of the milled melt extrudates samples of increased surface area. PXRD pattern of these samples showed that CX remained in amorphous state after three months storage at 40°C, 75% RH (Figure 4.9). These results indicate the efficiency of HME in producing stable solid molecular dispersions of CX using PVP as a hydrophilic matrix.
Figure 4.18. Dissolution profiles of CX-PVP hot-melt extruded tablets (HME) after 3 months storage at (40°C, 75% RH), without scCO₂ exposure (Δ); after scCO₂ exposure (▲) in comparison with dissolution profiles of the freshly prepared tablets, without scCO₂ (◼); after scCO₂ exposure (□). The data shown is the average of three replicates and in all cases the COV was < 6%.
4.4 CONCLUSIONS
Hot melt extruded solid dispersions of CX-PVP binary system were prepared successfully based on the solid-state plasticization effect of CX on PVP. DSC thermograms of the melt extrudates were devoid of CX melting endotherm and showed the formation of a miscible system (single phase) that has a single Tg in between the Tg of the amorphous drug and the polymer. PXRD confirmed the absence of any CX crystallinity within the melt extrudates. These DSC and PXRD results confirmed the formation of solid molecular dispersions of CX within PVP melt extrudates at all drug/polymer weight ratios (3:7, 1:1 and 7:3).

The Gordon-Taylor equation suggested the formation of intermolecular forces between CX and PVP within solid molecular dispersions that were stronger than the intermolecular forces between individual drug and polymer molecules. Hydrogen bonding interactions between CX and PVP were confirmed using FT-IR and FT-Raman spectroscopic studies. CX remained as an amorphous form within the melt extrudates containing up to 50 % (w/w) PVP stored at 40°C and 75% RH for three months. This solid-state stabilization of amorphous CX within the melt extrudates was mostly related to the strong drug/polymer hydrogen bonding and the anti-plasticization effect of PVP on amorphous CX that reduced the molecular mobility of amorphous CX within the melt extrudates.

The slow drug release rate from the prepared hot-melt extruded tablets was mostly related to the high density and hence low porosity of these tablets. To increase the surface area available for dissolution, the melt extrudates were further processed by milling or exposure to scCO\textsubscript{2}. Supercritical carbon dioxide (scCO\textsubscript{2}) treatment of hot-melt extruded tablets was highly efficient in enhancing CX dissolution rate achieving around 2-fold increase in dissolution rate after 1 h compared to the hot-melt extruded tablets without scCO\textsubscript{2} exposure. This significant enhancement in drug dissolution rate was mostly related to the efficiency of scCO\textsubscript{2} in acting as a foaming agent on the melt extrudates creating a foamed like structure of significantly increased surface area. The oral bioavailability of CX is highly dependent on the drug dissolution rate, so this significant enhancement in CX dissolution rate by scCO\textsubscript{2} may result in faster analgesic effect. There was no effect for scCO\textsubscript{2} on the solid state properties of CX within the melt extrudates or drug/polymer interactions at the processing conditions used in this study providing an additional advantage. Further
enhancement in the dissolution rate has been achieved by milling the melt extrudates, which may be attributed to the massive increase in the surface area of the milled samples. There was no significant change in the dissolution rate of the hot-melt extruded tablets with and without scCO₂ exposure after three months storage at 40°C and 75% RH, which may be attributed to the physical stability of the solid state of the melt extruded tablets.
AN INVESTIGATION INTO THE USE OF HOT-MELT EXTRUSION AND THE EFFECT OF PROCESS TEMPERATURE ON THE PHYSICOCHEMICAL PROPERTIES OF COLON TARGETED DRUG DELIVERY PLATFORM
5.1 INTRODUCTION
Colon drug delivery refers to targeted delivery of drugs to the lower GI tract, which occurs primarily in the large intestine (i.e., colon). Solid formulations for colonic delivery of drugs are advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel diseases (Crohn’s disease and ulcerative colitis), irritable bowel syndrome, and colon cancer (Yang et al., 2002). The local delivery of actives to the colon has advantages of reduced incidence of systemic side effects, administration of lower doses of drug, and maintenance of the drug in its intact form as close as possible to the target site. Colonic delivery for systemic delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, in particular therapeutic proteins and peptides such as insulin, calcitonin and vasopressin, has been shown to enhance oral bioavailability (Yang et al., 2002; Saffran et al., 1986; Antonin et al., 1992). Additionally, increasing bioavailability using a colon targeted approach has also been found to be effective in minimizing unwanted side-effects (Minko et al., 2004). Colonic delivery of drugs may be extremely useful when a delay in drug absorption is required e.g. in cases of diurnal asthma, angina, arthritis (Kinget et al., 1998).

To achieve these therapeutic benefits, a colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and provide an abrupt onset of drug release upon entry into the colon. This requires a triggering element in the system that can respond to physiological changes in the colon (Yang et al., 2002). The physiological changes along the GI tract can be generally characterized as a continuum, with decreases in enzymatic activity, motility, and fluid content and an increase in pH. The main strategies proposed for targeted colon delivery are prodrugs, pH- and time-dependent systems, and microflora-activated systems.

Prodrugs designed for colon delivery are able to achieve site specificity in which cleavage of the linkage bond between the drug and carrier occur by reduction and hydrolysis processes through the action of enzymes secreted by colon bacteria e.g. azoreductase, glycosidase, glucuronidase. Although prodrugs are efficient in delivering drugs to colon, from a regulatory perspective, they are considered as new chemical entities (Yang et al., 2002).
pH dependent systems designed by a combination of polymers with pH-dependent solubility take advantage of the pH changes along the GI tract. These systems effectively resist drug release under acidic conditions of the stomach however a considerable amount of drug may be released in the small intestine before it reaches the colon because of the similarity in pH between the small intestine and the colon (Evans et al., 1988). This unpredictable site-specificity of drug release makes these systems less reliable and does not allow reproducible drug delivery especially with the inter-/intra subject variation (Ashford et al., 1993a, 1993b; Leopold and Eikeler, 2000).

For time dependent systems designed for colon drug delivery, the location of initial drug release predominantly depends on the transit time of the system in the GI tract. Despite the relative consistency of transit times in the small intestine (Davis et al., 1986), the high variation of gastric retention times results in difficulties in predicting the accurate location of the drug release from these systems (Yang et al., 2002). Furthermore, due to intersubject variation, the drug release might occur in the small intestine in some patients, whereas in others the formulations may pass the ascending colon intact. Additionally, the pathophysiological conditions associated with the GI tract may affect the performance of a time-dependent formulation significantly. For example, accelerated transit through different regions of the colon has been observed in patients with irritable bowel syndrome (Vassallo et al., 1992), carcinoid syndrome and diarrhea (von der Ohe et al., 1993), and ulcerative colitis (Reddy et al., 1991). Therefore, time-dependent systems are not ideal to target drugs to the lower regions of the GI tract for the treatment of colonic diseases.

Microflora-activated systems based on fermentation of non-starch polysaccharides e.g. pectin, chitosan, cyclodextrin, dextran by colon anaerobic bacteria, are highly promising and preferable strategy for colon drug delivery because these polysaccharides can only be degraded in the colon in which there are high levels of polysaccharidases of microbial origin e.g. beta-D-glucosidase, beta-D-galactosidase, amylase, pectinase that are secreted by a variety of colon bacteria (Vandamme et al., 2002, Minko et al., 2004). The enzymatic degradation of these polysaccharides is a slow process (over 12 h), making these systems unsuitable to be
used when a bolus fashion release is needed upon entry into the colon (Yang et al., 2002).

Formulations for colonic delivery are delayed-release dosage forms providing either a 'burst release' or a sustained/prolonged release once they reach the colon. The factors that must be considered in the design of colonic formulations are (Singh, 2007):

a) pathology of the disease especially in the lower GI tract or physiology of the healthy colon if the formulation is not intended for localized treatment e.g. in normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH = 6.6 ± 0.5) to the terminal ileum (pH = 7.5 ± 0.4), a decrease in the cecum (pH = 6.4 ± 0.4), and then a slow rise from the right to the left colon with a final value of 7.0 ± 0.7 (Evans et al., 1988). It was reported that alterations in GI pH profiles may occur in patients with inflammatory bowel disease (Nugent et al., 2001).

b) physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery, and the desired release profile of the drug.

Generally, the dissolution and release rate from colonic formulations is thought to be decreased in the colon due to the fact that less fluid is present in the colon than in the small intestine (Takaya et al., 1998). The poor dissolution and release rate may lead to lower systemic availability of drugs. These issues could be more problematic when the drug is poorly water-soluble and/or requires higher doses for therapy. Therefore these drugs need to be delivered in a presolubilized form. Fast release microspheres containing solid dispersions of hydroxycamptothecin (HCPT) coated with a layer of Eudragit S100 to obtain colon specific microspheres (HCPT-CSMS) was developed by Lu and Zhang (2006). The in vitro cumulative release for free HCPT (large crystals) over a 24 h period in simulated colonic juice was only 0.56% whereas for HCPT-CSMS it was 80.1% (140 times larger) with over 60% of total HCPT released in an initial 5 h period. The solubility of free HCPT at 37±0.5 °C in simulated colonic juice was determined to be 11.57 mg/L and that of fast release microspheres of HCPT was 22.07 mg/L (two times larger). Animal studies using mice with colonic cancer showed a cancer inhibition rate of 61.4% compared to 39.8% for free HCPT.
Colorectal cancer (CRC) is one of the most common cancers worldwide and a prevalent cause of morbidity and mortality (Gill and Sinicrope, 2005). CRC is a leading cause of cancer death in the Western countries (Jemal et al., 2005), and its incidence is increasing globally as the dietary patterns and lifestyles of the industrialized Western countries are adopted worldwide (Ji et al., 1998; Yiu et al., 2004). The relatively slow progression of adenomatous polyps to colorectal cancer, that spans over 10 to 15 years, offers a great opportunity for colorectal cancer chemoprevention and treatment of premalignant lesions (Half and Arber, 2009). Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the subject of intensive investigation for their anti-carcinogenic effect on colorectal cancer. The up-regulated expression of cyclooxygenase-2 (COX-2) is well reported in a variety of malignancies, especially in colorectal cancer (Brown and DuBois, 2005). An elevated level of COX-2 is responsible for the increased biosynthesis of prostanoids that is believed to cause the malignancy in this disease. Prostanoids are derived from the action of COX-2 utilizing arachidonic acid as a substrate. The chemopreventative effect of nonsteroidal anti-inflammatory drugs (NSAIDs) against colon cancer is now well known. NSAIDs exert their effects principally by inhibiting COX activity, thereby decreasing the biosynthesis of all prostanoids, including a major product of COX, prostaglandin E2 (PGE2). It is reported, therefore, that the risk of developing colorectal cancer is decreased by 40% – 50% in persons regularly taking NSAIDs (Brown and DuBois, 2005).

Celecoxib (CX), a NSAID, is a selective cyclooxygenase-2 (COX-2) inhibitor. CX is used in chemoprevention of malignancy onset in familial adenomatous polyposis (FAP) patients and has recently been under clinical evaluation for the possibility of suppressing cancer recurrence post-surgery in a sporadic contest, and influencing metastatic disease (Gill and Sinicrope, 2005). The recent research have provided convincing evidence that the use of CX among patients with colonic adenomas reduces the risk of metachronous adenomas (Bertagnolli et al., 2006; Arber et al., 2006).
Direct administration of CX onto luminal growths is an attractive approach for focusing drug exposure and reducing the adverse side-effects associated with extensive systemic circulation. A colon drug delivery system composed of a biodegradable platform combination of two polysaccharides, a biodegradable guar gum and bioadhesive chitosan was developed for colorectal cancer therapy using CX as a model drug. *In vitro* and *in vivo* studies showed that the proliferation of cancer cells was impeded by the high local concentration of CX while chemoprevention has been demonstrated with low CX doses (Haupt *et al*., 2006). Furthermore, a colon specific fast release system utilizing enteric coated tablets was developed using CX as a model drug (Sinha *et al*., 2006). In this study, the effect of a super-disintegrant (crosslinked PVP), osmogens e.g. sodium chloride or potassium chloride, and the coating level were studied. *In vitro* drug release studies showed that super-disintegrants were more effective in providing a burst effect in the tablets compared to the osmogens, which were shown to provide a sustained drug release through the colon (Sinha *et al*., 2006).

HME is a plastics processing technology that has been used since the 1930s and is more recently gaining intense pharmaceutical interest because of the advantages that this technology can provide in comparison with traditional pharmaceutical processes used to manufacture solid dosage forms. The polymeric carrier during HME gradually melts or softens and the materials are mixed and compressed. The molten mixture finally passes through a die system, and after cooling, the extrudate may then be cut into tablets, granules or pelletized. HME offers several advantages in the preparation of modified release tablets. It is a fast, simple, continuous, solvent free process requiring fewer processing steps than traditional tableting techniques. Additionally, there are no requirements for compressibility of the materials used in the formulation (Breitenbach, 2002; Crowley *et al*., 2007).

Eudragit 4155F is a freeze dried product of Eudragit® FS 30 D. It is a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid. The ratio of the free carboxyl groups to the ester groups is approx. 1:10. The average molecular weight is approximately 220,000. Eudragit 4155F is a pH dependent anionic copolymer that dissolves at pH 7. Its chemical structure is shown in Figure 5.1.
Figure 5.1. Chemical structure of Eudragit 4155F copolymer
5.1.1 Aims and objectives

HME technology is an efficient technology for the production of immediate and controlled release drug delivery systems (Crowley et al., 2002; 2004b; Breitenbach et al., 2003; Forster et al., 2001b). HME was used efficiently to manufacture hot-melt extruded tablets for delivering 5-aminosalicylic acid to the colon using a polymeric matrix composed of Eudragit® S100 polymer (Bruce et al., 2005). Moreover, Eudragit FS 30D was used efficiently as a coating material for pellets for colon targeting (Gao et al., 2006). The efficiency of Eudragit 4155F to be used as a polymeric matrix for colon targeting has not been evaluated. In this study, HME was used to manufacture a colon-specific drug delivery platform composed of Eudragit 4155F as a polymeric matrix and using CX as a model drug.

The principle aims and objectives of this study are summarized as follows:

- Study the efficiency of Eudragit 4155F as a polymeric matrix that will allow for the production of HME colon targeting of CX.
- Physicochemical characterization of the manufactured CX-Eudragit binary system in terms of drug/polymer miscibility, solid state properties, drug/polymer interactions and in vitro drug release using different characterization techniques.
- Study the effect of the drug loading level and extrusion temperature on the solid-state properties and in vitro drug release properties of extruded tablets.
- Investigate the stability of the prepared CX-Eudragit 4155F hot melt extruded solid dispersions in terms of solid-state properties of CX under accelerated stability conditions and study the effect of polymer content on the stability of the solid dispersions.
- Study the effect of plasticizer type and amount and the incorporation of alkali salts on the drug release properties from the Eudragit 4155F polymeric matrix.
5.2 MATERIALS AND METHODS
5.2.1 Materials

Celecoxib (CX) was a kind gift from Hikma Pharmaceuticals Co. (Amman, Jordan). Eudragit 4155F was donated by Degussa Corp. Röhm GmbH (Dermstadt, Germany). DIBUTYL sebacate (DBS), magnesium carbonate basic (anhydrous) (MgCO₃) and sodium dodecyl sulfate (SDS) were all purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Triethyl citrate (TEC) was purchased from Morflex, Inc. (Greensboro, NC, USA). Sodium chloride (NaCl) and all other chemicals used were purchased from BDH Laboratory supplies (Poole, Dorset, England) and were of Analar grade or equivalent quality.

5.2.2 Preparation of CX-Eudragit melt extrudates

CX was mixed with Eudragit 4155F at drug/polymer weight ratios of 1:9, 3:7, 1:1, 7:3 using a mortar and pestle for 2 minutes. The physical mixtures were extruded using a co-rotating twin screw extruder (Minilab, Thermo Electron Corporation, Germany), fitted with a round die of 5 mm diameter, at a screw speed of 100 rpm. The physical mixtures at 1:9, 3:7 and 1:1 ratios were extruded at three different temperatures 100, 140 and 170 °C, whereas the 7:3 ratio was only extruded at 170 °C. The cylindrical melt extrudates were milled and passed through a 355 μm sieve. Melt extrudates at 1:9, 3:7 and 1:1 ratios were also cut into tablets having a weight equivalent to 50 mg CX (500±2 mg, 167±2 mg and 100±2 mg for 1:9, 3:7 and 1:1 ratios, respectively). It was not possible to cut the melt extrudates of 7:3 ratio as tablets because of their high friability. All samples were kept in glass vials in a dessicator over silica gel at 20 °C. A suitable quantity of the physical mixture from each drug loading was kept for analysis to compare to corresponding extruded formulations.

5.2.3 Preparation of hot-melt extruded tablet formulations

The composition of each hot-melt extruded tablet formulation is summarized in Table 5.1. The materials were mixed together using a mortar and pestle for 2 minutes. In preparation of formulations A, B, C and D, Eudragit 4155F powder was pre-plasticized with TEC or DBS by pipeting the liquid plasticizer over the powder bed and mixing the polymer and plasticizer together using a mortar and pestle for 2 minutes, after pre-plasticization of the polymer, CX was added and mixed for 2
minutes with the pre-plasticized polymer. This powder mix was then sieved through a 355 μm sieve twice to ensure a homogeneous mix of all tablet ingredients. All prepared physical mixtures were extruded at a temperature of 140 °C and a screw speed of 100 rpm using a co-rotating twin-screw extruder (Minilab, Thermo Electron Corporation, Germany) fitted with a round die of 5 mm diameter. The produced rod extrudates were cut into tablets having a weight that is equivalent to 50 mg CX (167±2 mg) stored within glass vials in a dessicator over silica gel at 20 °C.

Table 5.1. Hot-melt extruded tablet formulations

<table>
<thead>
<tr>
<th>Composition (%)</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>CX</td>
<td>30</td>
</tr>
<tr>
<td>Eudragit 4155F</td>
<td>62.5</td>
</tr>
<tr>
<td>TEC</td>
<td>7.5</td>
</tr>
<tr>
<td>DBS</td>
<td>-</td>
</tr>
<tr>
<td>NaCl</td>
<td>-</td>
</tr>
<tr>
<td>MgCO₃</td>
<td>-</td>
</tr>
</tbody>
</table>
5.2.4 Preparation of an amorphous CX-Eudragit 4155F physical mixture

Amorphous CX was prepared by heating CX up to 170 °C for 2 minutes using a stainless steel beaker then rapidly quench cooling the sample in an ice bath. The generation of amorphous CX was confirmed using DSC. The prepared amorphous CX was subsequently mixed with Eudragit 4155F at drug/polymer weight ratio of 3:7 using a mortar and pestle.

5.2.5 Thermogravimetric Analysis (TGA)

TGA analyses were performed according to the method described in chapter 2, section 2.2.4. The TGA ramp test for all formulation components was performed at 10 °C/min from 20 to 500 °C.

5.2.6 Differential Scanning Calorimetry (DSC)

DSC was used to characterize the thermal properties of CX and Eudragit 4155F; drug/polymer miscibility; and the solid state properties of CX within the melt extrudates manufactured at different extrusion temperatures. DSC analyses were performed according to the method described in chapter 2, section 2.2.5. For glass transition (Tg) determination, samples were subjected to heat-cool-heat cycle from 0 to 200 °C at 10°C/min, to remove the thermal history. The Tg was calculated as the midpoint of the step transition in the plot of heat flow versus temperature in the second heat cycle.

5.2.6.1 Gordon-Taylor calculations

The theoretical Tg values for the CX-Eudragit 4155F binary systems were predicted using the Gordon–Taylor equation (equation 3.1). The true density (ρ) of amorphous CX and Eudragit 4155F were 1.3477±0.0003 and 1.2232±0.0003 g/cm³, respectively, measured using an AccPyc 1330 helium pycnometer (Micromeritics®) (Norcross, USA). The Tg values predicted from the Gordon-Taylor equation were subsequently compared to the Tg of the melt extrudates observed experimentally by DSC.
5.2.7 Powder X-ray Diffractometry (PXRD)

PXRD analyses were performed according to the method described in chapter 2, section 2.2.6.

5.2.8 Fourier Transform Infrared (FT-IR) Spectroscopy

FTIR analyses were performed according to the method described in chapter 2, section 2.2.8.

5.2.9 Fourier Transform Raman (FT-Raman) Spectroscopy

Raman spectroscopic analyses were performed according to the method described in chapter 2, section 2.2.9.

5.2.10 In vitro drug release studies

The in vitro drug dissolution profiles of the prepared hot-melt extruded tablet formulations were examined according to the USP paddle method (USP30, 2007). Samples equivalent to 50 mg of CX were added to the test fluid (pH 1.2) (1000 mL), containing 0.5% (w/v) SDS to provide sink conditions, for 2 h at a temperature of 37 ± 0.2 °C, then the test fluid was replaced by phosphate buffer of pH 6.8 (0.5% SDS) (1000 mL) for 4 h. The pH of the test fluid was subsequently adjusted to pH 7.4 by the addition of 2 N NaOH. The solution was stirred with a rotating paddle at 100 rpm. Samples of 5 ml were withdrawn from each vessel at predetermined time intervals (2, 4, 6, 8, 10, 12, 14, 16, 18, 24 hr), filtered through a cellulose acetate filter of 0.45 μm (Nalgene Labware, Rochester, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd, Oxford, UK) UV-VIS spectrophotometer at 255 nm and a standard calibration curve that was linear over the concentration range (2.85-17.1 μg/mL) at pH 1.2, (2.75-19.25 μg/mL) at pH 6.8, and (2.5-20 μg/mL) at pH 7.4. The percent of CX dissolved for each sample (n=3) was plotted versus time. No interference from SDS or any of the excipients used in the formulations on CX assay was found at 255 nm.
5.2.11 Accelerated stability study

Stability studies were conducted at 40°C and 75% RH. Samples of milled melt extrudates of CX-Eudragit 4155F binary system, extruded at 170 °C, and a physical mixture of amorphous CX with Eudragit 4155F at a drug/polymer ratio of 3:7 were placed in open glass vials stored at 40 °C inside a dessicator containing a saturated sodium chloride solution to generate the appropriate relative humidity (75% RH). Relative humidity inside the dessicator was recorded using a thermohygrometer. PXRD was used to test the stored samples for crystalline content after 5 days storage for the physical mixture samples, whereas milled extrudates were tested after 1, 3 and 6 months.

5.2.12 Statistical analysis

Two-tailed one sample t-test was used to compare the experimental Tg values of CX-Eudragit 4155F system determined by DSC versus the theoretical values predicted by Gordon-Taylor equation (α = 0.05). The effect of the formulation and extrusion temperature on the drug release of the hot-melt extruded tablets were statistically analyzed using a repeated measures one-way ANOVA. Individual differences in drug dissolution between formulations were statistically identified using Fischer’s PSLD test. In all cases p<0.05 denoted significance.
5.3 \textbf{RESULTS AND DISCUSSION}
5.3.1 Thermal stability of the formulation materials

The most important prerequisite for the eligibility of materials for HME is their thermal stability (Crowley *et al.*, 2007). A TGA ramp test is commonly used to test the thermal stability of the materials prior to HME (Bruce *et al.*, 2005, Schilling *et al.*, 2008, Zhu *et al.*, 2006a). TGA analysis was used to test the thermal stability of the formulation components used in this study. It was shown in chapter 4 that CX was thermally stable at a temperature of 170 °C, which was the highest temperature used in this study. Additionally, the thermal stability of the liquid plasticizers, TEC and DBS, were examined in chapter 3, section 3.3.1. A TGA ramp test was conducted on Eudragit 4155F, MgCO₃ and NaCl. Negligible mass loss (0.5-1.5%) was detected at 170 °C during the TGA ramp test. These results confirm the thermal stability of these materials at the processing temperatures used.

5.3.2 Thermal analysis of CX-Eudragit 4155F binary system

Thermal properties of amorphous and crystalline CX were characterized in chapter 4 (section 4.3.1). Table 5.2 presents the most important thermal events of CX, Eudragit 4155F, and melt extrudates generated from the DSC analyses. Figures 5.2, 5.3 and 5.4 show the DSC thermograms of CX-Eudragit 4155F physical mixtures and melt extrudates prepared at different extrusion temperatures. In this study, miscibility between CX and Eudragit 4155F was characterized using DSC (Forster *et al.*, 2001a). Small quantities of CX-Eudragit 4155F binary mixtures at drug/polymer ratios 1:9, 3:7 and 1:1 were prepared and analyzed using DSC. The first heating cycle of the DSC thermograms of these physical mixtures showed significant broadness in CX melting endotherm with a significant decrease in its enthalpy (Figures 5.2, 5.3 and 5.4). These DSC results suggest that a significant amount of CX was miscible with the softened polymer during the DSC heating scan (Crowley *et al.*, 2004a). After heating the physical mixtures above the melting point of CX and subsequent cooling at 10°C/min and then re-heating again, the CX-Eudragit 4155F system showed a single Tg between the Tg of the drug and the polymer, indicating the formation of a miscible system (single phase) (Lu and Zografi, 1998). These DSC results indicate complete miscibility between CX and Eudragit 4155F after heating the physical mixtures above the melting point of CX and subsequent cooling. Drug/polymer miscibility is a pre-requisite for formation of solid molecular dispersions (glass solutions) (Leuner and Dressman, 2000).
Physical mixtures of CX-Eudragit 4155F at 1:9, 3:7, 1:1 and 7:3 ratios were prepared and extruded successfully at a temperature of 170 °C, which is above the melting temperature of CX (163.2 ± 0.9 °C). The transparent melt extrudates were analyzed immediately after preparation by DSC. The DSC traces of the melt extrudates at 1:9, 3:7, and 1:1 ratios were devoid of a melting endotherm characteristic of crystalline CX (Figures 5.2, 5.3 and 5.4) suggesting the presence of CX in the amorphous form within the prepared melt extrudates (Crowley et al., 2007). It was difficult to make definite conclusions about the miscibility between CX and Eudragit 4155F within the melt extrudates due to the small endotherm accompanying the Tg observed in these DSC traces. This endotherm is most probably related to the endothermic relaxation of Eudragit 4155F which overlaps the Tg of amorphous CX (58.9 ± 0.2 °C). In order to remove the endothermic relaxation and hence to get more accurate predictions about the Tg of CX-Eudragit 4155F binary systems, a heat-cool-heat cycle was used for the hot-melt extruded samples, in which the first heating cycle involved heating the sample to 70 °C. A single Tg was observed in the second heating cycle between the Tg of amorphous CX and the Tg of the polymer (Figure 5.6, Table 5.2). The absence of CX melting endotherm and the presence of a single Tg situated between the Tg of amorphous drug and polymer suggests the formation of miscible system (single phase) in which CX was dispersed at the molecular level in the melt extrudates (Lu and Zografi, 1998, Forster et al., 2001a).
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Table 5.2 Thermal properties of celecoxib (CX), Eudragit 4155F and the melt extrudates.

<table>
<thead>
<tr>
<th></th>
<th>Tm (°C)</th>
<th>Tg (°C) exp</th>
<th>Tg (°C) theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib (CX)</td>
<td>163.2 ±0.9</td>
<td>58.9 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Eudragit 4155F</td>
<td></td>
<td>49.23±0.05</td>
<td></td>
</tr>
</tbody>
</table>

Eudragit 4155F HME @170°C

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Tm (°C)</th>
<th>Tg (°C) exp</th>
<th>Tg (°C) theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:9</td>
<td>51.3 ± 0.56</td>
<td>51.3</td>
<td></td>
</tr>
<tr>
<td>3:7</td>
<td>52.7 ± 0.42</td>
<td>54.8</td>
<td></td>
</tr>
<tr>
<td>1:1</td>
<td>55.1 ± 0.15</td>
<td>57.4</td>
<td></td>
</tr>
<tr>
<td>7:3</td>
<td>59.2 ± 0.22</td>
<td>59.0</td>
<td></td>
</tr>
</tbody>
</table>

Tm = melting endotherm temperature, Tg_exp = experimentally observed glass transition temperature, Tg_theory = calculated using the Gordon-Taylor equation, HME denotes hot melt extrudate, The values presented in the table are the average ± standard deviation of three replicates (n=3).

The DSC thermogram of 7:3 melt extrudates (first heating cycle) exhibited a Tg that was followed by cold crystallization, typical for amorphous CX, followed by a melting endotherm for the re-crystallized CX (Figure 5.5), whereas DSC traces of melt extrudates at 1:9, 3:7 and 1:1 ratios, prepared at 170 °C, were devoid of such cold crystallization (Figures 5.2, 5.3 and 5.4). These results suggest the ability of Eudragit 4155F to act as a re-crystallization inhibitor for amorphous CX during the DSC heating scan up to 50% (w/w) polymer level. Although CX-Eudragit 4155F melt extrudates had Tg values lower than the Tg of amorphous CX, Eudragit 4155F was able to stabilize the amorphous CX efficiently up to 50% polymer content during the DSC heating scan. This solid state stabilization effect by Eudragit 4155F on amorphous CX may be related to the increase in the local viscosity of amorphous CX as a result of the intimate mixing with Eudragit 4155F in the hot melt extruded solid dispersion. This increase in the viscosity of amorphous CX by Eudragit 4155F would result in suppression of molecular mobility of amorphous CX and hence prevent re-crystallization during the DSC heating ramp. The viscosity of the carrier is a very important factor that can play a significant role in prevention of amorphous drug re-crystallization (Breitenbach, 2002). The increase in the viscosity of amorphous solid dispersions can result in a decrease in the diffusion of amorphous drug molecules necessary to form a lattice (Van den Mooter, et al., 2001). Additionally, complete
miscibility of drug and polymer and the formation of solid dispersions where the drug is dispersed at the molecular level and may be protected by the polymeric matrix can result in efficient retardation of re-crystallization (Six et al., 2004).

Figure 5.2. DSC thermograms of CX-Eudragit 4155F physical mixture (PM) and hot-melt extrudates (HME) at 1:9 ratio extruded at different temperatures (the first heating run of a heat-cool-heat cycle).

Figure 5.3. DSC thermograms of CX-Eudragit 4155F physical mixture (PM) and hot-melt extrudates (HME) at 3:7 ratio extruded at different temperatures (the first heating run of a heat-cool-heat cycle).
Figure 5.4. DSC thermograms of CX-Eudragit 4155F physical mixture (PM) and hot-melt extrudates (HME) at 1:1 ratio extruded at different temperatures (the first heating run of a heat-cool-heat cycle).

Figure 5.5. DSC thermogram of CX-Eudragit 4155F melt extrudates (HME) (7:3 ratio) hot (the first heating run of a heat-cool-heat cycle).
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The Gordon-Taylor equation was originally derived for compatible polymer blends and it has been used successfully for small drug molecules (Matsumoto and Zografi, 1999; Van den Mooter et al., 2001; Damian et al., 2001; Chokshi et al., 2005, Forster et al., 2001c). The goodness of fit of experimental Tg data to the theoretically predicted data by Gordon-Taylor equation indicates the ideality of mixing of the two components (Gupta et al., 2005). In this case the free volume of the binary system is an additive property of the free volume of individual component which means that the cohesive intermolecular forces between individual molecules equal the adhesive forces between the unlike molecules (Van den Mooter et al., 2001; Six et al., 2004). Deviation from ideal behaviour signifies differences in the strength of intermolecular interactions between individual components and those of the binary system (Gupta et al., 2005). The Tg values of the melt extrudates determined experimentally from the DSC thermograms (the second heating cycle) were compared with the Tg values predicted theoretically using the Gordon-Taylor equation (Table 5.2, Figures 5.6 and 5.7). At 10% w/w CX content, the experimentally determined Tg values of CX-Eudragit 4155F were nearly similar to the Tg values predicted by the Gordon-Taylor equation suggesting that CX at this low level had no effect on the net free volume of the binary blend. Conversely, increasing CX content in the CX-Eudragit 4155F binary system to 30 and 50% w/w resulted in significant negative deviations from the ideal mixing of the two components. This non-ideality of mixing (negative deviations) at these midrange compositions may be attributed to a higher free volume of binary system from that possible on ideal mixing, due to the lower strength of interaction between CX and Eudragit 4155F than between individual components. Further increase in CX content to 70% w/w resulted in no significant differences between the experimental and theoretical Tg values suggesting that Eudragit 4155F at the concentration of 30% w/w may not have considerable increase in free volume of the binary blend. Similar observations have been reported previously in felodipine-HPMC and felodidine-HPMCAS binary systems that showed non-ideal mixing based on negative deviations on the theoretical Tg predicted by Gordon-Taylor equation at the midrange compositions suggesting weaker drug/polymer interactions comparing to drug/drug or polymer/polymer interactions (Konno et al., 2006).
Figure 5.6 DSC thermograms of Eudragit 4155F, CX-Eudragit 4155F hot melt extrudates (HME) prepared at 170°C (the second heating run of a heat-cool-heat cycle).

Figure 5.7 Phase diagram of celecoxib (CX) polymer binary system (CX-Eudragit 4155F). Symbols (■) represent (Tg) measured experimentally while symbols (◊) represent (Tg) predicted by using the Gordon-Taylor equation.
To study the effect of the extrusion temperature on the solid state properties of CX within the melt extrudates, HME for the physical mixtures at 1:9, 3:7 and 1:1 ratios were further extruded at 100 and 140 °C. Eudragit 4155F has a low Tg value (49.23±0.05 °C) and usually a temperature above the Tg of the polymer by 15-60°C is required for HME (Crowley et al., 2007). HME for CX-Eudragit 4155F binary mixtures was not possible below a temperature of 100°C due to the high melt viscosity inside the extruder. Transparent melt extrudates were observed after HME of a binary mixture at 1:9 ratio at temperatures of 100 and 140°. On the other hand, melt extrudates at a ratio of 3:7 were opaque when extruded at 100°C, whereas they were transparent when extruded at 140°C. Transparent melt extrudates is indicative of the formation of glass solutions (miscible system) (Forster et al., 2001b). Melt extrudates at a ratio of 1:1 extruded at 100 °C were white suggesting the presence of high crystalline CX content, whereas drug crystallinity reduced significantly when the 1:1 binary mixture was extruded at 140°C resulting in opaque melt extrudates. These initial results suggest that the solid state properties of CX within the melt extrudates were highly dependent on the drug loading level and extrusion temperature.

The solid state properties of the prepared melt extrudates were further characterized using DSC. The enthalpy (J/g) of the CX melting endotherm determined from the DSC thermograms (first heating cycle) of the physical mixtures and melt extrudates prepared at different extrusion temperatures are summarized in Table 5.3. The DSC traces of the physical mixtures at different drug loading levels (Figures 5.2, 5.3 and 5.4) showed a significant decrease in the enthalpy of CX melting endotherm (Table 5.3) comparing to CX as a result of the miscibility of CX in the softened polymer. Drug miscibility in a polymer carrier usually increases during HME as a result of the elevated temperatures, high pressure, and intense mixing provided by HME (Crowley et al., 2007). The DSC traces of all melt extrudates had a lower enthalpy associated with melting of CX compared to the corresponding physically mixed samples, indicating that the prepared melt extrudates contained a lower relative crystallinity content compared to corresponding physical mixtures (Table 5.3). The melting enthalpy of CX determined from the DSC traces of the melt extrudates showed that this value was highly dependent on the drug loading level and the extrusion temperature (Table 5.3). At a constant extrusion temperature, an increase in the CX enthalpy was observed as the drug loading level increased, whereas increasing
the extrusion temperature resulted in significant decrease in CX crystallinity at fixed loading. For example, for a drug/polymer ratio of 1:1, as the extrusion temperature increased, the enthalpy of the melting endotherm of CX decreased significantly from 25.44 ± 0.8 J/g in the samples extruded at 100 °C to 10.1 ± 1.10 J/g in the samples extruded at 140 °C indicating a significant decrease in CX crystallinity as extrusion temperature increased. Similar trends of decreasing drug crystallinity with increasing extrusion temperature were observed for the 3:7 melt extrudates. There was no evidence of a melting endotherm in the DSC traces of 3:7 samples extruded at 140 °C suggesting that there was no crystalline CX present after HME at 140 °C, whereas a small endotherm was evident (16.83 ± 0.49 J/g) at 100 °C. DSC traces of 1:9 melt extrudates were devoid of a CX melting endotherm at all extrusion temperatures. The presence of melting endotherms in physically mixed samples strengthened the argument that HME was capable of generating amorphous CX at defined drug loading levels and extrusion temperatures (Crowley et al., 2007).

Table 5.3. The enthalpy (J/g) of the melting endotherm of celecoxib (CX) in the physical mixtures (PM) and in the hot-melt extrudates (HME).

<table>
<thead>
<tr>
<th>Drug/Polymer ratio</th>
<th>1:9</th>
<th>3:7</th>
<th>1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CX*</td>
<td>8.4</td>
<td>25.2</td>
<td>42.0</td>
</tr>
<tr>
<td>PM</td>
<td>2.45 ± 1.0</td>
<td>16.83 ± 0.49</td>
<td>38.31 ± 1.95</td>
</tr>
<tr>
<td>HME-100°C</td>
<td>n/a</td>
<td>1.21 ± 0.63</td>
<td>25.44 ± 0.8</td>
</tr>
<tr>
<td>HME-140°C</td>
<td>n/a</td>
<td>n/a</td>
<td>10.1 ± 1.10</td>
</tr>
<tr>
<td>HME-170°C</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

* The enthalpy for the melting endotherm of CX calculated by multiplying the average enthalpy of melting endotherm of CX, from the DSC traces of pure CX samples (ΔH=84.0±4.9 g/J) (section 4.3.1), by the ratio of CX in the CX-Eudragit 4155F binary system.

n/a: No melting endotherm could be detected (amorphous CX).
5.3.3 Crystalline properties of hot-melt extrudates

PXRD patterns of CX melt extrudates manufactured at different extrusion temperatures and the corresponding physical mixtures at 1:9, 3:7 and 1:1 ratios are shown in Figures 5.8, 5.9 and 5.10, respectively. Figure 5.11 shows the PXRD pattern of 7:3 melt extrudates. The most characteristic peaks in the PXRD pattern of CX crystalline located at 20 angles of 15.0°, 16.0°, 19.6°, 21.5°, 22.3°, 23.4°, 25.3°, and 29.4°. PXRD diffraction patterns of the physically mixed samples containing crystalline CX showed the characteristic peaks of crystalline CX albeit with lower intensities due to the dilution effect of the polymer. Eudragit 4155F is an amorphous polymer so its PXRD pattern had a characteristic amorphous "halo". The PXRD patterns of melt extrudates at 1:9, 3:7, 1:1 and 7:3 ratios extruded at 170 °C were similar in their shape to the PXRD pattern of Eudragit 4155F indicating the lack of crystallinity content within these melt extrudates. Similar results were obtained for 1:9 and 3:7 melt extrudates prepared at a temperature of 140 °C and for 1:9 prepared at a temperature of 100 °C. The PXRD results were in good agreement with the DSC suggesting drug/polymer miscibility at similar temperatures and drug loadings.

PXRD patterns showed a similar trend to the DSC results in that the solid state properties of CX within the melt extrudates were highly dependent on the drug loading level and the extrusion temperature (Figures 5.8, 5.9 and 5.10). For example, CX-Eudragit 4155F binary mixtures extruded at 100 °C had solid state properties that were dependent on the drug loading level. The PXRD pattern of melt extrudates containing CX/PVP at a 1:9 ratio showed complete absence of crystallinity whereas small peaks corresponding to crystalline CX were observed in the PXRD pattern of melt extrudates at 3:7 ratio which increased significantly in intensity in the PXRD pattern of the 1:1 sample. Melt extrudates, produced at 140 °C, showed complete absence of characteristic crystal peaks for 1:9 and 3:7 ratios, whereas characteristic crystal peaks were observed in the PXRD pattern of the 1:1 ratio, but with much smaller intensity in comparison to the PXRD pattern at the same loading level extruded at 100 °C. These PXRD results confirmed that the miscibility between CX and Eudragit 4155F was highly dependent on the drug loading level and the extrusion temperature. The increase in the extrusion temperature resulted in higher drug/polymer miscibility as a result of the decrease in the melt viscosity inside the
extruder and hence better efficiency in mixing and distribution of CX within the Eudragit 4155F polymeric matrix (Crowley et al., 2004b). In addition, increasing extrusion temperature resulted in larger heat energy that can significantly aid disruption of the crystal lattice of CX making it miscible within Eudragit 4155F. It was reported that the crystallinity of nifedipine within PEO melt extrudates decreased significantly by increasing the extrusion temperature above 70°C. A complete absence of nifedipine crystallinity was noted at extrusion temperatures exceeding 120°C (Li et al., 2006).

Figure 5.8. PXRD patterns of crystalline CX, Eudragit 4155F, CX-Eudragit 4155F (1:9) ratio physical mixture (PM) and hot-melt extrudates (HME) prepared at different extrusion temperatures.
Figure 5.9. PXRD patterns of CX-Eudragit 4155F (3:7) ratio physical mixture (PM) and hot-melt extrudates (HME) prepared at different extrusion temperatures.

Figure 5.10. PXRD patterns of CX-Eudragit 4155F (1:1) ratio physical mixture (PM) and hot-melt extrudates (HME) prepared at different extrusion temperatures.
Figure 5.11. PXRD pattern of CX-Eudragit 4155F (7:3) ratio hot-melt extrudates (HME) manufactured at a temperature of 170 °C.

Accelerated stability studies were conducted on the milled melt extrudates, manufactured at 170 °C, stored at 40 °C and 75% RH conditions up to three months. PXRD results (Figure 5.12) showed that Eudragit 4155F, despite its low glass transition temperature (Tg), was able, at the 90% (w/w) level, to prevent amorphous CX from re-crystallizing within the melt extrudates for three months. Polymer concentration at 70% (w/w) provided an efficient stabilizing effect on amorphous CX without any re-crystallization for 2 months, whereas small crystal peaks characteristic of CX were detected after 3 months storage. Both 1:1 and 7:3 ratios containing 50 and 30% (w/w) polymer, respectively, showed evidence of crystallinity after 1 month storage that increased after 2 and 3 months storage. In general, the PXRD results of stored melt extrudates, showed that Eudragit 4155F was highly efficient in inhibiting re-crystallization of amorphous CX from the melt extrudates. This stabilizing effect was highly dependent on the polymer concentration in the melt extrudates. Although some re-crystallization occurred at polymer concentrations of 50 and 30 % (w/w) after 1 month storage still the crystal peaks observed in the PXRD patterns of the samples stored for three months were much lower in their number and intensities compared to the amorphous CX-Eudragit 4155F physical mixtures stored under the same
conditions for 5 days. The rapid re-crystallization of amorphous CX from the physical mixture may be related to the high molecular mobility of the amorphous form of CX at this high storage humidity and temperature and the lack of intimate mixing or intermolecular interaction between drug and polymer, which are important factors that have been shown to reduce molecular mobility and enhance physical stability (Van den Mooter et al., 2001; Taylor and Zografi, 1997). These results suggest that HME of Eudragit 4155F with CX enhanced significantly the physical stability of amorphous CX as a result of the formation of solid molecular dispersions through intimate mixing between the two components. The molecular dispersion of CX within the viscous Eudragit 4155F polymeric matrix has resulted in the suppression of the molecular mobility of amorphous CX. Addition of polymers to an amorphous drug, even at modest levels, may cause stabilization by increasing the local viscosity and hence impeding diffusion of drug molecules (Bhugra and Pikal, 2008, Breitenbach, 2002, Van den Mooter et al., 2001). It was shown that increasing Eudragit 4155F concentration from 30 to 90% (w/w) resulted in a significant increase in the physical stability of amorphous CX within the melt extrudates. The enhanced stability as a function of increasing polymer concentration suggests that Eudragit 4155F acted as a diluent increasing the viscosity of the binary system and decreasing the diffusion of amorphous CX molecules necessary to form a lattice (Bhugra and Pikal, 2008). The viscosity enhancement increases the kinetic barrier to nucleation of amorphous CX and hence slows the re-crystallization process (Bhugra and Pikal, 2008).
Figure 5.12. PXRD of CX-Eudragit 4155F hot-melt extrudates (HME), manufactured at 170°C, in comparison to amorphous CX-Eudragit 4155F physical mixture (PM) stored at (40°C, 75% RH). From bottom to top: CX amorphous-Eudragit 4155F (PM) after 5 days; HME (1:9) after 3 months; HME (3:7) after 2 and 3 months; HME (1:1) after 1, 2 and 3 months; HME (7:3) after 1, 2 and 3 months.
5.3.4 Drug/polymer interactions

FTIR and Raman spectroscopic studies were conducted in order to investigate the nature of intermolecular interactions formed between CX and Eudragit 4155F during HME. Eudragit 4155F contains a proton donor group (the hydroxyl of the carboxylic acid group) and two proton acceptor sites (the carbonyl group of the carboxylate and the carbonyl group of the carboxylic acid) (Jeffery, 1997). As was discussed in chapter 4 (section 4.3.3), CX has a proton donor group (the NH2 of the sulfonamide group) and proton accepting groups (SO2, CF3 and the two nitrogen atoms of the pyrazole ring) (Kaushal et al., 2008). As carboxylic acids are generally moderate proton donor and acceptor groups (Jeffrey, 1997) and due to the presence of many proton acceptor groups in CX molecules in addition to the presence of the two easily donated protons of the sulfonamide group (NH2) (Adsmond et al., 2001), there is a possibility of formation of new hydrogen bonding interactions between CX and Eudragit 4155F during HME.

FT-IR spectra of the melt extrudates, manufactured at 170 °C, were generated and compared with the FT-IR spectra of Eudragit 4155F and physically mixed samples of Eudragit 4155F with crystalline or amorphous CX. In the FT-IR spectrum of Eudragit 4155F, the stretching vibration band of the carboxylic acid of the polymer could not be detected because it was overlapped by the stretching vibration band of the carboxylate group of Eudragit 4155F, which was located at 1734 cm⁻¹ in the FT-IR spectra of Eudragit 4155F and the melt extrudates without any significant changes. Due to this overlapping it was not possible to detect any changes in the stretching vibration of the carbonyl group of carboxylic acid of Eudragit 4155F in the melt extrudates. In general, there were not any significant changes in the FT-IR spectra of the melt extrudates when compared to the FT-IR spectra of physical mixtures containing amorphous CX. Figure 5.13 shows the FTIR spectra (3000-4000 cm⁻¹) region of CX-Eudragit melt extrudates at 3:7 ratio, the corresponding physical mixtures of crystalline or amorphous CX with Eudragit 4155F and the FTIR spectrum of Eudragit 4155F. The FT-IR spectrum of physically mixed samples containing crystalline CX showed clearly the doublet bands of the (NH2) of the sulfonamide group of CX, while they were not present in the FT-IR spectra of the melt extrudates and the physical mixture containing amorphous CX. The FTIR spectrum of
amorphous CX showed a significant broadness in the doublet bands of (NH$_2$) group of CX comparing to crystalline CX (section 4.3.3) (Kaushal et al., 2008). The absence of these doublet bands associated with the NH$_2$ group in the spectra of melt extrudates may be attributed to the broadness of these bands as a result of the presence of CX as an amorphous form within the melt extrudates and due to overlapping from the broad band of the hydroxyl group of the carboxylic acid of Eudragit 4155F. These findings made the detection of any change in these doublet bands in the melt extrudates very difficult. Although FT-IR was efficient in characterizing the solid state properties of CX in the melt extrudates (amorphous), it was not sufficient to prove evidence for the presence of any sort of intermolecular interactions between the two components. Thus Raman spectroscopic studies were conducted in an attempt to further examine the binary systems that were manufactured using HME.

![Figure 5.13. FT-IR spectra (3000-4000 cm$^{-1}$) of Eudragit 4155F, CX-Eudragit 4155F hot melt extrudates (HME) and physical mixtures (PM).](image)
Figure 5.14 shows the characteristic peaks of CX in the Raman spectra (1100-1700 cm\(^{-1}\) region) for the melt extrudates at drug/polymer ratio of 3:7 in comparison to the Raman spectra of the corresponding physically mixed samples containing amorphous or crystalline CX. Raman spectra generated for the melt extrudates, extruded at 170 °C, generally were similar to the Raman spectrum of physically mixed samples of amorphous CX with Eudragit 4155F due to the presence of CX in an amorphous form within these melt extrudates. These results suggest the efficiency of Raman spectroscopy in characterizing the solid state properties of CX within the melt extrudates.

Figure 5.14. Raman spectra (1100-1700 cm\(^{-1}\) region) of CX-Eudragit 4155F melt extrudates (3:7) ratio and the corresponding physical mixtures of amorphous and crystalline celecoxib (CX) with Eudragit 4155F.
To characterize the presence of any intermolecular interactions between CX and Eudragit 4155F, Raman spectra of the melt extrudates were compared to the Raman spectra of physically mixed samples of amorphous CX with Eudragit 4155F. A significant shift in the position of the stretching vibration band of the sulfonyl (SO$_2$) group to 1163 cm$^{-1}$ has been observed in the Raman spectra of the melt extrudates, whereas it was located at 1155 cm$^{-1}$ in the Raman spectra of physically mixed samples (Figure 5.15). Previously it has been shown that the oxygen atom of the sulfonamide group in amorphous CX was involved in a stronger interaction with the NH$_2$ group than in crystalline CX resulting in downward shift (chapter 4, section 4.3.3) (Kuashal et al., 2008). The significant shift to higher frequency in the stretching vibration band of the sulfonyl group in the melt extrudates may be attributed to the formation of new weaker hydrogen bonding between the sulfonyl group of CX and the hydroxyl group of the carboxylic acid of Eudragit 4155F. Another possibility for this significant upward shift may be related to the formation of new stronger hydrogen bonding interaction between the carbonyl group of Eudragit 4155F and the NH$_2$ group of CX in preference to the existing hydrogen bonding with the sulfonyl group in amorphous CX. It has been reported that the carbonyl group is a much stronger proton acceptor than the sulfonyl group (Adsmond, 2001). Similar findings were observed in the Raman spectra of the CX-PVP melt extrudates in comparison to physically mixed samples of amorphous CX with PVP (chapter 4, section 4.3.3). Gupta and Bansal (2005) suggest the formation of strong hydrogen bonding interactions between the NH$_2$ group of CX and the carbonyl group of N-methyl-2-pyrrolidone in a CX-NMP binary system. It was not possible to confirm the exact reason for the upward shifting in the stretching band of the sulfonyl group of CX in the melt extrudates particularly given that there were not any significant changes detected in the peak of the carbonyl group of Eudragit 4155F located at 1733 cm$^{-1}$ in the spectra of melt extrudates and physically mixed samples containing amorphous CX.
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5.3.5 In vitro drug release studies

5.3.5.1 Effect of extrusion temperature

Figures 5.16, 5.17 and 5.18 show the drug dissolution profiles of CX-Eudragit 4155F hot-melt extruded tablets prepared at different extrusion temperatures and ratios. CX-Eudragit hot melt extruded tablets showed negligible drug release (0.27-1.32 %) after 2 h at pH 1.2. Less than 19 % drug release was observed from the tablets after 4 h at pH 6.8 with a percentage drug release range of 3.22-18.52% depending on the drug/polymer ratio and the extrusion temperature. Statistically significant differences \((P<0.0001)\) were observed between the percentage drug release from hot-melt extruded tablets at a ratio of 1:9 prepared at 170 °C (3.2±1.01 %) compared to tablets extruded at 100 °C at 1:1 ratio (18.52±0.89 %) after 4 h at pH 6.8. These results may be attributed to the amount of polymer present within the tablets and the extrusion temperature. The higher the polymer concentration within the hot-melt extruded tablets, the lower percentage drug release from the tablets at pH 6.8. Eudragit 4155F is an anionic polymer with pH dependent solubility and only soluble at pH above 7, so increasing the polymer concentration in the tablets resulted in a decrease in the drug release rate at pH 6.8. A significant decrease in indomethacin
release has been observed with increasing Eudragit EPO, only soluble at pH below 5, concentration in solid dispersions at pH 6.8 (Chokshi et al., 2008). Higher extrusion temperatures resulted in a lowering of melt viscosity during the HME and hence melt extrudates of greater density were produced which had slower drug release (Crowley et al., 2004b). The drug dissolution results obtained in this chapter at pH 1.2 and 6.8 showed that HME of CX using Eudragit 4155F as a polymeric matrix was efficient in releasing CX to in-vitro simulated colon medium (pH 7.4). It was reported that tablets manufactured by HME composed of Eudragit S100, a pH dependent polymer which is soluble at pH values exceeding 7, was used efficiently to release 5-aminosalicylic acid to in-vitro simulated colon medium (pH 7.4) (Bruce et al., 2005). These efficient colon drug delivery systems containing solid dispersions of CX may result in improving the chemoprevention effect of CX against colorectal cancer. A fast release microsphere system containing solid dispersions preparation of hydroxycamptothecin (HCPT) coated with Eudragit S100 for colon delivery have been shown to result in a greater colonic cancer inhibition rate (Lu and Zhang, 2006).

Drug dissolution profiles from the hot-melt extruded tablets at pH 7.4 were also highly dependent on the extrusion temperature. In general, at a constant drug/polymer ratio, as the extrusion temperature increased, there was a decrease in the drug dissolution rate (Figures 5.16, 5.17 and 5.18). For example, at a drug/polymer ratio of 1:9 (Figure 5.16), the percentage drug release achieved was 56.36±2.19 and 82.1±3.39 % after 6 and 12 hr, respectively, from the tablets extruded at 100 °C. The percentage drug release was decreased to 51.73±0.79 % (p = 0.0099) and 78.13±0.51 % (p = 0.0633) after 6 and 12 h, respectively, when the tablets were extruded at higher temperature (140°C). The percentage drug release was decreased more significantly when the tablets were extruded at 170°C achieving a percentage drug release of only 27.7±1.25 % and 53.07±1.38 % after 6 and 12 h, respectively, (p <0.0001 in all cases). Similarly decreasing drug release rate was observed as temperature increased with the other drug/polymer ratios (Figures 5.17 and 5.18). The dependency of drug release on the extrusion temperature may be attributed to the decrease in the melt viscosity of the drug/polymer melt as the extrusion temperature increased resulting in increased miscibility between CX and Eudragit 4155F during the extrusion and hence more dense extrudates of lower porosity. The increase in the density of the hot-melt extruded tablets would decrease the penetration rate of the
dissolution medium through the matrix leading to slower drug release rate. It was reported that tablets prepared by HME have slower drug release rates than those prepared by traditional methods due to a lowering of matrix porosity (Crowley et al., 2004b). Furthermore, it has been reported that thermal treatment of amorphous polymers may result in a decrease of the free volume between polymer chains (Follonier et al., 1995). Guaifenesin release from ethylcellulose polymeric matrix was reduced when it was extruded at a higher extrusion temperature due to the decrease of tablet porosity (Crowley et al., 2004b).

![Figure 5.16. Dissolution profiles of CX-Eudragit 4155F binary system of 1:9 (w/w) extruded at different temperatures. Each point represents the mean ± standard deviation, n = 3, and in all cases the COV was < 10%.](image-url)
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Figure 5.17. Dissolution profiles of CX-Eudragit 4155F binary system of 3:7 (w/w) extruded at different temperatures. Each point represents the mean ± standard deviation, \( n = 3 \), and in all cases the COV was < 10%.

Figure 5.18. Dissolution profiles of CX-Eudragit 4155F binary system of 1:1 (w/w) extruded at different temperatures. Each point represents the mean ± standard deviation, \( n = 3 \), and in all cases the COV was < 10%.
5.3.5.2 Effect of plasticizer on drug release

The effect of plasticizer type and concentration on drug release properties of the melt extruded tablets were studied. Two different liquid plasticizers: triethyl citrate (TEC), a water-soluble plasticizer, and dibutyl sebacate (DBS), a water-insoluble plasticizer were used in formulations A, B, C and D at two different concentrations 7.5% and 15% (w/w) Table 5.1. The drug release profiles of these formulations were compared to the drug release profiles of reference tablets, which were the melt extruded tablets at drug/polymer ratio of 3:7 that had the same drug loading (30% w/w) and tablet weight (167±2 mg) and extruded at same temperature (140 °C) (Figure 5.19). The resultant drug release profiles were highly dependent on the type and concentration of plasticizer used. Negligible percentage drug release was obtained from hot-melt extruded tablets of formulations A, B, C and D after 2 h at pH 1.2 (0.11-1.48%). After 4 h at pH 6.8, the percentage drug release was in the range of 5.17-16.99%, which was dependent on the plasticizer type and its concentration. The highest percentage drug release (16.99±0.89 %) was obtained from tablets of formulation B (15% w/w, TEC), whereas the lowest percentage drug release (5.17±0.34 %) was obtained from tablets of formulation C (15.0 % w/w, DBS). For comparison, the reference tablets showed a percentage drug release of 9.64±0.37 % after 4 h at pH 6.8. These results indicate that HME of these formulations was still efficient in releasing CX to in-vitro simulated colon medium.

There was no significant increase in percentage drug release after 6 and 12 h at pH 7.4 from tablets of formulation A (7.5% w/w, TEC), which showed (50.43±1.04 %) (p = 0.139) and (77.39±0.85 %) (p = 0.0754) after 6 and 12 h, respectively, compared to reference tablets which showed percentage drug release of 48.83±1.3 % and 75.52±1.66 % after 6 and 12 h, respectively. Increasing TEC concentration up to 15% (w/w) showed a significant enhancement in percentage drug release 57.33±1.1 % and 93.31±1.29 % after 6 h and 12 h, respectively, (p <0.0001 in all cases) compared to the tablets of formulation A (7.5% w/w, TEC) and the reference tablets. As TEC is a water-soluble plasticizer, it has a tendency to leach from the tablets during dissolution forming channels through the polymeric matrix facilitating the dissolution of the drug. Similar effects have been observed for TEC in a study of the release of 5-aminosalicylic from Eudragit S100 hot melt extruded tablets (Bruce et al., 2005).
Conversely, significant decrease in percentage drug release was observed when DBS was used at two different concentrations 7.5 and 15% (w/w). At a DBS concentration of 7.5% (w/w) (formulation C), the percentage drug release decreased significantly to (31.20±1.54 %) and (45.61±0.87 %) after 6 and 12 h, respectively (p<0.0001 in all cases) compared to the reference tablets. Increasing DBS concentration up to 15% (w/w) (formulation D) resulted in a further significant decrease in the drug release rate 15.7±0.77 % and 32.32±0.89 % after 6 and 12 h, respectively (p<0.0001 in all cases). The significant decrease in drug release from tablets containing DBS may be attributed to the lipophilicity of DBS which prevented the plasticizer from leaching out from the extruded tablets hence decreases the permeability of the extruded tablets and the penetration rate of the dissolution medium through the polymeric matrix. Additionally, shrinkage of the melt extruded tablets was observed during dissolution, which may be attributed to the retention of DBS within the melt extrudates and the resultant low permeability of the aqueous medium. A significant decrease in theophylline release from pellets coated with ethyl cellulose using DBS as a plasticizer has been previously reported by Frohoff-Hülsmann et al (1999). The decrease in theophylline release was attributed to the decrease in the permeability of the coating due to the lipophilicity of DBS which remained intact during dissolution resulting in a significant decrease in the free volume between the polymer chains and hence shrinkage of the coating (Frohoff-Hülsmann et al., 1999).
Figure 5.19. The effect of plasticizer type and amount on drug release profiles of CX-Eudragit 4155F hot-melt extruded tablets. Each point represents the mean ± standard deviation, $n = 3$, and in all cases the COV was < 10%.

5.3.5.3 Effect of alkali salts on drug release

The effect of alkali salts on the drug release profiles of CX from Eudragit 4155F polymeric matrix prepared by HME was studied. A water-soluble salt, sodium chloride (NaCl), and a water-insoluble salt, MgCO₃, at two different concentrations 7.5 and 15% (w/w) (formulations E, F, G and H) were used (Table 5.1). Drug release profile of CX-Eudragit 4155F melt-extruded tablets at 3:7 ratio that had the same drug loading (30% w/w) and tablet weight (167±2 mg) and were extruded at same extrusion temperature (140 °C) was used as a reference. Drug dissolution profiles of hot-melt extruded tablets containing alkali salts compared to the reference tablets are shown in Figure 5.20. The percentage drug release that has been occurred from formulations E, F, G and H after 2 h at pH 1.2 were in the range of 2.01-2.77 %, while the percentage drug release from these formulations after 4 h at pH 6.8 were in the range of 12.34-17.58%. These results suggest that these formulations containing these alkali salts still efficient in delivering CX into the in-vitro simulated colonic medium of pH 7.4.
At pH 7.4, there was a significant increase in drug release rate from formulations containing MgCO₃ in comparison to the drug release rate from the reference tablets. Formulation G (7.5% w/w, MgCO₃) showed a significant increase in the percentage drug release (57.56±0.46 %) and (83.63±0.8 %) after 6 and 12 h, respectively, \((p<0.0001\) in all cases) compared to the reference tablets which showed (48.83±1.3 %) and (75.52±1.66 %) after 6 and 12 h, respectively. Increasing MgCO₃ concentration up to 15% w/w (formulation H) resulted in a significant increase in the percentage drug release (61.87±0.66 %) and (88.20±0.74 %) after 6 and 12 h, respectively, \((p<0.0001\) in all cases) compared to the tablets of formulation G (7.5 % w/w, MgCO₃). This significant increase in the percentage drug release achieved by increasing MgCO₃ concentration may be attributed to the greater effect of MgCO₃ at higher concentration to increase the microenvironment pH of the Eudragit 4155F polymeric matrix, resulting in greater ionization of the polymer and higher polymer erosion and hence higher drug release.

Tablets of formulations (E and F) containing 7.5 and 15% (w/w) NaCl, respectively showed a lower percentage drug release comparing to the corresponding tablets containing MgCO₃. There was no significant increase in percentage drug release from tablets of formulation E (7.5% w/w, NaCl) (47.78±1.18 %) \((p = 0.2937)\) and (75.88±0.78 %) \((p = 0.7307)\) after 6 and 12 h, respectively, compared to the percentage drug release from the reference tablets. A slight increase in the percentage drug release was achieved by increasing NaCl concentration up to 15% w/w (formulation F), which showed a percentage drug release of 50.90±0.83 % \((p = 0.0143)\) and 78.26±1.05 % \((p = 0.0545)\) after 6 and 12 h, respectively, compared to the tablets of formulation D (7.5% w/w, NaCl).

A statistically significant increase in percentage drug release has been observed for tablets containing MgCO₃ in comparison to the corresponding NaCl concentration after 6 h and 12 h \((p<0.0001\) in all cases). This significant increase in the drug release rate using MgCO₃ may be attributed to the lower aqueous solubility of MgCO₃. This lower aqueous solubility of MgCO₃ allowed it to be retained within the polymeric matrix for longer time than NaCl which has very high aqueous solubility and released so rapidly from the matrix resulted in too short retention time of NaCl inside the matrix to provide an efficient alkaline micro-environment pH
during dissolution. Schilling et al. (2008) reported that citric acid monohydrate was inefficient in producing an acidic pH microenvironment due to its very rapid release rate from Eudragit® RS PO matrix. Although the high aqueous solubility of NaCl may result in pore formation within the polymer matrix, NaCl was not efficient in enhancing the drug release rate from the polymeric matrix. This finding may be attributed to that the ability of NaCl to improve drug diffusion by pore formation did not exceed the pore forming capacity of CX itself during dissolution under sink conditions. It was reported that formulations containing pore forming agents e.g. sucrose, NaCl, PEG 3350 were inefficient in increasing diltiazem HCl release rate from Eudragit RS PO as a result of the less efficiency of these pore forming agents comparing to the pore forming efficiency of the drug during dissolution under sink conditions (Schilling et al., 2008). The longer retention time of MgCO₃ within the polymeric matrix as a result of its low aqueous solubility enabled it to be in close contact with Eudragit 4155F for longer period of time than NaCl and hence resulted in higher efficiency in increasing the pH microenvironment of Eudragit 4155F polymeric matrix. This increase in the microenvironment pH of Eudragit 4155F matrix resulted in a greater ionization for its free carboxylic groups and hence a faster matrix erosion and drug release from the polymeric matrix. It was reported that the addition of water-soluble salts of weak acids (sodium carbonate and sodium citrate) failed to achieve pH-independent release for 8-Prenynaringenin (8-PN), a weakly acidic drug with a pH dependent solubility, whereas the addition of water-insoluble salts of a strong base (magnesium hydroxide) significantly increased the 8-PN release in 0.1 N HCl resulting in drug release profiles at pH 1 almost overlapped with the drug release profiles at pH 6.8. This pH-independent release for 8-PN from the mini tablet matrix was attributed to the ability of magnesium hydroxide to remain in the matrix tablet during drug release as a result of its low aqueous solubility generating high pH-values within the mini matrix tablets over the entire dissolution period (Riis et al., 2007).
Figure 5.20. The effect of alkali salt type and amount on drug release profiles of CX-Eudragit 4155F hot-melt extruded tablets. Each point represents the mean ± standard deviation, $n = 3$, and in all cases the COV was $< 10\%$. 

![Graph showing drug release profiles](image)
5.4 CONCLUSIONS
HME technology was efficient in manufacturing hot-melt extruded tablets that may act as colon targeted delivery systems for CX using Eudragit 4155F as a polymeric matrix. Thermal analysis using DSC and PXRD showed that the solid state properties of CX within the hot melt extruded solid dispersions were highly dependent on the melt-extrusion temperature and drug loading. Increasing the melt extrusion temperature resulted in a significant decrease in drug crystallinity. DSC and PXRD confirmed the formation of solid molecular dispersions within the CX-Eudragit 4155F melt extrudates at drug/polymer ratios (1:9, 3:7, 1:1 and 7:3) prepared at a temperature of 170°C.

Despite the low glass transition temperature of Eudragit 4155F, the binary CX-Eudragit 4155F systems were efficient in stabilizing amorphous CX under accelerated conditions. This polymer stabilization effect was dependent on the polymer concentration in the melt extrudates. Increasing polymer concentration resulted in a greater stabilization effect for amorphous CX. This effect may be attributed to the intimate mixing between the two components within the melt extrudates due to the formation of solid molecular dispersions. The increase in the local viscosity of amorphous CX due to the presence of Eudragit 4155F was considered the most dominant mechanism resulting in enhanced physical stability. The significant negative deviations on the theoretical Tg predicted by Gordon-Taylor equation in the midrange compositions of CX:Eudragit 4155F (3:7 and 1:1 w/w) suggested the formation of non-ideal mixing in these systems in which the intermolecular interactions between CX and Eudragit 4155F were weaker than the interactions between the individual components. Spectroscopic techniques (FTIR and Raman) were efficient in characterizing the solid state properties within the melt extrudates. FTIR was not sufficient to provide information about drug/polymer interaction within the melt extrudates, whereas Raman spectroscopy confirmed the presence of such drug/polymer interactions.

In vitro drug release studies, in sink conditions, for hot-melt extruded tablets containing CX-Eudragit binary system showed that the polymeric matrix composed of Eudragit 4155F was efficient in releasing CX at pH values representative of the colon. The drug release from the extruded tablets was highly dependent on the melt-extrusion temperature. An increase in melt-extrusion temperature resulted in slower
drug release rates as a result of increasing the drug/polymer miscibility and hence producing more dense melt extrudates with lower porosity. Functional excipients used in this study e.g liquid plasticizers and alkali salts acted efficiently as drug release modifiers but maintained the efficiency of the polymeric matrix to act as an efficient colonic drug delivery system. These efficient hot melt extruded solid dispersions formulations designed for the delivery of CX to colon may result in significant enhancement in the chemoprevention effects of CX against colorectal polyps.
COMPARISON OF POLYVINPYRROLIDONE AND EUDRAGIT 4155F AS CARRIERS FOR CELECOXIB HOT-MELT EXTRUDED SOLID DISPERSIONS
6.1 \textbf{INTRODUCTION}
Amorphous drug forms have received considerable attention because they represent an energetic solid state of a material (Figure 6.1), and thus should provide the biggest advantage in terms of solubility and bioavailability (Hancock and Zografi, 1997). Generation of amorphous (glass) drug forms using solid dispersions is highly attractive for enhancing the dissolution rate of BCS class II drugs, which have limited oral bioavailability as a result of their low aqueous solubility (Leuner and Dressman, 2002; Serajuddin, 1999). Several research groups have demonstrated the viability of HME in manufacturing solid molecular dispersions (Forster et al., 2001b; Breitenbach, 2003; Patterson et al., 2007; Chockshi et al., 2005). The advantages of HME (chapter 1, section 1.3.3) make this technology more attractive than other traditional methods used in manufacturing solid dispersions e.g. solvent evaporation methods and other hot methods.

The pharmaceutical advantage of amorphous drug forms having higher solubility and hence oral bioavailability compared to crystalline forms (Chiou and Riegelman, 1971) is compromised by their poor thermodynamic stability. The low physical stability of amorphous drug forms of high free energy (Figure 6.1), and the spontaneous tendency for the amorphous form to re-crystallize often negates the advantage of high solubility (Hancock and Zografi, 1997; Serajuddin, 1999).

Carriers used in manufacturing amorphous solid dispersions can play critical roles in enhancing physical stability by reducing molecular mobility through the formation of secondary interactions. The rational use of polymeric carriers is very important in stabilizing amorphous drugs. In this respect, the fundamental physicochemical parameters that have been shown to be important include molecular weight, glass transition temperature (Van den Mooter et al., 2001), miscibility (Marsac et al., 2006b) or hydrogen bonding interactions with the drug (Forster et al., 2001b; Taylor and Zografi, 1997, Aso et al., 2002).
To achieve the full benefit of solid dispersion technology it is necessary to stabilize a supersaturated concentration of drug during dissolution. Polymers used to manufacture amorphous solid dispersions can act as stabilizing agents to maintain supersaturated levels achieved by dissolution of amorphous drug forms (Gupta et al., 2004, Tanno et al., 2004). Additionally, amorphous solid dispersions may generate higher solution concentrations than those achieved with the pure amorphous drug (Gupta et al., 2004) suggesting that certain polymers may act as solubilising agents through complex formation with the drug during dissolution achieving drug concentrations higher than the solubility of pure amorphous drug (Usui et al., 1997; Loftsson et al., 1996).

It is important to define the solubility of an amorphous drug and to draw a comparison to the equilibrium solubility of the crystalline form in order to determine the significance of increasing the solubility of the drug and hence give an approximation about its oral bioavailability. In addition, the effect of the polymer used in preparing amorphous solid dispersions can be investigated more properly if the solubility of the amorphous drug is known. If the drug concentrations achieved from amorphous solid dispersions are greater than the solubility of the amorphous drug, this may suggest that the polymer has a solubilising effect on the drug resulting
in achieving drug concentrations greater than what can be achieved only from the
solubility of amorphous drug (Gupta et al., 2004). Similar or drug concentrations
lower than the solubility of the amorphous form is indicative that the polymer may
only have a stabilizing effect on supersaturated drug levels without any solubilising
effect.

Due to the rapid re-crystallization of the amorphous drug, it is very difficult to
measure the solubility enhancement experimentally. This has often resulted in
difficulty in estimating the solubility and hence the bioavailability improvement that
can be achieved through use of amorphous drug forms. It has been previously
reported that experimental determination of the solubility of amorphous drugs is
extremely difficult due to their rapid re-crystallization upon exposure to dissolution
media resulting in experimental solubility values that were considerably lower than
the true value for these drugs (Hancock and Parks, 2000, Konno et al., 2008)

The theoretical solubility of an amorphous form is often predicted to be much
higher than the experimentally observed value. A simple thermodynamic approach
based on the difference in the free energy between the amorphous and crystalline
forms of a drug has been used to estimate the theoretical maximum solubility
improvement that may be achieved using amorphous drugs (Hancock and Parks,
2000). In this study, the theoretical relative solubilities of various crystalline and
amorphous forms of several drugs were predicted and compared with the
experimentally determined values at various temperatures. The solubility advantage of
amorphous forms compared to the most stable crystalline form was predicted to be in
the range from 10 to 1600 fold. The observed solubility advantage was considerably
less than predicted and was attributed to the difficulty in determining the solubility of
amorphous materials under true equilibrium conditions due to re-crystallization from
solution. It was concluded that simple thermodynamic predictions can provide a
useful indication of the theoretical maximum solubility advantage for amorphous
drugs.
Recently, the effect of polymeric carriers in stabilizing dissolution of amorphous solid dispersions has received considerable attention. It has been reported that the combination of Eudragit EPO and PVP/VA64 provided amorphous solid dispersions of itraconazole with significant increase in dissolution rate and maximum solubility compared to solid dispersions manufactured using PVP/VA64 alone. These solid dispersions did not show any drug precipitation during the dissolution, whereas amorphous solid dispersions of Eudragit EPO alone showed very rapid drug release (80% after 30 min) with re-crystallization after 2 h. Thus, the combination of two polymers provided a solid dispersion with good dissolution properties and improved physical stability compared with the mono-polymeric solid dispersions of itraconazole (Six et al., 2004). In another study using itraconazole, the addition of Carbopol® 974P to a Eudragit® L 100-55 carrier prolonged the supersaturated level of itraconazole following an acidic-to neutral pH transition. Furthermore, a five-fold improvement in itraconazole absorption at a concentration of 20% Carbopol® 974P versus Eudragit® L 100-55 was also observed (Miller et al. 2008). It was shown that the addition of 5% Eudragit NE to felodipine solid dispersions prepared by HME technology using Eudragit® E100 was efficient in inhibiting felodipine re-crystallization from solid dispersions and in maintaining supersaturated levels of felodipine. The stabilizing effect of Eudragit® NE at this concentration was attributed to the change in the local structure of Eudragit® E 100 in a non-additive way through the addition of minor amounts of Eudragit® NE (Nollenberger et al. 2008). Furthermore, in another study on felodipine, the dissolution behavior of amorphous solid dispersions prepared with different polymers were compared by Konno et al. (2008). Solid dispersions formulated with hydroxypropyl methylcellulose acetate succinate (HPMCAS) were found to result in solutions with the highest extent of supersaturation, whereas hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP) were less effective. In addition, in the same study in experiments conducted to examine the inhibitory effect of felodipine re-crystallization from supersaturated solutions, HPMCAS was the most efficient polymer examined and maintained the highest level of supersaturation for the longest duration, whereas PVP was found to be the least effective crystallization inhibitor. In this study, no justification was presented by the authors to explain the differences in the ability of the polymers tested to maintain different levels of supersaturation.
6.1.1 Aims and objectives

It was shown in chapter 5 that Eudragit 4155F acted efficiently as a polymeric matrix for colon targeting using CX as a model drug. Eudragit 4155F was efficient as a solid state stabilizer for amorphous CX after HME especially at a high polymer concentration. The physico-chemical properties of solid dispersions containing poorly soluble drugs using Eudragit 4155F as a carrier have not been investigated in the literature. As was discussed in chapter 5, colonic medium is characterized by lower motility and a fluid content with higher viscosity in comparison to the upper part of GI tract (Takaya et al., 1998). These conditions in the colonic medium may be problematic in terms of solubilisation especially for poorly soluble drugs delivered for the local treatment of colonic diseases or for systemic absorption through the colon. Solubilisation problems may significantly affect the therapeutic and clinical performance of these drugs. Consequently there is a need to deliver these drugs in formulations that can increase their solubility in colonic fluid and hence improve therapeutic response. As an example, improved clinical outcomes have been achieved by delivering hydroxyl-camptothecin (HCPT), an anticancer drug used for treatment of colon cancer, as a solid dispersion (Lu and Zhang, 2006). In this chapter, the effect of Eudragit 4155F on the dissolution properties of solid molecular dispersions containing CX, a poorly soluble drug, which is used for chemoprevention of colorectal cancer, was evaluated and compared with corresponding solid molecular dispersions containing PVP.

The principle aims and objectives of this study are summarized as follows:

- Evaluate the ability of Eudragit 4155F to act as a solubilising agent for CX and to compare this to PVP.
- Evaluate the in vitro dissolution properties of CX-Eudragit 4155F solid molecular dispersions compared to CX-PVP solid molecular dispersions under non-sink conditions.
- To examine the inhibitory effects of Eudragit 4155F and PVP against CX crystallization from supersaturated solution.
- To investigate drug/polymer interactions using solution $^1$H nuclear magnetic resonance (NMR) analytical technique.
- Find a correlation between the information given by solution NMR and the in vitro drug release profiles observed for the solid molecular dispersions.
6.2 MATERIALS AND METHODS
6.2.1 Materials

Celecoxib (CX) was a kind gift from Hikma Pharmaceuticals Co. (Amman, Jordan), Eudragit 4155F was donated by Degussa Corp. Röhm GmbH (Dermstadt, Germany). Polyvinylpyrrolidone K25 (molecular weight 24,000 Daltons) (PVP K25) was purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). All other chemicals used were purchased from BDH Laboratory supplies (Poole, Dorset, England) and were of Analar grade or equivalent quality.

6.2.2 Preparation of melt extrudates

CX was mixed with PVP or Eudragit 4155F at drug/polymer weight ratios of 1:9, 3:7, 1:1, and 7:3 using a mortar and pestle for 2 minutes. The prepared physical mixtures were extruded using a co-rotating twin-screw extruder (Mini lab. Thermo Electron Corporation, Germany) at a screw speed of 100 rpm. HME for all prepared CX-Eudragit mixtures was performed at a temperature of 170 °C. CX-PVP physical mixtures containing 1:1 and 7:3 weight ratios were extruded at a temperature of 150 °C, whereas 3:7 weight ratio was extruded at 170 °C. CX-PVP physical mixture 1:9 weight ratio could not be extruded. Melt extrudates were milled, passed through a 355 μm sieve and stored within glass vials in a dessicator over silica gel at 20 °C. A suitable quantity of the physical mixture from each drug loading was kept for analysis to compare to corresponding extruded formulations.

6.2.3 Preparation of an amorphous CX-Eudragit 4155F physical mixture

Amorphous CX was prepared by heating CX up to 170 °C for 2 minutes using a stainless steel beaker followed by quench cooling in an ice bath. The generation of amorphous CX was confirmed using DSC (as described in chapter 4 section 4.2.6). The prepared amorphous CX was subsequently mixed with Eudragit 4155F at drug/polymer weight ratio of 1:9 using a mortar and pestle.
6.2.4 Effect of polymer on the solubility of CX

The equilibrium solubility of crystalline CX was measured at 37 ± 0.2°C using phosphate buffer (pH 7.4) (PBS 7.4) in the presence or absence of the polymer of interest. 50 mg of crystalline CX was dispersed in 500 mL of the test fluid, in which 500 and 1000 mg of polymer (PVP or Eudragit 4155F) had been previously dissolved, leading to a final polymer concentration of 1.0 and 2.0 mg/mL. The solution was stirred with a rotating paddle at 100 rpm. Samples of 5 ml were withdrawn from each vessel at predetermined time intervals (24, 48 and 72 hr), filtered through a cellulose acetate filter of 0.45 μm (Nalgene Labware, Rochester, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd, Oxford, UK) UV-VIS spectrophotometer at 250 nm and a standard calibration curve that was linear over the concentration range (2.5-20 μg/mL). No interference from the PVP or Eudragit 4155F on the CX assay was found at 250 nm. The solubility of CX in PBS 7.4 in the absence of polymer was also evaluated. All measurements were carried out in triplicate.

6.2.5 Inhibitory effect of polymers on re-crystallization from supersaturated solutions

The inhibitory effect of PVP and Eudragit 4155F against crystallization of CX from supersaturated solutions was evaluated. A concentrated solution of CX in methanol was prepared by dissolving 25 mg of crystalline CX in a small volume of methanol (5 mL) and then added to 500 mL of PBS 7.4 at a temperature of 37 ± 0.2 °C to generate initial drug solution concentration of 50 (μg/mL) in PBS 7.4, in which 500, 117, 50 or 20 mg of polymer (PVP or Eudragit 4155F) had been previously dissolved leading to a final polymer concentration of 1000, 234, 100 or 43 (μg/mL), respectively. The solution was stirred with a rotating paddle at 100 rpm. Samples of 5 mL were taken from each vessel at predetermined time intervals at (5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 min) filtered through a cellulose acetate filter of 0.45 μm (Nalgene Labware, Rochester, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd, Oxford, UK) UV-VIS spectrophotometer at 250 nm and a standard calibration curve that was linear over the concentration range (2.5-20 μg/mL). The percent of CX dissolved for each formula (n = 3) was plotted versus
time. No interference from the PVP or Eudragit 4155F on the CX assay was found at 250 nm. The same experiments were performed in PBS 7.4 in the absence of any polymer and the results were compared to the results with PBS 7.4 in which the polymer had been dissolved.

6.2.6 In vitro dissolution studies of solid dispersions

The in vitro drug dissolution properties of solid dispersions and physical mixtures were examined according to the USP paddle method (USP 30, 2007). Samples equivalent to 50 mg of CX were added to 500 mL of PBS 7.4 at a temperature of 37 ± 0.2°C. The solution was stirred with a rotating paddle at 100 rpm. For the physical mixtures at a drug/polymer weight ratio of 1:9 containing either crystalline or amorphous CX with Eudragit 4155F and all solid dispersions, samples of 5 mL were withdrawn from each vessel at predetermined time intervals at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 1440 (24 h), 2880 (48 h), and 4320 minutes (72 h), whereas 5 mL samples were taken only at 24, 48 and 72 h time intervals for the other physical mixtures (PMs). All samples taken were filtered through a cellulose acetate filter of 0.45 µm (Nalgene Labware, Rochester, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd, Oxford, UK) UV-VIS spectrophotometer at 250 nm and a standard calibration curve that was linear over the concentration range (2.5-20 µg/mL). The percent of CX dissolved for each formula (n = 3) was plotted versus time. No interference from the PVP or Eudragit 4155F on the CX assay was found at 250 nm. In addition to the test fluid of pH 7.4, some experiments were performed on Eudragit 4155F solid dispersions using a test fluid of pH 9.4.

6.2.7 Solution nuclear magnetic resonance (solution NMR)

$^1$H NMR spectra were recorded on a Bruker DRX spectrometer (Switzerland) operating at 500.13 MHZ, and using a 5-mm multinuclear probe with π/2 pulses of 6.0 µs. The measurements were performed at 27°C in deuterochloroform (CDCl$_3$) solution and with tetramethylsilane (TMS) as internal standard.
6.2.8 Statistical analysis

The effect of polymer type and concentration on the equilibrium solubility of CX and on the drug release from the solid dispersions were statistically analyzed. Individual differences in drug dissolution between formulations were statistically identified using Fischer's PSID test. In all cases $p<0.05$ denoted significance. Additionally, similar statistical methods were used to analyze the ability of the polymer to inhibit drug crystallization from supersaturated solutions generated by concentrated drug solutions.
6.3 RESULTS AND DISCUSSION
6.3.1 Thermal stability of CX and the polymers

The thermal stability of CX, PVP and Eudragit 4155F were investigated using thermogravimetric analysis (TGA) in previous chapters (4 and 5), and the results showed that the drug and the polymers were thermally stable in terms of volatile degradants at 170 °C, which was the highest extrusion temperature used in this study.

6.3.2 Solid state characterization of the melt extrudates

The solid state properties of CX within PVP or Eudragit 4155F melt extrudates were characterized in previous chapters (4 and 5). It was confirmed by DSC and PXRD techniques that CX was present as solid molecular dispersions within the melt extrudates manufactured at all drug/polymer weight ratios and the extrusion conditions used in this study. It was shown that both polymers acted efficiently as stabilizers for CX in the solid state under accelerated storage conditions (40°C and 75% RH) in comparison to the corresponding physical mixtures containing amorphous CX. PVP was more efficient in inhibiting re-crystallization of CX than Eudragit 4155F in the solid state. The dissolution properties of these solid molecular dispersions discussed in following sections of this chapter.

6.3.3 Equilibrium solubility of CX in the presence of polymers

To examine the solubilising effect of PVP or Eudragit 4155F on CX, the equilibrium solubility of crystalline CX in PBS 7.4 containing 1.0 and 2.0 mg/mL of each of the polymers was determined and compared to the equilibrium solubility in a PBS 7.4 containing no polymer. The polymer concentrations of 1.0 and 2.0 mg/mL in PBS 7.4 far exceed the concentrations that can be produced by dissolving PVP from the solid dispersions, while a polymer concentration of 1.0 mg/mL is equivalent to the concentration that can be produced by dissolving Eudragit 4155F from the solid dispersions at a drug/polymer ratio of 1:9. All solutions, with and without added polymer, reached equilibrium after 48 h which was confirmed by the similarity in the solution concentrations measured after 48 and 72 h.
Table 6.1 shows the equilibrium solubility of CX measured after 72 h in PBS 7.4. As shown in Table 6.1, the equilibrium solubility of CX did not change significantly \((P = 0.7759)\) when PVP was present in PBS 7.4 at 1.0 and 2.0 mg/mL, while there was a significant increase \((p<0.0001)\) in the equilibrium solubility of CX when Eudragit 4155F was present in PBS 7.4 at 1.0 mg/mL (1.32-fold) and 2.0 mg/mL (2.63-fold). These results indicate that Eudragit 4155F has a solubilising effect on CX, whereas PVP has no such effect.

Carriers used to prepare solid dispersions may increase the solubility of drugs by forming weakly soluble complexes similar to those reported for cyclodextrins (Craig, 2002). The solubility of the drug in concentrated solutions of the carrier can determine whether the mechanism of dissolution from the solid dispersions is either carrier or drug controlled release (Craig, 2002). It has been reported in previous studies that the solubility of poorly soluble drugs were enhanced significantly in aqueous solutions in which hydrophilic carriers had been dissolved as a result of the formation of weakly soluble complexes due to drug/polymer interactions (electrostatic interactions or hydrogen bonding). For example, the solubility of rofecoxib and ibuprofen have been enhanced significantly in aqueous solutions in which PVP or PEG was dissolved (Cirri et al., 2004, Ahuja et al., 2007). Sethia and Squilante (2004) found a linear correlation between the solubility of carbamazepine and the concentration of PVP in aqueous solutions as a result of formation of a soluble complex. Conversely, in studying the effect of different polymers (HPMCAS, HPMC and PVP) on the solubility of felodipine, no significant increase in the solubility of the drug was achieved in test fluids of pH 6.8 in which the polymers had been dissolved indicating no solubilising effects by the polymers on felodipine (Konno et al., 2008).
Table 6.1 Equilibrium solubility of celecoxib (CX) in PBS pH 7.4 with or without dissolved polymer at 37 ± 0.2 °C.

<table>
<thead>
<tr>
<th>Added polymer (mg/mL)</th>
<th>Equilibrium Solubility of celecoxib (CX) in pH 7.4 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without polymer</td>
<td>1.58 (0.04)</td>
</tr>
<tr>
<td>PVP</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>1.57 (0.03)</td>
</tr>
<tr>
<td>2.0</td>
<td>1.59 (0.03)</td>
</tr>
<tr>
<td>Eudragit 4155F</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>2.08 (0.09)</td>
</tr>
<tr>
<td>2.0</td>
<td>4.12 (0.08)</td>
</tr>
</tbody>
</table>

Values in parentheses represent the standard deviations, n=3.

6.3.4 Inhibitory effect of polymers on re-crystallization from supersaturated solutions

Amorphous materials have a higher apparent solubility than their crystalline counterparts as a result of their disordered structure and the presence of only short range intermolecular interactions in contrast to their crystalline counterparts where the lattice has to be disrupted for the material to dissolve (Hancock and Zografi, 1997). The theoretical pharmaceutical advantage of amorphous materials is compromised by physical instability (re-crystallization) during dissolution. This leads to difficulty in terms of measuring the practical solubility of amorphous materials experimentally, and hence in providing predictable in vivo/in vitro correlation (Hancock and Parks, 2000).

The model developed by Parks and co-workers (equation 6.1) (Parks et al., 1928, 1934), which was applied pharmaceutically for the first time by Hancock and Parks (2000), was used to study and predict the relative solubility of the amorphous and crystalline forms of CX based on the difference in their free energy (ΔG) where the solubility ratio (Sₐ/Sₜ) of the two forms (amorphous = a; crystalline = c) at a certain temperature is directly related to the free energy difference (ΔG) between these two forms.
\[ \Delta G = RT \ln \frac{S_{amorphous}}{S_{crystalline}} \]  

Equation 6.1

where \( R \) is the gas constant, \( T \) is the temperature, and \( S \) is the solubility.

The Hoffman equation can be used to calculate the free energy difference between the amorphous and crystalline forms if the melting temperature \( (T_m) \) and the heat of fusion \( (\Delta H_f) \) of the crystalline form are known as shown in equation 6.2.

\[ \Delta G = \frac{\Delta H_f (T_m - T) T}{T_m^2} \]  

Equation 6.2

The Hoffman equation was used successfully by Marsac et al. (2006a) to give good estimates for the free energy difference between amorphous and crystalline felodipine. Using equation 6.2, it can be deduced that the higher the melting point and heat of fusion of a compound, the greater the solubility enhancement that may be achieved through utilization of an amorphous drug form.

By applying equations 6.1 and 6.2, the solubility ratio \( (S^a/S^c) \) of the amorphous (a) and crystalline (c) forms of CX at pH 7.4 and at 37 °C was predicted to be approximately 12, which means that the theoretical solubility of amorphous CX is 12 times that of crystalline CX. The equilibrium solubility of crystalline CX was 1.58 (µg/mL) (Table 6.1), so the apparent solubility of amorphous CX was estimated to be 19.0 (µg/mL).

The inhibitory effects of the polymers (PVP or Eudragit 4155F) against crystallization of CX from a supersaturated solution were evaluated by adding a concentrated solution of CX to PBS 7.4, in which the polymers had been dissolved and monitoring the solution concentration as a function of time. Figures 6.2 and 6.3 show results obtained at different polymer solution concentrations, 1000, 234, 100 and 43 (µg/mL), which correspond to the polymer solution concentration that would be produced by total dissolution of solid dispersions containing 90, 70, 50 and 30% of polymer, respectively. The results obtained for PBS 7.4 without any polymer
dissolved is shown for reference. PVP concentration of 1000 μg/mL was tested just for comparison and does not correspond to any solid dispersions as CX-PVP physical mixture at drug/polymer ratio of 1:9 could not be extruded without the addition of a plasticizer which might affect storage stability and/or the drug release properties. In these experiments, the initial solution concentration of CX that was generated by dilution of the concentrated methanol drug solution was 50 μg/mL. As shown in Figure 6.2, in the absence of polymer, the CX concentration decreased rapidly reaching 14.07±0.19 μg/mL after 5 minutes and then continued to decrease until achieving a plateau after 45 minutes with concentrations close to the equilibrium solubility of crystalline CX. This rapid decrease in CX concentration suggested that CX re-crystallized from a supersaturated concentration immediately. Therefore dissolution of amorphous CX will result in rapid re-crystallization and loss of any pharmaceutical advantage of solid form engineering. These results are in good agreement with data presented by Konno et al. (2008) wherein felodipine rapidly re-crystallized in the absence of polymeric excipients.

For PVP (Figure 6.2), the initial drug concentration measured after 5 minutes of adding the concentrated solution of CX was significantly higher in PBS 7.4 containing 1000 μg/mL of the polymer than the other lower concentrations (p<0.0001). In addition, statistically less significant differences were observed between the CX concentrations achieved after 5 minutes at PBS 7.4 containing 243 μg/mL and the other lower PVP concentrations 100 μg/mL (p = 0.0042) and 43 μg/mL (p = 0.0015). Conversely, there was no significant difference between the drug concentrations achieved in PBS 7.4 containing PVP concentrations of 100 and 43 μg/mL (p = 0.5413). The initial CX concentration measured after 5 minutes was 30.54±0.09 μg/mL, for 1000 μg/mL PVP concentration, whereas it was 22.8±0.13, 21.41±0.06 and 21.15±0.13 μg/mL for PVP concentrations of 234, 100 and 43 μg/mL, respectively. These results indicate that there was highly significant inhibition effect by PVP against re-crystallization of CX from concentrated solution after 5 minutes at all PVP concentrations used compared to the results of PBS 7.4 in which no polymer had been dissolved (p<0.0001 in all cases).
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Figure 6.2. Inhibitory effects of PVP on re-crystallization of a supersaturated solution of celecoxib (CX) (50µg/mL) at PBS pH 7.4 containing 1000 (■), 234 (□), 100 (▲), 43 (▲) (µg/mL) of PVP and in the absence of any polymer(s) (○). The data shown is the average of three replicates and in all cases the COV was < 6.

After 6 h, CX reached concentrations of 14.75±0.26, 13.63±0.15, 13.03±0.15 and 9.27±0.07 µg/mL in PBS 7.4 in which PVP was present in concentrations of 1000, 234, 100 and 43 µg/mL, respectively. The differences in drug concentration achieved after 6 h were statistically significant (p<0.0001) for all PVP concentrations with the exception of PVP at concentrations of 243 and 100 µg/mL (p = 0.0008). These results indicate that the stabilizing effect of PVP against re-crystallization of CX from concentrated drug solutions was dependent on PVP concentrations present in PBS 7.4. It was shown that the inhibitory effects of HPMC, HPC and PVP on the precipitation rate of a water-insoluble drug, RS-8359, from supersaturated levels generated by concentrated drug solution was dependent on the polymers concentrations in the PBS pH 6.8 (Usui et al., 1997). In this study, it was shown that the precipitation rate of RS-8359 decreased with increasing polymer concentrations. The achieved CX concentrations after 6 h were significantly higher than the equilibrium solubility of crystalline CX (1.58 µg/mL) (p<0.0001 in all cases), indicating the ability of PVP to maintain supersaturated levels of CX efficiently at all concentrations used. The crystallization rate of CX at a PVP concentration of 1000 µg/mL was the fastest among all other PVP concentrations especially during the first 2 h, 5.05 µg/mL.h⁻¹ (p<0.0001), calculated within the time period between 5 and 120
minutes, comparing to the re-crystallization rates (2.47, 3.24, 3.89 μg/ml.h⁻¹) of other lower PVP concentrations of 243, 100 and 43 μg/mL respectively. These results may be attributed to the greatest supersaturated level achieved after 5 minutes. Since the nucleation rate is strongly dependent on the degree of supersaturation, the nucleation rate is expected to be higher in the more concentrated solution, leading to the creation of more particles and hence a more extensive initial decrease in the concentration (Konno et al., 2008). Greater supersaturated levels result in a greater tendency to nucleate and precipitate from solution as it is thermodynamically less stable. Thus the PVP concentrations that had greater supersaturated levels will re-crystallize faster until the system decreases in concentration to a level where nucleation is no longer spontaneous (Konno et al., 2008).

In contrast to PVP, Eudragit 4155F did not show any inhibition of re-crystallization of CX from supersaturated solution in PBS 7.4 in which Eudragit 4155F had been dissolved at different concentrations (Figure 6.3). There were statistically significant differences in CX concentrations achieved after 5 minutes at PBS 7.4 in which Eudragit 4155F had been dissolved compared to PBS 7.4 with no polymer (p<0.0001). This significantly greater initial CX concentrations at PBS 7.4 containing Eudragit 4155F may be attributed to the viscosity effect from Eudragit 4155F polymer in the dissolution medium that may result in some delay in CX re-crystallization (Usui et al., 1997). Thereafter CX concentrations at PBS 7.4 containing Eudragit 4155F rapidly diminish until a plateau is achieved after 45 minutes with concentrations close to the equilibrium solubility of crystalline CX (Figure 6.3). The re-crystallization rates determined by comparison of drug solubility at 5 minutes and 20 minutes for CX were 0.968, 1.05, 0.970, 0.918 μg/mL.min⁻¹, calculated in a time period between 5 and 20 minutes, in PBS 7.4 containing Eudragit 4155F concentrations at 1000, 243, 100 and 43 μg/mL, respectively, were significantly higher than in PBS 7.4 without any polymer (0.711 μg/mL.min⁻¹) (p<0.0001 in all cases). This significantly faster re-crystallization rates may be attributed to the greater supersaturated solutions achieved by Eudragit 4155F solutions after 5 minutes which resulted in a greater tendency for the drug to nucleate and precipitate from solution until a concentration wherein nucleation is no longer spontaneous was achieved (Konno et al., 2008). PBS 7.4 containing Eudragit 4155F and without any polymer
achieved a plateau after 45 minutes with concentrations close to the equilibrium solubility of crystalline CX.

These results suggest that PVP was significantly more efficient in stabilizing CX from concentrated solution when added to PBS 7.4 than Eudragit 4155F, which did not show any considerable stabilization effect. These dissolution results suggest that PVP has a potential to act as an efficient stabilizer during dissolution of amorphous solid dispersions.

![Graph](image)

**Figure 6.3.** Inhibitory effects of Eudragit 4155F on the recrystallization of a supersaturated solution of celecoxib (CX) (50μg/mL) at PBS pH 7.4 containing 1000 (■), 234 (□), 100 (▲), 43 (△) (μg/mL) of Eudragit 4155F and in the absence of any polymer(s) (○). The data shown is the average of three replicates and in all cases the COV was < 6.

The mechanism of stabilization against crystallization from supersaturated drug solutions is not fully understood (Konno et al., 2008). The differences in the ability of PVP and Eudragit 4155F to stabilize the supersaturated levels of CX may be attributed to the differences in the type of drug/polymer interactions that may be generated in solution, which have been characterized using solution NMR in the following sections of this chapter. It was shown that small amounts of water-soluble polymers HPMC, HPC and PVP dissolved in PBS 6.8, have inhibitory effects on the precipitation of RS-8359, a water insoluble compound, from supersaturated solutions.
generated by concentrated drug solutions (Usui et al., 1997). Although all the polymers decreased the precipitation rates of RS-8359, the stabilization effect of HPMC and HPC, which were very similar, was greater than that of PVP. It was concluded that the inhibitory effects of the polymers on the precipitation of the drug were caused not only by the increase in viscosity but also by interaction between the drug and the polymers particularly given that the precipitates collected following dissolution showed incorporation of the polymer with the drug. SEM images showed that the precipitates from PBS solutions containing the polymers were agglomerates. The crystal habit of the drug was different in the precipitates in comparison to the polymer-free PBS solution (plate-shaped crystals) and from the PBS containing the polymer (agglomerates). Furthermore, XRD confirmed that peak intensity of the agglomerates was significantly different from the precipitate obtained from the polymer-free solution. This change in the crystal habit was caused by adhesion of the polymer on the growing plane of the crystal. In a further study conducted to examine the efficiency of different polymers to maintain supersaturated levels of felodipine, HPMCAS was the most efficient polymer examined and maintained the highest level of supersaturation for the longest duration, whereas PVP was found to be the least effective crystallization inhibitor (Konno et al., 2008). According to the authors the reasons behind these differences are unclear. Goddeeris et al. (2008) tested the efficiency of different concentrations of many hydrophilic polymers, PEG, PVP, PVP/VA, HPMC, poloxamer, Kollicoat and Eudragit E100, in inhibiting the crystallization of UC 781, an anti-HIV drug, from supersaturated levels generated from concentrated methanol drug solutions. It was shown that Eudragit E100 was the most efficient polymer in stabilizing the supersaturated levels of the drug. This stabilizing effect of Eudragit E100 on the drug was concentration dependent. The authors did not give any explanation for such stabilization by Eudragit E100 and they used these experiments as a screening study to select the best stabilizer for the dissolution from UC-781-TPGS using solid dispersions formulations.
6.3.5 In vitro dissolution study of drug/polymer binary systems

6.3.5.1 CX-PVP binary system

Figure 6.4 shows the dissolution profiles of CX from solid dispersions containing various amounts of PVP. Table 6.2 shows the CX concentrations (μg/mL) generated from CX-PVP and CX-Eudragit 4155F solid dispersions and physical mixtures after 24, 48 and 72 h. Dissolution from PVP solid dispersions resulted in higher solution concentrations than the equilibrium solubility of crystalline CX (1.58 μg/mL), indicating that supersaturated solutions were generated. Figure 6.4 shows that the supersaturation levels generated increased with increasing polymer amount in the solid dispersion. The drug dissolution profiles from PVP solid dispersions at a drug/polymer weight ratio of 3:7 showed a concentration of 20.52±0.13 μg/mL after 5 h that remained stable for up to 72 h achieving a final concentration of 21.46±0.35 μg/mL (Table 6.2). The stabilized solution concentrations of CX were close to the theoretical solubility of amorphous CX (19.0 μg/mL), predicted from equation (6.1), which means that PVP at 70% (w/w) inhibited the entire amount of CX that was generated from the dissolution of the amorphous solid dispersions and it was able at this concentration to maintain these supersaturated levels of CX without any re-crystallization. The drug solution concentrations from dissolution of amorphous solid dispersions containing 50% (w/w) PVP achieved a plateau after 5 h with a drug concentration of 17.03±0.21 μg/mL. Thereafter a decrease in drug concentration was observed as a result of re-crystallization with a concentration of 13.61±0.46 μg/mL being achieved after 72 h. CX-PVP amorphous solid dispersions containing drug:polymer ratio of 7:3 achieved a plateau after 4 h with a drug concentration of 10.93±0.17 μg/mL. Again a small but significant decrease of drug concentration was observed (7.41±0.08 μg/mL) after 72 h as a result of CX re-crystallization.
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Figure 6.4. Dissolution profiles of celecoxib (CX) (100 μg/mL) from solid dispersions with different amounts of PVP; 70% (∆), 50% (■) and 30% (▲) in PBS 7.4. The data shown is the average of three replicates and in all cases the COV was < 8.

These dissolution results indicate that PVP solid dispersions at all concentrations maintained supersaturated levels of CX achieving drug concentrations significantly higher than the equilibrium solubility of crystalline CX (1.58 μg/mL) for the whole period of the dissolution study (72 h) (p < 0.0001 in all cases). By comparing the dissolution results obtained from PVP solid dispersions to the theoretical equilibrium solubility of amorphous CX predicted from equation 6.1 (19 μg/mL), it can be deduced that PVP was highly efficient as a stabilizer for amorphous CX.

The ability of PVP to act as solubilizer for CX was further evaluated by determining the equilibrium solubility of CX in PBS pH 7.4 from physically mixed samples containing crystalline CX. There was no significant difference in the equilibrium solubility of CX obtained from the physically mixed samples of CX/PVP 3:7 (p = 0.4248), 1:1 (p = 0.5206) and 7:3 (p = 0.8559) ratios compared to the crystalline CX (Table 6.2). These results confirmed that there was not any significant solubilising effect of PVP on CX during dissolution from the solid dispersions and the supersaturated levels achieved were related to the solubility of the amorphous drug and the stabilizing effect by PVP that was efficient in maintaining supersaturation.
These results were in agreement with the results obtained from experiments examining the inhibitory effects of PVP against CX crystallization from supersaturated solution illustrating the significant stabilizing effect of PVP.

The supersaturated concentrations achieved by the dissolution of amorphous solid dispersions were mostly related to the stabilizing effect of PVP during the dissolution given that there was no observed solubilising effect for PVP on CX from physically mixed samples. These results were confirmed by the fact that the concentrations achieved from PVP amorphous solid dispersions did not exceed the theoretical solubility of amorphous CX. It was reported by Gupta et al. (2004) that amorphous CX re-crystallized so rapidly during dissolution in water resulting in concentrations that were very close to the equilibrium solubility of crystalline CX. The rapid re-crystallization of amorphous CX during dissolution may be attributed to the powerful plasticization effect by water molecules once amorphous CX contacts the aqueous medium, particularly given the low Tg values of amorphous CX. PVP has a high Tg value (154.6±0.7 °C) and because of the miscibility with CX it formed solid molecular dispersions (single phase) that had a single Tg between the Tg of the two components (section 4.3.1) (Lu and Zografi, 1998). The increased Tg of the solid molecular dispersions may result in greater physical stability during dissolution (Gupta et al., 2004). Thus the greater supersaturated levels generated for CX with increasing PVP concentration may be attributed to the higher Tg values for CX-PVP system at higher PVP concentration. This anti-plasticization effect by PVP on amorphous CX may enable CX to stay in an amorphous form for longer periods of time especially given that it is in intimate contact with PVP during the dissolution process. Thus the intimate contact between CX and PVP achievable in solid molecular dispersions during HME resulting in greater supersaturated levels of CX (Gupta et al., 2004, Konno et al., 2008). The ability of PVP to maintain such supersaturated levels achieved by amorphous CX may be attributed to drug/polymer interactions formed in solution (Usui et al., 1997), which were investigated further in the following sections of this chapter using solution NMR.
Table 6.2. Solubility of various formulations of celecoxib (CX)/polymer binary system in BPS pH 7.4 after 24, 48 and 72 h at 37 ± 0.2 °C.

<table>
<thead>
<tr>
<th>Formulation with PVP (drug:polymer)</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3:7) PM</td>
<td>1.28 (0.09)</td>
<td>1.62 (0.08)</td>
<td>1.64 (0.11)</td>
</tr>
<tr>
<td>(1:1) PM</td>
<td>1.32 (0.08)</td>
<td>1.58 (0.12)</td>
<td>1.62 (0.09)</td>
</tr>
<tr>
<td>(7:3) PM</td>
<td>0.94 (0.05)</td>
<td>1.56 (0.07)</td>
<td>1.59 (0.08)</td>
</tr>
<tr>
<td>(3:7) SD</td>
<td>21.36 (0.14)</td>
<td>21.69 (0.14)</td>
<td>21.92 (0.07)</td>
</tr>
<tr>
<td>(1:1) SD</td>
<td>14.37 (0.7)</td>
<td>13.91 (0.5)</td>
<td>13.61 (0.5)</td>
</tr>
<tr>
<td>(7:3) SD</td>
<td>8.23 (0.06)</td>
<td>7.82 (0.09)</td>
<td>7.41 (0.08)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Formulation with Eudragit 4155F (drug:polymer)</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1:9) PM</td>
<td>62.33 (1.24)</td>
<td>63.56 (1.35)</td>
<td>64.25 (1.04)</td>
</tr>
<tr>
<td>(3:7) PM</td>
<td>6.67 (0.20)</td>
<td>7.01 (0.04)</td>
<td>7.04 (0.02)</td>
</tr>
<tr>
<td>(1:1) PM</td>
<td>3.04 (0.02)</td>
<td>4.88 (0.09)</td>
<td>5.05 (0.03)</td>
</tr>
<tr>
<td>(7:3) PM</td>
<td>1.60 (0.07)</td>
<td>2.46 (0.01)</td>
<td>2.47 (0.01)</td>
</tr>
<tr>
<td>(1:9) SD</td>
<td>100.73 (0.14)</td>
<td>100.59 (0.31)</td>
<td>100.67 (0.30)</td>
</tr>
<tr>
<td>(3:7) SD</td>
<td>71.61 (0.32)</td>
<td>56.09 (0.19)</td>
<td>53.37 (0.28)</td>
</tr>
<tr>
<td>(1:1) SD</td>
<td>12.30 (0.30)</td>
<td>13.24 (0.21)</td>
<td>10.96 (0.16)</td>
</tr>
<tr>
<td>(7:3) SD</td>
<td>4.77 (0.02)</td>
<td>4.67 (0.04)</td>
<td>4.65 (0.04)</td>
</tr>
</tbody>
</table>

Values in parentheses represent the standard deviations.
PM denotes to the physical mixtures containing crystalline CX.

6.3.5.2 CX-Eudragit 4155F binary system

From Table 6.2, the CX concentrations achieved from the solid dispersions in PBS 7.4 after 72 h were significantly higher than the equilibrium solubility of crystalline CX (1.58±0.04 µg/mL) (p<0.0001 in all cases), indicating that supersaturated levels of CX were generated and maintained for up to 72 h at all drug/polymer ratios. The supersaturated levels generated by dissolution of the amorphous solid dispersions were mostly attributed to the solubilising effect by Eudragit 4155F on CX given that the drug concentrations achieved by 1:9 and 3:7 ratios after 72 h (100.67±0.3 and 53.37±0.3 µg/mL, respectively) far exceeded the theoretical solubility of amorphous CX (19 µg/mL).

The solubilising effect of Eudragit 4155F on crystalline CX was shown in section 6.3.3 wherein there was a significant increase in the equilibrium solubility of crystalline CX in PBS 7.4 in which Eudragit 4155F had been previously dissolved at concentrations of 1.0 and 2.0 mg/mL (Table 6.1). This solubilising effect was further confirmed by the significant increase in the equilibrium solubility of crystalline CX
achieved from physically mixed samples containing crystalline CX (Table 6.2) \((p<0.0001\text{ in all cases})\). The equilibrium solubility of crystalline CX increased with increasing polymer concentration in the physical mixtures, indicating the ability of Eudragit 4155F to act as an efficient solubilizer for CX. The equilibrium solubility of crystalline CX in PBS 7.4 achieved from the physical mixture samples at drug/polymer weight ratio of 1:9, which produced a polymer concentration of 1.0 mg/mL, were 31.0 and 15.5-fold greater than the equilibrium solubility achieved from the PBS 7.4 in which Eudragit 4155F had been previously dissolved at a polymer concentration of 1.0 and 2.0 mg/mL, respectively. These results may be attributed to the increased contact of CX with Eudragit 4155F during dissolution from the physical mixture samples, enhancing the solubilising effect of the polymer. Moreover, the dissolution properties of CX were further increased from solid dispersions of Eudragit 4155F in comparison to the corresponding physical mixture samples (Table 6.2). These results were mostly attributed to the intimate contact between CX and Eudragit 4155F achievable in solid molecular dispersions during HME resulting in greater enhancement of CX dissolution.

Figure 6.5 shows the dissolution profiles of CX from solid dispersions containing various amounts of Eudragit 4155F in PBS 7.4. Drug release properties of CX from Eudragit 4155F solid molecular dispersions were highly dependent on the amount of polymer in the solid dispersions. Increasing polymer concentration in the solid dispersions resulted in greater dissolution enhancement. At a drug/polymer weight ratio of 1:9 complete drug release was achieved after 60 minutes without any evidence of re-crystallization for up to 72 h. After achieving a drug concentration of 71.61±0.32 \(\mu\)g/mL after 24 h from the 3:7 solid dispersions, CX re-crystallized thereafter reaching a concentration of 56.09±0.19 and 53.37±0.28 \(\mu\)g/mL after 48 and 72 h, respectively. Solid dispersions at a drug/polymer weight ratio of 1:1 achieved a drug concentration of 13.24±0.21 \(\mu\)g/mL after 48 h, then re-crystallization of CX occurred after 72 h (10.96±0.16 \(\mu\)g/mL). Conversely, solid dispersions with a drug/polymer weight ratio of 7:3 achieved a steady but reduced CX concentration compared to other drug/polymer ratios (between 4 and 5 \(\mu\)g/mL) after 24 h.
Previously it has been reported in the literature that polymers that have pH dependent solubility can enhance the dissolution properties of poorly soluble drugs from solid dispersions at pH in which these polymers are soluble. Eudragit EPO, a cationic polymer, is soluble at pH less than 5 and permeable at higher pH values (Chokshi et al., 2008). Melt extrudates prepared using Eudragit EPO showed significant enhancement in indomethacin solubility compared to physically mixed samples in simulated gastric fluid (SGF) pH 1.5. This enhancement in drug solubility in SGF was greater from the solid dispersion at higher polymer concentrations. Conversely, in simulated intestinal fluid (SIF) pH 6.8, the improvement of drug solubility was significantly lower compared to SGF and the increase in solubility was inversely related to polymer concentration due to the poor solubility of EPO at pH 6.8 (Chokshi et al., 2008). Moreover, Eudragit L100-55 polymer, which is soluble at pH ≥ 5.5, was used to prepare itraconazole solid dispersions (Overhoff et al., 2007). The drug dissolution from the prepared solid dispersions generated significantly greater supersaturated drug levels in pH 6.8 at higher polymer to drug ratio than lower ratios. Furthermore, HPMCAS (Type MF) polymer, soluble at pH ≥ 6.0, generated greater supersaturated levels of felodipine at pH 6.8 and maintained these concentrations for
longer times compared to PVP and HPMC (Konno et al., 2008). The supersaturated levels generated by the polymers increased with increasing polymer concentration in the solid dispersions.

The role of Eudragit 4155F in enhancing drug solubility was further confirmed when nearly comparable dissolution profiles (Figure 6.6) were generated from the physically mixed samples containing crystalline or amorphous CX at a drug/polymer weight ratio of (1:9) achieving an equilibrium concentration of 64.25±1.04 and 64.91±0.35 (µg/mL) ($p = 0.3563$), respectively, after 72 hr. These results confirmed that drug release properties of CX from Eudragit 4155F solid molecular dispersions were highly dependent on the polymer and the intimate mixing between the drug and the polymer rather than the solid state properties of CX.

![Figure 6.6. Dissolution profiles of celecoxib (CX) (100µg/mL) from CX-Eudragit binary system at 90% Eudragit 4155F in PBS 7.4; solid dispersions (▲), physical mixture (PM) containing crystalline (CX) (○), physical mixture (PM) containing amorphous (CX) (●). The data shown is the average of three replicates and in all cases the COV was < 8.](image)
Furthermore, the release of CX from Eudragit 4155F solid dispersions was highly dependent on the pH of the test fluid. To further examine pH dependent solubility, dissolution experiments were conducted at elevated pH using a dissolution medium with a pH of 9.4. A significant enhancement in CX drug release from the solid dispersions was achieved in comparison to dissolution at pH 7.4 (Figures 6.7 and 6.8). Solid dispersions containing drug/polymer weight ratio of 1:9 reached complete drug release in shorter time periods (within 30 minutes) and remained at this level for 72 h. A drug/polymer weight ratio of 3:7 showed complete drug release after 30 minutes. This was maintained for 5 h then re-crystallization occurred and a concentration of 83.63±0.14 µg/mL was observed after 6 h which stabilized at 72 h (80.83±0.79 µg/mL). A drug/polymer weight ratio at 1:1 showed a maximum concentration of 34.95±0.31 µg/mL after 2 h and then re-crystallized rapidly reaching a concentration of 13.18±0.03 µg/mL after 6 h then achieving an equilibrium concentration of 9.30±0.07 µg/mL after 72 h. A drug/polymer ratio of 7:3 showed a peak concentration after 2 h of 9.58±0.19 µg/mL then decreased slightly and stabilized at a concentration 4.83±0.16 µg/mL after 72 h. The significant increase in the drug dissolution properties from the solid dispersions may be attributed to the higher dissolution properties of Eudragit 4155F at pH 9.4 than at pH 7.4, given that the equilibrium solubility of crystalline CX at pH 9.4 was not significantly different than at pH 7.4 (1.56±0.12 µg/mL) ($p = 0.7978$). Eudragit 4155F is an anionic polymer which has a pH dependent solubility and it is only soluble at pH ≥ 7.0, so increasing the pH of test fluid to 9.4 resulted in more ionization of the free carboxylic acid of Eudragit 4155F and hence faster drug release properties from the solid dispersions. The drug release rate of 5-aminosalicylic acid from Eudragit S100, an anionic polymer which is soluble at pH ≥ 7.0, increased significantly when the pH increased from 6.8 to 7.4 as a result of increasing ionization of its free carboxylic acid (Bruce et al., 2005).
Figure 6.7. Dissolution profiles of celecoxib (CX) (100 µg/mL) from solid dispersions with different amounts of Eudragit 4155F at different pHs; 90% pH 7.4 (Δ), 90% pH 9.4 (▲), 70% pH 7.4 (■), 70% pH 9.4 (□). The data shown is the average of three replicates and in all cases the COV was < 8.

Figure 6.8. Dissolution profiles of celecoxib (CX) (100 µg/mL) from solid dispersions with different amounts of Eudragit 4155F at different pHs; 50% pH 7.4 (Δ), 50% pH 9.4 (■), 30% pH 7.4 (□), 30% pH 9.4 (▲). The data shown is the average of three replicates and in all cases the COV was < 8.
Supersaturated solutions generated by dissolution of the amorphous solid dispersions can either arise from stabilizing effects of polymers (Gupta et al., 2004, Tanno et al., 2004, Konno et al., 2008), and/or by the increase in the equilibrium solubility of the crystalline drug due to complexation in solution with the polymer and hence a reduced extent of supersaturation and a lowered thermodynamic driving force for crystallization (Konno et al., 2008, Loftson et al., 1996). Based on the results of dissolution of the amorphous solid dispersions at 1:9 and 3:7 ratios, which showed significantly greater drug concentrations compared to the theoretical solubility of amorphous CX, it is suggested that the later mechanism may be more applicable in the CX-Eudragit 4155F system given the significant increase in the solubility of crystalline CX in the PBS 7.4 in which the polymer had been dissolved or from the physically mixed samples. The possibility of formation of a soluble complex in solution between CX and Eudragit 4155F has been further investigated in the following sections of this chapter using solution $^1$H NMR. It was reported that the enhancement in intrinsic dissolution rate of carbamazepine from PVP solid dispersions was related to formation of a soluble complex between carbamazepine and PVP during dissolution (Sethia and Squillante, 2004). Felodipine solubility has been enhanced significantly from solid dispersions using PVP concentrations over 75% w/w due to the formation of soluble complex at these PVP concentrations as was confirmed by solution $^1$H NMR (Karavas et al., 2006). Therefore, it is not unreasonable to assume a similar mechanism of dissolution enhancement is operating within the CX-Eudragit 4155F solid dispersions.
6.3.6 Solution NMR

It was shown that PVP and Eudragit amorphous solid dispersions generated supersaturated concentrations of CX at PBS 7.4. The mechanism by which each system generated these supersaturated concentrations was different. The solubilising effect of Eudragit 4155F and the stabilizing effect of PVP were the most dominant mechanisms for achieving such supersaturation. In an attempt to understand the basis behind these polymer effects, solution NMR studies were conducted.

$^1$H NMR spectroscopic studies were performed in order to investigate the presence of any drug-polymer interactions which may occur in solution and to try to correlate this data with the results obtained from the experiments of dissolution of solid dispersions and the inhibition of crystallization by the polymer excipients from supersaturated solutions of CX in PBS 7.4.

Solution $^1$H NMR spectra were generated for CX, polymers and solid dispersions in order to investigate whether the electron density around the H atoms of CX was changed in solution as a result of interactions between CX and the polymers. In $^1$H NMR spectroscopic experiments the nuclei of hydrogen atoms of a material absorb energy at slightly different magnetic field strengths for a given frequency of electromagnetic radiation. Magnetic field strength is measured in units of parts per million (ppm) on a delta (δ) scale (chemical shift) along the bottom of the spectrum. The magnetic field strength increases from left (downfield) to right (upfield). The actual field strength at which absorption occurs is highly dependent on the magnetic environment of each proton which depends on the magnetic fields generated by circulating electrons of the other nearby protons generating tiny magnetic fields (induced field). This resulted in being some hydrogen nuclei are in regions of greater electron density than others. The induced magnetic field at the proton opposes the external magnetic field, so the actual magnetic field sensed by the proton is slightly less than the external field i.e. the proton is shielded by the electrons. Thus a shielded proton will absorb at higher external field strengths depending on the relative electron density around the proton (Solomons, 1992).
The $^1$H chemical shifts can be used as indicators of the strength of H-bonding (Brown and Spiess, 2001). If interactions occur it should be reflected in chemical shift variations, since the electron density at the interacting atoms will be changed (Van den Mooter et al., 2001). The chemical shift ($\delta$) values of the H atoms of CX in crystalline CX and in the solid dispersions are summarized in Tables 6.3 and 6.4. The change in the chemical shift ($\Delta\delta$) for the H atoms of CX was calculated as the difference between the chemical shift ($\delta$) of the H atoms of CX in the solid dispersions samples and the chemical shift ($\delta$) of the corresponding H atoms in pure CX samples.

Figure 6.9 shows the chemical structure of CX with protons assigned. The position of the chemical shift ($\delta$) of CX protons have been shifted in Eudragit 4155F solid dispersions particularly in the aromatic protons containing the sulfonamide group $-\text{SO}_2\text{NH}_2$ (H-la and H-lb) compared to the corresponding protons in pure CX. Downfield shifts to higher values (deshielding) is evident for (H-la) $\Delta\delta$ (0.002-0.014) and (H-lb) $\Delta\delta$ (0.009-0.020) within the Eudragit 4155F solid dispersions. These deshielding effects on the aromatic protons containing the sulfonamide group suggest a change in electron density as a result of interaction with the carbonyl group of Eudragit 4155F. Electronegative groups like carbonyl groups can withdraw electrons from the aromatic ring resulting in a decrease in the electron density of the aromatic ring and hence deshielding (Solomons, 1992).

Interestingly there is a correlation between the magnitude of shift ($\Delta\delta$) and the concentration of the polymer (Eudragit 4155F) present in the solid dispersions. As the concentration of Eudragit 4155F increased, the chemical shift ($\delta$) of (H-la and H-lb) increased (Table 6.3) (Figure 6.10). These results correlate well with the solubilising effect of Eudragit 4155F on CX, which showed that the enhancement in the dissolution properties of CX as a function of increasing polymer concentration in the solid dispersions and physical mixtures. These findings strongly suggest the interaction (complex formation) between CX and Eudragit 4155F during the dissolution process that resulted in significant enhancement in drug solubility. It has been found that hydrophilic carriers can interact with drug molecules in solution forming weakly soluble complexes mainly by electrostatic forces (ion-ion, ion-dipole, ion-dipole interactions).
and dipole-dipole bonds) and occasionally other types of forces like van der Waals forces and hydrogen bonding (Cirri et al., 2004, Ahuja et al., 2007). Complexation between β-cyclodextrin (β-CD) and fluconazole was confirmed by solution $^1$H NMR which showed deshielding of the aromatic protons of fluconazole (m-difluorophenyl ring). The proximity of these protons to an electronegative atom like the oxygen of β-CD withdraws electrons from the aromatic ring, resulting in deshielding and hence movement to a higher position (ppm). These results were confirmed using molecular modelling studies that showed the m-difluorophenyl ring of fluconazole enter into the torus cavity of β-CD from the wider end (Upadhyay and Kumar, 2009). Similar effect may have been occurred in CX-Eudragit 4155F solid dispersions during dissolution as a result of the effect of the electronegative carbonyl groups of Eudragit 4155F that may withdraw electrons from the aromatic protons of CX which resulted in the deshielding effects on these protons and the formation of a soluble complex.

Similar suggestions by several other research groups have been described within the literature for the possible mechanism of the solubility enhancement of several drugs. Sinha et al. (2005, 2007) confirmed complex formation between CX and β-Cyclodextrin using solution $^1$H NMR based on downfield shifts for CX (H-1a and H-1b) protons in the presence of β-Cyclodextrin which resulted in significant enhancement in the solubility of CX. Additionally, solution $^1$H NMR suggested complex formation between PVP and felodipine at higher polymer concentrations (>75% w/w). This complex formation was formed as a result of hydrogen bonding interactions between the carbonyl group of PVP and the amino group of felodipine resulting in significant enhancement in drug solubility at these higher polymer concentrations. The interactions were confirmed by changes in the chemical shift of the amino group to a higher position (deshielding) in dispersions containing 75% PVP. Interestingly, no such shift was observed in solid dispersions containing 50% PVP. These interactions were significantly increased at polymer concentrations exceeding 75 % w/w. No significant enhancement in the drug solubility from the solid dispersions was obtained for polymer concentrations up to 70% w/w whereas at polymer concentrations exceeding 75% w/w, a significant increase in the drug solubility was achieved. These results suggest that the intensity of interaction significantly affects dissolution enhancement (Karavas et al., 2006).
Figure 6.9 Chemical structure of celecoxib (CX) with protons assignment.

Table 6.3. Chemical shifts (ppm) for the protons of celecoxib (CX) in pure state and in solid dispersions using Eudragit 4155F as carrier obtained from solution $^1$H NMR.

<table>
<thead>
<tr>
<th>Celecoxib Proton</th>
<th>$\delta_{\text{CX}(\text{free})}$</th>
<th>$\delta_{\text{SD 1:9}}$</th>
<th>$\Delta\delta_{\text{SD 1:9}}$</th>
<th>$\delta_{\text{SD 3:7}}$</th>
<th>$\Delta\delta_{\text{SD 3:7}}$</th>
<th>$\delta_{\text{SD 1:1}}$</th>
<th>$\Delta\delta_{\text{SD 1:1}}$</th>
<th>$\delta_{\text{SD 7:3}}$</th>
<th>$\Delta\delta_{\text{SD 7:3}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>2.378 (singlet)</td>
<td>2.385</td>
<td>0.007</td>
<td>2.382</td>
<td>0.004</td>
<td>2.383</td>
<td>0.005</td>
<td>2.830</td>
<td>0.002</td>
</tr>
<tr>
<td>H-1a</td>
<td>7.467 (doublet)</td>
<td>7.481</td>
<td>0.014</td>
<td>7.477</td>
<td>0.010</td>
<td>7.476</td>
<td>0.010</td>
<td>7.469</td>
<td>0.002</td>
</tr>
<tr>
<td>H-1b</td>
<td>7.895 (doublet)</td>
<td>7.915</td>
<td>0.020</td>
<td>7.911</td>
<td>0.016</td>
<td>7.910</td>
<td>0.015</td>
<td>7.904</td>
<td>0.009</td>
</tr>
<tr>
<td>H-5a, H-5b</td>
<td>7.144 (doublet of doublet)</td>
<td>7.147</td>
<td>0.003</td>
<td>7.146</td>
<td>0.002</td>
<td>7.147</td>
<td>0.003</td>
<td>7.146</td>
<td>0.001</td>
</tr>
<tr>
<td>H-4</td>
<td>6.742 (singlet)</td>
<td>6.740</td>
<td>-0.002</td>
<td>6.740</td>
<td>-0.002</td>
<td>6.744</td>
<td>0.002</td>
<td>6.744</td>
<td>0.002</td>
</tr>
</tbody>
</table>

($\Delta\delta = \delta_{\text{SD}} - \delta_{\text{CX}}$)
Figure 6.10. Solution $^1$H NMR spectra of CX, Eudragit 4155F and CX-Eudragit 4155F solid dispersions (SD).
The most interesting differences between the $^1$H NMR spectra of CX-PVP solid dispersions and CX were the deshielding and shielding effects on protons (H-1a) and (H-1b) of the aromatic ring containing the sulfonamide group (Figure 6.11) (Table 6.4). These effects suggest changes in the electron density due to interaction with PVP in solution. The aromatic protons (H-1b) were shifted downfield to higher chemical shifts (deshielding) especially at higher polymer concentrations $\Delta\delta = 0.010$ and 0.022 in CX:PVP (1:1) and (3:7) ratios, respectively. Conversely, the aromatic protons (H-1a) were shifted upfield to lower chemical shifts (shielding) $\Delta\delta$ (0.021-0.028) (Table 6.4). These different effects suggest that CX interacts in a different way with PVP in comparison to Eudragit 4155F in solution which may explain the different effects of the polymers towards inhibition of CX re-crystallization and during dissolution of amorphous solid dispersions. The deshielding effects of PVP on the aromatic protons adjacent to the sulfonamide group of CX (H-1b) indicate the formation of strong intermolecular interactions between individual CX and PVP which may be stronger than the intermolecular interactions between individual CX molecules (Tobyn et al., 2009). The electronegativity of the carbonyl group of PVP increases the withdrawal of electrons from the aromatic protons (H-1b) and hence resulted in decreasing their electron density (deshielding). This deshielding effect increased with increasing PVP concentration in the solid dispersions suggesting stronger interactions between CX and PVP with increasing PVP concentration. These results were in good agreement with the experiments of the inhibition of crystallization from supersaturated solutions and the dissolution of amorphous solid dispersions which showed greater supersaturated concentrations of CX at higher PVP concentrations. These interactions may explain the stabilizing effect of PVP in preventing CX re-crystallization from supersaturated concentrations particularly given that there was not any solubilising effect observed for PVP on CX which may exclude the formation of a soluble complex as was proposed for Eudragit 4155F. Certain types of molecular association are needed to achieve crystallization, so disruption of the molecular interactions between drug molecules may result in inhibition of a crystal lattice (Tang et al., 2002). The strong interactions between CX and PVP may prevent CX molecules in solution from ordering themselves to form the required intermolecular forces needed to form the crystal lattice and hence inhibit re-crystallization. It was difficult to justify the shielding effects of PVP on the (H-1a)
protons based on only $^1$H NMR. These shielding effects on these protons may be attributed to some weak interactions between CX and PVP due to the increase in their electron density by the effect of the $\pi$ electrons of the carbonyl group of PVP (Solomons, 1992).

Table 6.4. Chemical shifts (ppm) for the protons of celecoxib in pure state and in PVP solid dispersions obtained from solution $^1$H NMR.

<table>
<thead>
<tr>
<th>Celecoxib Proton</th>
<th>$\delta_{\text{CX (free)}}$</th>
<th>$\delta_{\text{SD 3:7}}$</th>
<th>$\Delta \delta_{\text{SD 3:7}}$</th>
<th>$\delta_{\text{SD 1:1}}$</th>
<th>$\Delta \delta_{\text{SD 1:1}}$</th>
<th>$\delta_{\text{SD 7:3}}$</th>
<th>$\Delta \delta_{\text{SD 7:3}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3$</td>
<td>2.378 (singlet)</td>
<td>2.377</td>
<td>-0.001</td>
<td>2.371</td>
<td>-0.007</td>
<td>2.365</td>
<td>-0.013</td>
</tr>
<tr>
<td>$\text{H-1a}$</td>
<td>7.467 (doublet)</td>
<td>7.446</td>
<td>-0.021</td>
<td>7.442</td>
<td>-0.024</td>
<td>7.439</td>
<td>-0.028</td>
</tr>
<tr>
<td>$\text{H-1b}$</td>
<td>7.895 (doublet)</td>
<td>7.916</td>
<td>0.022</td>
<td>7.905</td>
<td>0.010</td>
<td>7.891</td>
<td>-0.004</td>
</tr>
<tr>
<td>$\text{H-5a, H-5b}$</td>
<td>7.144 (doublet of doublet)</td>
<td>7.142</td>
<td>-0.002</td>
<td>7.138</td>
<td>-0.007</td>
<td>7.144</td>
<td>-0.010</td>
</tr>
<tr>
<td>$\text{H-4}$</td>
<td>6.742 (singlet)</td>
<td>6.738</td>
<td>-0.004</td>
<td>6.735</td>
<td>-0.007</td>
<td>6.733</td>
<td>-0.009</td>
</tr>
</tbody>
</table>

($\Delta \delta = \delta_{\text{complex}} - \delta_{\text{celecoxib (free)}}$)
Figure 6.11. Solution $^1$H NMR spectra of CX, PVP and CX-PVP solid dispersions (SD).
6.4 CONCLUSIONS
Polymers used as carriers in solid dispersions have significant effects in determining the physicochemical properties of these dosage forms. In this study, the effects of PVP and Eudragit 4155F on the dissolution properties of CX solid molecular dispersions manufactured using HME were evaluated. It was shown that Eudragit 4155F acted efficiently as a solubilizer for CX. The solubility of CX in PBS 7.4 from physically mixed samples was greater than corresponding systems in which polymer had been pre-dissolved. A further significant enhancement in CX solubility was achieved from the solid molecular dispersions indicating the importance of drug/polymer miscibility and the need for intimate contact during dissolution to achieve a high solubility enhancement.

Solid molecular dispersions manufactured using HME, in which intimate mixing between the drug and polymer at a molecular level occurs provide the maximum possible contact between the drug and polymer during dissolution. Significantly higher solubility enhancement of CX was achieved from Eudragit 4155F solid molecular dispersions compared to corresponding physical mixtures. This solubilising effect of Eudragit 4155F on CX was mostly related to complex formation between CX and Eudragit 4155F in solution.

The solubilising effect of Eudragit 4155F during dissolution was the dominant mechanism for release of CX from these solid dispersions. Dissolution from Eudragit 4155F solid dispersions was highly dependent on the polymer concentration and the pH of the test fluid rather than the solid state properties of the drug. Comparable drug dissolution-time profiles were generated from physically mixed samples (amorphous and crystalline CX). Additionally, the drug concentrations achieved during dissolution of solid dispersions were significantly higher than the theoretical solubility of amorphous CX. An increase in the dissolution properties of CX was achieved by increasing the polymer : drug ratio within the solid dispersions as a result of the solubilising effect of Eudragit 4155F on CX. Moreover, the increase in pH of the test fluid resulted in a significant increase in the dissolution properties of CX from solid dispersions as a result of increasing polymer solubility at higher pH.
Chapter 6

The significant enhancement in the solubility of CX achieved by formation of solid molecular dispersions using Eudragit 4155F in pH 7.4 may have a significant enhancement in the solubilisation of CX in colonic medium, in which there is low motility and fluid content. These colon physiological conditions necessitate delivering CX in a highly solubilised dosage form in order to achieve significantly improved therapeutic outcomes.

Conversely no solubilising effects by PVP was observed in which PVP had been dissolved or from physical mixtures. However, the supersaturated levels generated by amorphous CX from PVP solid dispersions were stabilized efficiently by PVP for up to 72 h without any significant re-crystallization. This stabilizing effect of PVP may be attributed to the strong interactions between CX and PVP in solution (confirmed using solution NMR). These strong interactions prevented the molecular association of CX required to form a stable crystal lattice during re-crystallization.

Solution $^1$H NMR was highly efficient in providing information about the drug release mechanisms of CX from the solid dispersions and the roles of drug/polymer intermolecular interactions formed during dissolution in maintaining the supersaturated levels of CX based on the solubilising effects of Eudragit 4155F and the stabilizing effects of PVP on CX.
Conclusions
Formulation of poorly soluble drugs for oral delivery is one of the most significant challenges to formulation scientists (Leuner and Dressman, 2000). This challenge may be attributed to the recent advent of high throughput screening in the drug discovery process, which resulted in increasing the number of poorly soluble drugs (Lipinski et al., 1997). Poorly soluble drugs, BCS class II drugs (Amidon et al., 1995), have low bioavailability because of their aqueous solubility. Solid dispersions, in which the drug is dispersed in a hydrophilic matrix, have been extensively studied for improving the aqueous solubility of poorly water-soluble drugs (Serajuddin, 1999).

HME is considered as one of the most attractive methods used to prepare solid dispersions. This technology is highly advantageous in that it is a solvent free process and thus it is environment friendly and cost effective (Chokshi et al., 2005). HME may also be used for thermally labile drugs even though the process is non-ambient as a result of the short residence time inside the extruder (Verreck et al., 2006a). Several research groups have demonstrated that HME is a viable technology in producing solid dispersions (Forster et al., 2001b; Chokshi et al., 2008; Nollenberger et al., 2009).

Although highly advantageous in terms of improving aqueous solubility, the number of commercial pharmaceutical products containing amorphous drugs on the market is extremely low (Serajuddin, 1999). This low commercial productivity is mostly related to the physical instability of amorphous drug forms and their high tendency to re-crystallize as a result of their high free energy (Hancock and Parks, 2000). Amorphous solid dispersions using pharmaceutical polymers can enhance the physical stability of the amorphous forms. The rational use of polymeric carriers is very important to achieve such stabilization based on miscibility (Marsac et al., 2006b), interactions with the drug (Taylor and Zografi, 1997), and increasing the Tg (Van den Mooter et al., 2001) and viscosity of amorphous drug forms (Bhugra and Pikal, 2008).
Hot melt extruded solid dispersions of bicalutamide (BL) were manufactured successfully using PEO or PVP as hydrophilic carriers at drug : polymer weight ratios 1:10, 2:10 and 3:10. The solid state properties of BL within the melt extrudates, characterized by DSC, PXRD and SEM, confirmed the formation of amorphous solid dispersions within PVP melt extrudates in which BL was molecularly dispersed at all drug/polymer ratios, whereas BL-PEO melt extrudates at 1:10 and 2:10 ratios contained mainly BL in the amorphous form in addition to very small BL crystals. Conversely, BL-PEO melt extrudates at 3:10 ratio contained significant BL in the crystalline form. FTIR and Raman spectroscopy were efficient in characterizing the differences in the interactions at the molecular level between amorphous and crystalline BL and hence to characterize the solid state properties of BL within the melt extrudates confirming the results obtained by DSC, PXRD and SEM.

Approximately, a 2-fold increase in the percentage drug release was achieved from PVP physically mixed samples, whereas no significant change was observed for the percent of BL released from PEO physically mixed samples in comparison with the pure drug. HME of BL with PEO or PVP resulted in a significant enhancement in the dissolution properties of BL compared to pure BL and the corresponding physically mixed samples. These results suggest the efficiency of HME in preparing solid dispersions exhibiting enhanced dissolution properties and hence improved oral bioavailability for poorly soluble drugs that have absorption limited by their dissolution properties in the gastrointestinal tract. The drug release properties from the melt extrudates were highly dependent on the polymer concentration within the melt extrudates. The higher drug : polymer ratio, the greater the increase in percentage BL released. In comparison to pure BL, a 22-fold increase in the percent drug release after 60 min was observed from BL/PEO melt extrudates at a ratio of 1:10, whereas a 4.36-fold and a 2.55-fold increase were observed from the 2:10 and 3:10 melt extrudates, respectively. A significantly greater enhancement in percent drug release was achieved from PVP melt extrudates in comparison to PEO melt extrudates at equivalent drug/polymer ratios. The percentage of BL released from the PVP 1:10 extrudates was 8.93-fold greater than that observed for pure BL after 60 min, whereas increases of 8.05 and 7.53-fold were observed for drug:polymer ratios of 2:10 and 3:10, respectively. This significant increase in the dissolution properties of BL from PVP melt extrudates may be attributed to the ability of PVP to enhance the wetting properties of BL particularly given that BL was molecularly dispersed within the melt.
extrudates. Additionally, the particle size of BL within PVP melt extrudates was reduced to minimum (molecular dimensions) which may result in increasing the surface area available for dissolution. This significant enhancement in the dissolution properties of BL may result in significant enhancement in its oral bioavailability.

Amorphous solid dispersions prepared using PVP were more physically stable than PEO solid dispersions stored at 20°C and 65% RH. For these PVP systems recrystallization was inhibited at all drug : polymer ratios for 1 month storage, whereas corresponding PEO solid dispersions showed significant drug re-crystallization. These results indicate that PVP was a more efficient solid-state stabilizer for BL than PEO. This may be attributed to the synergistic effects resulting from the increase in the Tg value of amorphous BL and hence a decrease of molecular mobility as a result of formation of solid molecular dispersions and the presence of strong drug/polymer interactions. Conversely, the low physical stability of BL-PEO solid dispersions may be attributed to many factors including the solid state plasticization effect by PEO on amorphous BL, the lack of any strong specific hydrogen bonding between BL and PEO and the presence of small amounts of crystals embedded within the melt extrudates which may act as nuclei to accelerate crystal growth. There was a significant decrease in the dissolution properties of BL from the PEO melt extrudates after 6 months storage at (RH 65%, 20°C). Although the presence of small BL crystals were evident in PVP melt extrudates stored for 6 months, there were no significant differences in the drug release profiles compared to those tested immediately following manufacture. This suggests that these small crystals have negligible contribution to the drug release properties and the overall release properties may be attributed to both dissolution of amorphous and crystalline BL. The latter being greatly facilitated by the small crystalline size and the increased wettability of BL due to dispersion within a hydrophilic polymer (PVP).
In chapter 4, PVP was used to prepare hot melt extruded solid dispersions of celecoxib (CX). CX was shown to act as a solid-state plasticizer for PVP and hence HME was possible without the need for conventional plasticizer or processing aid. Three drug : polymer ratios were prepared 3:7, 1:1 and 7:3. DSC and PXRD confirmed the formation of solid molecular dispersions of CX within PVP melt extrudates at all drug loading levels. The prepared hot melt extruded solid dispersions were highly stable after three months storage at 40°C and 75% RH. There was no evidence of re-crystallization in melt extrudates at drug : polymer ratios of 3:7 and 1:1, whereas small crystal peaks were detected in the PXRD pattern of melt extrudates at a ratio of 7:3. The physical stabilization of amorphous CX by PVP may be attributed to the reduced molecular mobility resulting from the increase in the glass transition values of the melt extrudates in comparison to the glass transition of amorphous CX. In addition, drug/polymer intermolecular interactions had a significant role in achieving such solid state stabilization. The theoretical glass transition values predicted by the Gordon-Taylor equation were greater than the glass transition values determined experimentally using DSC. These results suggest that the newly formed intermolecular forces between PVP and CX (adhesive forces) were greater than the intermolecular forces already existing between individual molecules of PVP and CX (cohesive forces). In an attempt to characterize the nature of such intermolecular forces formed during HME, spectroscopic studies (FTIR and Raman) were conducted on melt extrudates and compared to physically mixed samples containing amorphous and crystalline CX. FTIR and Raman studies confirmed the presence of hydrogen bonding between CX and PVP. A red shift in the stretching vibration band of the carbonyl group of PVP was observed in the FTIR spectra of the melt extrudates in comparison to the corresponding physically mixed samples containing amorphous CX and PVP. This red shift was attributed to strong hydrogen bonding interactions between the carbonyl group of PVP and the amino group (NH2) of CX. Raman spectroscopy showed a blue shift in the stretching vibration band of the sulfonyl group of CX as a result of the weakening in the existing hydrogen bonding with the NH2 group which formed instead new strong hydrogen bonding with the carbonyl group of PVP particularly given that the carbonyl group is a stronger proton acceptor than the sulfonyl group. This strong hydrogen bonding significantly affects the physical stability of amorphous CX in addition the anti-plasticization effect of PVP on the Tg of amorphous CX further improves drug stability.
In addition to being poorly soluble in intestinal fluids, CX has poor powder handling properties that make preparation of CX as solid oral dosage forms using traditional tableting processes difficult (Leonard and Patricia, 2001). However, HME was used efficiently to manufacture fast release tablets containing CX-PVP solid molecular dispersions. These prepared tablets had a slow drug release rate due to their high density and low porosity. To increase the surface area available for dissolution and hence to achieve faster drug release, melt extrudates were further processed either by milling or exposure to supercritical carbon dioxide (scCO₂). Both milling and scCO₂ exposure were efficient in increasing the dissolution rate of CX-PVP hot-melt extruded tablets. A more significant enhancement in percentage drug release (5-fold) was achieved after 1 h by milling the extrudates, whereas only a 2-fold increase in percentage drug release was achieved from the hot-melt extruded tablets exposed to scCO₂ for 24 h. These results may be attributed to the significant increase in the surface area due to milling in comparison to the treated melt extrudates by scCO₂. The significant enhancement in the drug release rate from the treated tablets by scCO₂ in comparison to the non-treated tablets was attributed to the formation of a foamed like structure of increased porosity and surface area. The significant enhancement in drug release may result in significant increase in the absorption rate of CX through the GI tract and hence in producing a faster analgesic effect. Exposure to scCO₂ and storage of the milled extrudates at (40°C, 75% RH) did not affect the solid state properties which retained the amorphous character of CX. There was no significant change in the drug release profiles of the hot-melt extruded tablets after six months storage at 40°C, 75% RH conditions which may be related to high physical stability of the melt extruded tablets, and hence maintenance of the amorphous form of CX.

In chapter 5, Eudragit 4155F was used as a polymeric matrix platform for colonic delivery of CX. Hot melt extruded tablets prepared at different extrusion temperatures (100, 140 and 170 °C) and drug : polymer ratios (1:9, 3:7, 1:1) showed efficient release of CX during in-vitro simulated colonic media (pH 7.4) under sink conditions. The solid state properties within the melt extrudates were highly dependent on the drug loading level and extrusion temperature. At constant drug loading levels, increasing the extrusion temperature resulted in higher solid state miscibility and hence lower crystallinity, whereas increasing the drug loading level at constant extrusion temperature resulted in greater crystallinity within the melt.
extrudates. Amorphous solid dispersions were generated using HME for CX-Eudragit 4155F binary mixtures at a ratio of 1:9 ratio at all extrusion temperatures (100, 140 and 170 °C). The 3:7 melt extrudates prepared at temperatures of 140 and 170°C were amorphous solid dispersions, whereas the PXRD pattern of the melt extrudates prepared at 100°C confirmed the presence of crystalline CX. Only HME of the 1:1 ratio at 170°C generated amorphous solid dispersions, whereas for other temperatures (100 and 140 °C) significant drug crystallinity was observed in the PXRD pattern. Melt extrudates prepared at 100°C had distinct crystalline bands that decreased in intensity when extruded at 140°C. Storage of CX-Eudragit 4155F solid molecular dispersions prepared at 170°C at 40°C, 75% RH, resulted in stability patterns that were polymer concentration dependent. Melt extrudates at 1:9 ratio remained in an amorphous form, whereas a 3:7 ratio was able to withstand the high stress conditions of humidity and temperature up to 2 months, thereafter small crystal peaks characteristic of crystalline CX were recorded in the PXRD pattern at the three months stage. Both 1:1 and 7:3 drug : polymer ratios showed re-crystallization after one month storage which increased after 2 and 3 months but still were significantly lower than the crystal peaks detected in the PXRD pattern of the amorphous CX that was physically mixed with Eudragit 4155F and stored up to 5 days. This solid state physical stabilization of Eudragit 4155F on amorphous CX may be attributed to the increase in the local viscosity of the amorphous form of CX that resulting in reduced molecular mobility. In vitro drug release profiles of the hot-melt extruded tablets showed high dependency on the extrusion temperature in pH 6.8 and 7.4 dissolution media, whereas negligible drug release was observed at pH 1.2. Increasing extrusion temperature at constant drug loading level resulted in a decrease in the percentage drug release in pH 6.8 and 7.4 release media.

In chapter 6, the dissolution properties of CX from Eudragit 4155F solid dispersions were compared with the dissolution properties of PVP solid dispersions at PBS 7.4 (non-sink conditions). Eudragit 4155F amorphous solid dispersions generated supersaturated concentrations as a result of the solubilising effect of Eudragit 4155F. It was shown that Eudragit 4155F significantly increased the solubility of crystalline CX in PBS 7.4 in which the polymer had been dissolved and more significantly from the physically mixed samples. The solubility of CX was further increased from the solid dispersions compared to the corresponding physically
mixed samples. For example, a 63-fold increase in CX solubility was achieved from solid dispersions at a 1:9 ratio, whereas a 41-fold increase in CX solubility was achieved from the physically mixed samples at a similar drug : polymer ratio. These results suggest the importance of the intimate contact between CX and Eudragit 4155F in enhancing the drug solubility. The solubilising effect of Eudragit 4155F may be attributed to the formation of a soluble complex during dissolution resulting in increased equilibrium solubility, as confirmed by $^1$H NMR. The efficiency of the Eudragit 4155F hot-melt extruded polymeric matrix to release CX within simulated colon media and the efficient solubilising effect of Eudragit 4155F on CX may have a significant effect in improving the chemoprevention effect of CX against colorectal polyps especially with the physiological properties of the colon that characterized by the low motility and fluid content (Takaya et al., 1998).

In comparison to Eudragit 4155F amorphous solid dispersions, PVP amorphous solid dispersions at all prepared drug loading levels achieved concentrations that were significantly greater than the equilibrium solubility of CX suggesting the generation of supersaturated solutions. These supersaturated levels were maintained efficiently by PVP for up to 72 h. There was no solubilising effect on CX by PVP and the supersaturated concentrations achieved by amorphous solid dispersions did not significantly exceed the solubility of amorphous CX predicted by the model developed by Parks and co-workers (1928, 1934) (equation 6.1). Additionally, there was not any solubilising effect of PVP on CX in the physically mixed samples. These results indicate that the supersaturated levels achieved by PVP amorphous solid dispersions may be attributed to the solubility of amorphous CX which are maintained efficiently through the stabilizing effect of PVP. This stabilizing effect of PVP in solution may be attributed to the formation of new drug/polymer interactions between CX and PVP during the dissolution of amorphous solid dispersions as confirmed by solution $^1$H NMR.
BIBLIOGRAPHY


Bibliography


Bibliography


Bibliography


Bibliography


315
Publications & Presentations

Publications


Oral Presentations


- "**Hot melt extrusion technology for enhancing drug solubility by producing solid molecular dispersions : Bicalutamide**" All Ireland Schools of pharmacy, 30th Research Seminar, April 3-4, 2008, University College Cork, School of Pharmacy, Cork, Ireland.

Posters


"**The influence of supercritical carbon dioxide (scCO2) in enhancing the dissolution rate of celecoxib (CX) from polyvinylpyrrolidone (PVP) hot melt extrudates**" British Pharmaceutical Conference (BPC), September 2008, Manchester, UK.

"**The Manufacture and Characterization of Hot Melt Extruded Eudragit 415SF Solid Solution**" American Association of Pharmaceutical Scientists (AAPS) 2008, Annual Meeting and Exposition, November 16-20, 2008, Georgia World Congress Center, Atlanta, Georgia, USA