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The design and development of high drug loading amorphous solid dispersion for hot-melt extrusion platform

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Amorphous solid dispersion (ASD) is a formulation strategy extensively used to enhance the bioavailability of poorly water soluble drugs. Despite this, they are limited by various factors such as limited drug loading, poor stability, drug-excipient miscibility and the choice of process platforms. In this work, we have developed a strategy for the manufacture of high drug loaded ASD (HDASD) using hot-melt extrusion (HME) based platform. Three drug-polymer combinations, indomethacin-Eudragit®E, naproxen-Eudragit®E and ibuprofen-Eudragit®E, were used as the model systems. The design spaces were predicted through Flory-Huggins based theory, and the selected HDASDs at pre-defined conditions were manufactured using HME and quench-cooled melt methods. These HDASD systems were also extensively characterised via small angle/wide angle x-ray scattering, differential scanning calorimetry, Infrared and Raman spectroscopy and atomic force microscopy. It was verified that HDASDs were successfully produced via HME platform at the pre-defined conditions, with maximum drug loadings of 0.65, 0.70 and 0.60 w/w for drug indomethacin, ibuprofen and naproxen respectively. Enhanced physical stability was further confirmed by high humidity (95%RH) storage stability studies. Through this work, we have demonstrated that by the implementation of predictive thermodynamic modelling, HDASD formulation design can be integrated into the HME process design to ensure the desired quality of the final dosage form.
1. INTRODUCTION

Poor aqueous solubility and subsequent limited bioavailability of many active pharmaceutical ingredients (APIs) is a significant issue in the current pharmaceutical industry with approximately, 90% of new chemical entities in the development pipeline characterised as poorly water-soluble compounds (Kalepu and Nekkanti, 2015). New, sophisticated formulation strategies have been implemented, of which, the amorphous form has proved to be a promising strategy (Repka et al., 2018). The amorphous form exists as a higher energy state, due to the lack of long range order, resulting in increased free energy level and molecular mobility compared to their crystalline counterparts, thus, provides a desirable route to increase solubility and dissolution performances (Hancock and Zografi, 1997). To capture these advantages, amorphous solid dispersion (ASD) has been widely utilised. The concept of solid dispersions was first proposed in 1960s where the drug molecule is homogenously distributed within a suitable carrier(s), typically a polymer-based material, to improve its physical stability. This approach has enabled a number of marketed products with significant bioavailability enhancement (Zhang et al., 2018). Noticeable progresses may also be highlighted for the development of fix-dose combination products, such as kalydeco®, ORKAMBI®, symdeco® and trikafta™, where the efficacy of the main compound ivacaftor was successfully enhanced by amorphous solid dispersion strategy (FDA, 2019a, 2019b, 2015, 2012).

Despite the successes achieved in exploration of ASD for enabling formulation development, majority of excipient selections are still based on trial-and-error methodologies with a handful of tried tested polymeric systems (Zhang et al.,
We are still deficient in selecting of excipients for a given drug molecule to be formulated into a stable ASD, particularly with the integration of various manufacturing technologies, such as spray drying, hot-melt extrusion or cryo-milling. Several parameters are proposed to be influential for the stability of ASDs, such as; glass transition temperature, molecular mobility, hydrogen-bonding interactions, ionic interaction and other non-specific interactions (Anderson, 2018; Mistry et al., 2015; Quinteros et al., 2008; Song et al., 2015). However, it is still not certain what manufacturing technology is the most suited for a given drug-polymer combination at various process conditions. For example, high drug loading amorphous solid dispersion (HDASD, drug loading >50% w/w), may offer numerous advantages such as reduce the dose size, pill burden and increase the therapeutic compliance, in addition to the enhanced solubility of the amorphous system (Alshahrani et al., 2015; Dedroog et al., 2019). However, HDASD system has not been widely explored due to the potential stability issues. When the drug weight fraction increases, associated processability, inhomogeneity and potential phase separation will undoubtedly affect the quality and performances of the final product. Spray drying and cryo-milling, widely recognising as the preferred techniques for these HDASD systems, are possessed with various limitations (Caron et al., 2011; Tian et al., 2014).

Quality by Design (QbD) aiming to improve the integration of pharmaceutical formulation design and product realisation leads itself into the area of predictive science. The implementation of fundamental principles and data-driven digital frameworks using *in silico* methods, such as, thermodynamic modelling, molecular dynamic/metadynamic simulation and machine learning, will unquestionably improve the productivity of quality-orientated research and development for the
amorphous solid dosage forms (Baird et al., 2010; Edueng et al., 2017; Graeser et al., 2009; Knopp et al., 2015; Luebbert et al., 2017; Mahlin and Bergström, 2013; Schammé et al., 2018; Tian et al., 2013). This field of cross-disciplinary research between advanced therapeutics, computational tools and manufacturing technologies under the umbrella of QbD based digital frameworks will ultimately transform the amorphous formulation design and process into a new field of predictive science. Subsequently, we believe that the specific knowledge and expertise will be combined to develop reliable amorphous formulation and process design tools for quality and rapid realisation of advanced therapies in the foreseeable future (Dadou et al., 2020). Therefore, the development of digital framework based on both thermodynamic and kinetic principles for drug-polymer combinations integrated with specific manufacturing techniques will be vital for this industry.

Here, we have investigated the interesting properties of one particular category of amorphous solid dispersion for the formation of HDASD via hot-melt extrusion platform, where strong intermolecular interaction between drug and polymer can provide the main mechanism for amorphisation during high temperature processing. This type of drug-polymer combination has been reported for amorphous systems such as drug lapatinib with HPMCP (Araujo et al., 2017) and drug naproxen with Eudragit® E (Ueda et al., 2015). A significant increase in the drug loading and amorphous stability is commonly reported for these systems. We suggest that the formation of strong intermolecular interaction, such as strong hydrogen-bonding or ionic interaction, should be considered as one of the key
principles for formulation design based on the HME platform. High drug loading capacity, improved processability and amorphous stability and reduced drug thermodegradation may be achieved through this principle. In this study, the thermodynamic aspects of formulation design integrated with HME platform were investigated, where the weak acidic drugs (indomethacin, ibuprofen and naproxen) with amorphous polymeric carrier Eudragit® E (EPO) were considered as the suitable combinations. The thermodynamic phase diagrams for three HDASD systems were constructed and utilised to guide the design of the hot-melt extrusion process. The processability and storage stability of HDASDs were further investigated using various conventional and advanced analytical techniques.
2. MATERIALS AND METHODS

2.1 Materials

Indomethacin (IND), naproxen (NPX) and ibuprofen (IBU) with a purity of 99% were purchased from Sigma Aldrich (Irvine, UK) and Kemprotec (Kent, UK). Polymer Eudragit® E (EPO) is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate with a ratio of 2:1:1, was generously donated by Evonik GmbH (Darmstadt, Germany). The chemical structures of the polymer and drugs are shown in Figure 1 and the physicochemical properties of these substances used in this study are summarised in Table 1.

2.2 Methods

2.2.1 Physical mixture preparations

Drug and polymer mixtures with different compositions were firstly mixed using a mortar and pestle followed by a ball mill mixer (Retsch, model MM200, Germany). In a typical procedure, drug and polymer powder sample totalling 500mg was milled inside the ball mill mixer with two stainless steel ball at 20 Hz, except for IBU where 15Hz was used. A high milling frequency would normally result a fully amorphous IBU samples up to 0.5 w/w. A pre-defined milling time of two minutes was chosen which was subsequently followed by a two-minute interval. This procedure was repeated to a maximum of up to ten mill-stop cycles (max 20-minutes mill time). The ball-milled samples were subjected to a range of thermal analyses for the construction of phase diagram.

2.2.2 Temperature dependent small angle/wide angle x-ray scattering
The solid-state properties of ball-milled samples and the dissolution/melting behaviours of crystalline drug into the polymeric matrix as a function of temperature were analysed using a small angle/wide angle x-ray scattering (SAXS/WAXS, Ganesha 300XL, Xenocs, France). Powerful microfocus x-ray was generated from a copper source with a motorised collimation system of 4-blad single crystal slits. Movable solid-state photon-counting detector (PILATUS 300K, Dectris AG, Switzerland) was mounted on an uninhibited transverse rail alone the beamline. A total 1.4-meter movement on the detector allows for instant interchange between SAXS and WAXS configurations. The temperature control of the sample was realised by a modified Linkam stage vertically installed inside the vacuum chamber. The SAXS/WAXS system was carefully calibrated using lanthanum hexaboride and validated again before each measurement. In a typical temperature-dependent SAXS/WAXS experiment, a ball milled sample (~ 20 milligrams) was packed in an envelope of aluminium foil, secured on the centre of the heating plate on Linkam stage, and was then subjected to a heat-cool-heat cycle similar to the differential scanning calorimetry experiment. The sample was heated from 25°C to 160°C at rate of 5 °C/min, then fast cooled to -40°C at rate of 40 °C/min. A second heating procedure was conducted from -40°C to 160°C at rate of 5 °C/min. The WAXS was collected every 60 seconds at exposure time of 30 seconds during the heat-cool-heat cycle. SAXS was also collected on selected samples with 600 seconds of exposure time at key temperature points.

2.2.3 Hot-melt extrusion

Hot-melt extrusion of drug-polymer physical mixtures were conducted using 10mm diameter co-rotating twin-screw extruder (Rondol microlab, France). Drug
and polymer premixes at defined ratios were firstly prepared using mortar and
pestle, then fed into the extruder using a twin-screw powder feeder at a constant
rate. The process conditions (screw speed and temperature) for extrusion were
selected based on the phase diagrams (solubility curve) constructed within this
study (Table 2).

2.2.4 Thermal analysis

Power compensation differential scanning calorimetry (DSC8000, Perkin Elmer,
UK) was used throughout to study the physical properties of drug and polymer
systems before and after HME process. Nitrogen was used as the purge gas for low
speed scanning (1-50 °C/min); helium gas was used for high speed scanning (≥
100 °C/min). A 5-10 mg powder sample was packed into an aluminium pan with
a lid. A pinhole was made in the lid to allow moisture to escape. Before conducting
the experiments, all ball-milled samples were dried in a vacuum oven for at least
24 hours. Melting depression experiments were conducted at heating rate of
1°C/min from -40 °C to 200 °C. The endpoint of the melting endothermic peak was
calculated from the intercept point of the endothermic trace and the post-melting
baseline. Given that the drug-polymer particle surface interaction is a critical
requirement for melting point depression experiments, different milling cycles
were tested to achieve the optimal depression results. The choice of optimal
milling time for preparing the physical mixtures was reported in our previous
work (Donnelly et al., 2014; Tian et al., 2013).

For identification of glass transition temperatures for HDASDs immediately after
HME processing, freshly prepared samples were cut into small pieces and placed
directly into the DSC pan, a scan rate of 10 °C/min was used across a temperature range between -50 to 180°C.

To validate the phase separation in IBU-EPO HDASD, high scanning rate was also used (100 °C/min). The freshly prepared HDASD was first held at various conditions relevance to the theoretical spinodal boundary of the system for prolonged period, then subjected to a quench-cooling and fast scanning procedure. The temperature ranges were chosen between -50 to 100°C for IBU samples. It is noted that only IBU-EPO was suitable for this study, because the predicted spinodal boundary was above the melting temperature and below the thermal degradation temperature of IBU. For IND-EPO and NPX-EPO systems, the predicted spinodal boundaries were both above the thermal degradation temperature of the drugs.

Thermogravimetric analysis (TGA) was also employed to assess the thermal degradation temperature of the drugs and polymer EPO. In a typical procedure, small amount of sample was loaded to an open aluminium pan after initial taring step, subjecting to a heating process from room temperature to 250 °C at a rate of 10 °C/min. The onset temperatures of any significant weight loss (>10% w/w) for drugs and polymer EOP were recorded.

2.2.5 Attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR)

Analysis on the drug-polymer interactions of ASDs were conducted using ATR-FTIR spectroscopy (Spectrum 2, Perkin Elmer, UK). Extruded samples (outside and cross section) were directly placed on the ATR stage and spectrum range of 4000 – 650 cm\(^{-1}\) was collected based on 4 cm\(^{-1}\) resolutions, 64 runs.
2.2.6 Atomic force microscopy (AFM)

The NaioAFM (Nanosurf, Switzerland) instrument was used to obtain topographic and phase images, allowing calculation of the surface roughness of the solid dispersions. Samples of extrudate were softened immediately after HME between two flat glass slides and then cooled on metal block. The slides were then carefully removed, and the solid sample was placed on the sample holder. Both topographic and phase images were generated with the instrument operating in dynamic mode using a Tap 190Al-G cantilever (BudgetSensors, Bulgaria). Image sizes were 10x10 μm or 25x25 μm, taken at a speed of 0.8 seconds per line. Additional parameters were varied depending on each sample and optimum sensitivity. The setpoint of the cantilever was varied from 50% to 60% of the free vibrational amplitude, which was varied from 200-1000 mV. Nanosurf Naio software was used to control, obtain the data and Image J was used to further analyse the images.

2.2.7 microRaman Spectroscopy

The recrystallisation of the drug from HDASDs during high humidity storage study were studied using a RamanStation R3 (Avalon, Instruments, Belfast, UK) coupled with a RamanMicro 300 Raman microscope (PerkinElmer, Waltham, MA, USA) with objectives at various magnifications (~ 1.25 μm/pixel). A laser source of 785 nm was used and the Raman scattering of the samples was collected between 3200-400 cm⁻¹ using an acquisition time of 20 s at resolution of 2 cm⁻¹.

2.2.8 Statistical Analysis

The statistical analysis for the effects of temperature on F-H interaction parameters for all three drug-EPO combinations was carried out using Kruskal-Wallis one-way ANOVA followed by Tukey-Kramer post hoc tests; p < 0.05 was
considered as significant. For comparison of the spectra from microRaman chemical mapping and surface roughness of the freshly extruded samples (AFM), a two-tailed t test was performed $p<0.05$.

3. RESULTS AND DISCUSSIONS:

3.1 In situ temperature dependent SAXS/WAXS analysis

Small angle/wide angle x-ray scattering has the capacity to provide the spatial distribution of the dynamic features of a particle (small molecules, peptides and proteins) at nano/micro-scale ranges. It has suggested that strong intermolecular interactions can drive the formation of amorphous system under gentle mixing and moderate heating (Dave et al., 2007). Thus, in this study, it would be of significant interests to directly observe the temperature dependences of x-ray scattering pattern for the crystalline drugs (IND, NPX and IBU) in the presence of polymeric carrier. In general, the dissolution of the crystalline drug into polymeric matrix can result in the decrease of scattering intensity in the WAXS graph and eventually, completely loss of the well-defined scattering pattern (Figure 2). Examples of 3D Bragg’s peak for the physical mixtures (three drugs at 0.7 w/w) as a function of temperature are shown in Figure 2 with WAXS scattering graphs provided at four key temperature points. Due to the strong intermolecular interactions between drugs and the polymeric carrier EPO, a gradual decrease in the intensity of Bragg’s peaks associated with crystalline component can be observed with increased temperatures.

For example, in IND-EPO physical mixtures, the temperature for complete dissolution of 0.7 w/w IND was recorded at 125 to 130 °C which is approximate 30°C lower than the melting temperature of pure IND (DSC, 160°C). Whilst, for
NPX-EPO and IBU-EPO systems containing 0.7 w/w drug loading, the solubilisation temperatures were also recorded at 120-125°C and 50-55 °C respectively (Figure 2 b and c). This information is particularly useful for the design of hot-melt extrusion process, where a fully amorphous solid dispersion can be generated at conditions that are i) significantly lower than the melting of the crystalline drug (e.g. 30°C lower in IND-EPO case); ii) at much high drug loadings (~0.7 w/w for IND-EPO system). The unwanted thermodegradation associated with melting of the drug may be completely avoided since the amorphisation of crystalline drug is driven by the dissolution rather than melting. The in situ temperature dependent SAXS/WAXS analysis (complementary to DSC) can also be used to provide a very direct observation at conditions that can be related to the hot-melt extrusion platform (Sylvie, Tencé-Girault et al., 2019).

3.2 The drug-polymer temperature-composition phase diagram

Flory-Huggins theory (F-H), first established to estimate the miscibility of solvent-polymer system, has now been expanded to many areas. There have been several published drug-polymer binary systems employed using the Flory-Huggins theory to investigate the level of drug-excipient interactions, from drug-solvent activity derived interaction to drug-small molecule interaction and full temperature-composition drug-polymer phase diagram (Huang et al., 2017; Keen et al., 2014; Lin and Huang, 2010; Pajula et al., 2010; Tian et al., 2018, 2015). The implementation of this classic theory in predicting the miscibility of small molecules within macromolecular matrices has provided an simple and important route for ASD design (DiNunzio et al., 2010). The integration of this classical theory into the formulation design and process development based upon selected
advanced process technologies would have undoubtedly offered great advancement for the future of pharmaceutical manufacturing (Badman and Trout, 2014).

For an informative design of ASD based on hot-melt extrusion for all three model drugs, small scale DSC based F-H approach to construct the temperature-composition phase diagram was used. Through the ball milling process, a range of uniform drug-polymer physical mixtures at various ratios were prepared. Although, the selection of optimum ball-milling time has been previous discussed, the resultant physical mixtures were deemed not suitable for the systems in this study. Particularly for drugs with low glass transition temperature in its amorphous state (IBU and NPX), a rubber mixture was usually obtained after a very short period of milling. For example, for 0.5 w/w IBU-EPO system, the physical mixture can be converted to full amorphous within only 10 minutes of ball-milling at frequency of 15 Hz (confirmed by DSC and SAXS/WAXS, Figure 3). Therefore, to achieve sufficient experimental points from the DSC measurement for construction of thermodynamic phase diagram, the drug/polymer ratio was selected from 0.95 – 0.7 w/w. An example of the DSC thermogram for the IND-EPO system is shown in Figure 4. For all three EPO based systems, melting endpoint was not observed at a drug-polymer ratio lower than 0.7 w/w. Nevertheless, a quick estimation of the drug-EPO interaction parameters for all three drugs at multiple compositions may be obtained with a minimum four experimental points. A plot of interaction parameter, $\chi$, versus temperature for these systems were shown in Figure 5a. The fitting constants at selected temperature regions were obtained for IND-EPO, NPX-EPO and IBU-EPO with goodness of fit ranging from 0.93, 0.94 to 0.97 respectively. The obtained interaction parameter constants
for all three systems are summarised in Table 3. It should be highlighted that, from all the published phase diagrams for various drug-polymer combinations, an upper critical solution temperature (UCST) where a positive B and a negative A were obtained for the drug-polymer interaction parameters (Lin and Huang, 2010; Marsac et al., 2009, 2006; Tian et al., 2018, 2013; Zhao et al., 2010). Thus, it was very interesting to observe that a concave spinodal profile was obtained for all three HDASD systems (B < 0 and A > 0) indicating the lower critical solution temperature (LCST) behaviour (Table 3). Such behaviour has been observed for many temperature responsive polymer-water systems where a polymer solution to gel transition can be observed as the temperature increases (Jones, 2004; Mori et al., 2010). Similar behaviours were also reported in polymer-polymer mixtures (Kapnistos et al., 1996; Meredith and Amis, 2000). However, it is to our knowledge, a LCST behaviour for drug-polymer binary ASD was rarely reported in the literature so far apart from the combination of carbamazepine-AFFINISOL™ (Huang et al., 2016). All three systems IND, NPX and IBU with polymer EPO have exhibited LCST behaviour with B < 0 and A > 0 at the experimental temperature range. As the temperature decreases, the experimental values for the $\chi$ became more negative suggesting a stronger drug-polymer interaction and increased drug-polymer miscibility at lower temperature range.

Furthermore, it should also be highlighted that the values of F-H interaction parameter constants (B and A) of the three drug-EPO systems were very different from the previously published systems (Tian et al., 2014). In all our previously published drug-polymer systems such as felodipine-HPMCAS, felodipine-Soluplus and felodipine-PVP, weaker intermolecular interactions were proposed at high temperatures (close to the melting point of the drug) resulting a positive B and
negative A values. The value of B highly depends on the strength of drug-polymer interaction where stronger felodipine-polymer interaction normally results a smaller B value (felodipine-PVP). Therefore, the miscibility ranking between three polymers with neutral drug felodipine was suggested to be PVP > Soluplus > HPMCAS (Tian et al., 2014). The F-H interaction parameter $\chi$ is assumed to be consisted of enthalpic term (B) and entropic term (A) fitting constants (Rubinstein and Colby, 2003). In comparison to weak hydrogen-bonding based ASDs, strong intermolecular interactions between drugs IND, NPX and IBU and polymer EPO were suggested. Therefore, it is perhaps not surprised that the change from a positive B to a negative B value may be due to the negative enthalpic contributions to the system. The exact mechanisms of such strong drug-polymer interaction between a weakly acidic drug with weakly basic polymer or vice versa in a non-aqueous environment should be further investigated, particularly for the application of HME platform (Mistry et al., 2015; Ueda et al., 2015). Indeed, similar negative enthalpic contribution to the mixing of the system has been widely discussed and utilised for the formation of molten salts, ionic liquids or eutectic mixtures (Dave et al., 2007; Emel'yanenko et al., 2007).

With the interaction parameter constants for all three drug-EPO systems obtained at various temperatures, the maximum drug solubility in polymer EPO may be approximated. As expected, with a strong enthalpic contribution from the drug-EPO systems, large drug solubility values in polymer were predicted for all three drug-EPO systems (Figure 6). The solid-liquid curves represent the extrapolation of dissolution/melting endpoints for drug IND, NPX and IBU with polymer EPO based on the temperature-dependent interaction parameters. The experimental glass transition temperatures for all three HDASDs at various compositions are
summarised within the graphs. The theoretical glass transition temperatures were calculated using Gordon-Taylor model (Baird and Taylor, 2012). The theoretical spinodal curves for IND-EPO, NPX-EPO and IBU-EPO derived from the temperature-dependent interaction parameters (χ) are also plotted in the graphs (Figure 6).

Considering the previously published drug-polymer phase diagrams, we clearly observe a significant increase on the predicted solubility values of drug IND, NPX and IBU with the polymer EPO. Approximate 0.63 w/w for IND-EPO, 0.473 w/w for NPX-EPO and 0.55 w/w for IBU-EPO were predicted as the maximum drug solubility in polymer EPO at temperature 20°C. A gradually increase on the maximum drug solubility within EPO can also be observed for all three drugs with elevated temperatures, however such a change was not as dramatic since the inverse contributed of the entropic term (A). The predicted solubility values for all three drugs within polymer EPO at several critical temperatures were summarised in Table 4. Similar high drug-polymer solubility has also been reported in literature when a strong interaction was proved to be the main cause. For example, Mistry et al. (2015) has discussed that the strong ionic interactions between weakly basic drug ketoconazole and polymer poly (acrylic acid) can be probed by both infrared and solid-state NMR (Mistry et al., 2015). The strong drug-polymer interaction has also resulted a very high drug solubility value (0.6 w/w). Ueda et al. (2015) have also reported a high solubility for weakly acidic drug NPX in cationic polymer EPO (Ueda et al., 2015). A crystallisation was observed for NPX only when the drug loading was increased to 0.7 w/w or more.
3.3 The importance of phase diagram for QbD of amorphous solid dispersion

To accommodate the needs of emerging pharmaceutical formulations, there is a continuous requirement for parallel innovation in process development and quality control/assurance of the final drug products. In response, the ICH and FDA released Quality by Design (QbD) frameworks to facilitate the implementation of digital innovation in the pharmaceutical industry. QbD allows quality to be built into the formulation/process design in a predictive manner. In order to successfully implement the QbD framework, the consideration of specific process platform must be integrated into the Design Space. It is critical to be aware that the crystalline drug solubility and amorphous drug miscibility with amorphous polymer are two separate definitions. Particularly, when the second component polymer is a long chain macromolecule where the dynamic aspect of phase separation can be extremely slow and highly temperature/environment dependent. In most scenarios, ASDs are produced at higher temperature or solvent-assisted environment using various process platforms. The amorphous drug is kinetically “trapped” in a non-equilibrium state attributing to both the drug-polymer interaction and other kinetic factors related to both polymeric carrier and preparation method (Paudel et al., 2012). Hence, most experimental results show significantly higher apparent drug miscibility with polymeric carrier than the predicted thermodynamic solubility. It is imperative that we can access the kinetic behaviours of the “trapped” non-equilibrium state and relate it to the physical stability of ASD systems through the identification of the miscibility curve. The thermodynamic miscibility curve for the system can be predicted by the phase diagram as the liquid-solid line, whilst, the binodal and spinodal curves are together defined as the metastability boundary between one phase...
amorphous state and amorphous-amorphous phase separation (AAPS) (Luebbert et al., 2017; Tian et al., 2019). The position of AAPS in relation to the thermodynamic liquid-solid curve will certainly provide vital information on the kinetic stability of the system (Tanaka and Nishi, 1989). An illustration of three possible positions for spinodal curves in relation to the liquid-solid line is postulated in Figure 7 for the LCST behaviours.

The position of spinodal curve to the liquid-solid curve can strongly affect the kinetics of amorphous-amorphous phase separation (Tian et al., 2015). The verification of these positions will provide significant advances to the understandings of stability of ASD systems. Luebbert et al., (2018) recently reported a phase diagram (constructed by Perturbed-Chain Statistical Associating Fluid Theory) exemplified as UCST behaviour with AAPS inserted through the solid-liquid curve (Luebbert et al., 2018). An AAPS was evidenced at high temperatures that are well above the melting point of the drug. Purohit and Taylor also reported a study using high spatial resolution atomic force microscopy techniques to probe the AAPS in freshly prepared ASDs, nano-scale spherical domains were obtained on the surface of ASD films representing a classical binodal pattern within the phase diagram (Purohit and Taylor, 2015). In comparison, we are reporting a LCST behaviour for all three HDASD systems, IND-EPO, NPX-EPO and IBU-EPO, where the estimated positions for binodal, spinodal and solid-liquid curves may be described by Figure 7. From the theoretical point of view, a thermodynamic stable drug-EPO amorphous system without the potential of AAPS (temperature dependent) is indeed possible at this LCST scenario, particularly for drug loading below 0.5 w/w. For example, a red dot is used to illustrate a condition for LCST behaviour. The position is sitting below the
spinodal curve meaning the system will remain one phase during HME process. In addition, the position is sitting outside of the liquid-solid line indicating a lower free energy level for the ASD in comparison to the crystalline system. Therefore, with suitable mechanical energy input to overcome the viscosity barrier, the crystalline drug-polymer physical mixture at this condition will be converted into a homogenous ASD without AAPS.

To validate the phase diagram and the position of spinodal demixing, the IBU-EPO system was chosen due to the reason that predicted spinodal demixing region was well below the temperatures of thermodegradation for both components. For IND-EPO and NPX-EPO systems, the predicted spinodal demixing regions were above their thermodegradation temperatures, thus, experimental validation was not conducted (Figure 6). A physical mixture of 0.5 w/w IBU to EPO was prepared as described in method section followed by quench-cooling to form a homogeneous ASD. The freshly prepared 0.5 w/w IBU-EPO ASD sample was then subjected to annealing experiments at two temperatures, 70 °C and 110 °C. These two temperatures (T_{annealing} > T_m of IBU) were identified as one-phase amorphous region and AAPS region for system 0.5 w/w IBU-EPO respectively (Figure 6c).

Through the characterisations of PLM and microRaman chemical mapping, an AAPS ASD was obtained after annealed at 110 °C for 24 hours, whilst the ASD stayed homogeneous after annealed at 70 °C for similar time-scale (Support Information Figure S1).

3.4 In situ formation of HDASDs via HME

With the guidance from thermodynamic phase diagram, it was possible to design the HME process for all three HDASDs. The exact process conditions and initial
crystalline drug loadings are presented in Table 2. The location of these HDASDs were also marked in the phase diagrams in Figure 6. In each drug-EPO combinations two drug loadings were selected to be in the one-phase amorphous region and one drug loading was selected to be near the crystalline region. The extrusion process temperatures were chosen to be below the melting points of the parent crystalline drug but above the glass transition of the polymer EPO as guided by the phase diagrams.

The freshly prepared extrudates were then characterised using DSC and ATR-FTIR and directly compared with the results collected from the physical mixtures (PM) and ASDs prepared by quench-cooled method (QCPM). A similar trend was obtained for the thermograms of all three drug-EPO systems, outlining the in situ formation of one-phased HDASDs by HME at pre-defined conditions predicted by phase diagrams (Figure 6). Previously, HME methods relied on higher temperatures amorphisation and mixing of the crystalline drug into the polymer were commonly documented. However, the presence of a single distinctive glass transition with the absence of melting endothermic event was observed for all drug-EPO systems prepared by HME at predicted conditions (Figure 6, EXT denoted for extruded samples). When comparing the thermograms of EXT samples to the PM and QCPM, several clear differences can be summarised: 1) the number of glass transitions, 2) the temperature of glass transitions and 3) the melting event from the residual crystalline drug (Table 5-7).

In the case of IBU-EPO system, a homogeneous ASD can be achieved by both ball milling and HME at drug loading below 0.6 w/w, whilst, HME can further facilitate the generation of one phase IBU ASD up to 0.65 w/w with EPO (Table 5). The high
amorphisation capability of HME may be attributed to the fact that processing
temperature is very close to the melting point of IBU. Additional shearing induced
temperature elevation during HME can contribute to further dissolution of IBU
into EPO carrier (Censi et al., 2018; Liu et al., 2010). In addition, a higher $T_g$
obtained from the EXT samples also indicates a more stable amorphous solid
dispersion system in comparison to the QCPMs.

In the case of NPX-EPO system, given the predicted NPX solubility in EPO was
0.614 w/w at the processing temperature (120 °C, Table 4), it was anticipated that
one-phase ASDs should be obtained for 0.45 and 0.60 w/w NPX-EPO system. This
was first validated by the thermal analysis, where a single $T_g$ with the absence of
melting event from NPX was recorded for NPX-EPO EXT samples (Table 6). Again
higher $T_g$s were recorded for all NPX-EPO EXT samples in comparison to the PM
or QCPM samples, where the presence of two $T_g$s and/or melting event was
recorded. It was apparent that the use of HME enhanced the level of mixing
allowing for amorphisation of NPX-EPO at temperatures well below the melting of
crystalline NPX. Furthermore, for the PM sample containing 0.65 w/w NPX, there
was a broad melting endothermic peak observed before the crystalline NPX.

In the case of IND-EPO system, similar to the thermograms of NPX-EPO, both PM
and HME have converted the crystalline IND to amorphous at drug loading < 0.6
w/w (Table 7). In addition, two $T_g$s were observed for PM IND-EPO at 0.6 w/w
without the presence of melting events. It is clear that high drug loaded ASD can
be created well below the melting of the drug, with the use of F-H interaction
parameter as a guide, highlighting again the excellent miscibility of drug to
polymer in the selected HDASDs. Furthermore, the $T_g$s of all systems were also significantly higher than the values predicted by the Gordon Taylor equation.

The implementation of HDASD systems in the design of HME process has enabled the drug to dissolve in the polymeric carrier, reduced the viscosity of the system and further enhanced amorphisation. The strength of the drug-polymer interaction was further assessed using of the ATR-FTIR where the ASDs prepared by HME and quench-cooled methods were compared. The IR absorption peaks highlighting the carbonyl regions of the NSAIDs and amine regions of the EPO were summarised in Table 8.

Based on the standard IR spectra for all the individual components, the characteristic peak of the carbonyl group from EPO is normally observed at 1728 cm$^{-1}$, whilst, the carbonyl group for amorphous and crystalline IBU was recorded at 1730 cm$^{-1}$ and 1705 cm$^{-1}$ respectively. These original IR absorption peaks of IBU and EPO were used as the reference points as shown in Table 8. The changes of these characteristic peaks after formation of ASD may indicate the level of interactions within the system. An additional broadened peak was recorded at 1576 cm$^{-1}$ for extruded IBU-EPO samples at all drug loadings. This peak was recorded to 1566 cm$^{-1}$ in QCPM at 0.4 w/w IBU-EPO, but absent from higher drug loadings. This peak was suggested to be the N-O stretching after the formation of strong hydrogen-bonding (Moustafine et al., 2006). The broadening of the spectrum is more prevalent in the extruded samples, highlighting the formation of a strong hydrogen-bonding interaction during the production (Abu Ali et al., 2016). Carbonyl peak shifts were observed at the positions of 1709 to 1719 cm$^{-1}$ for IBU after extruded with EPO. These peak shifts represent the breaking of
carbonyl (C=O) dimer structure in the original crystalline IBU. Interestingly, a
strong absorption peak at this position was observed in all extruded IBU-EPO
sample in comparison to the ASDs prepared by quench-cooled method.
Additionally, peak at 1716 cm$^{-1}$ in 0.7 w/w IBU-EPO QCPM samples also suggests
the presence of crystalline IBU.

Similar to the IBU-EPO case, a stronger drug-polymer interaction between IND
and EPO was also suggested in the extruded ASDs in comparison to the quench-
cooled method (Figure 9). Peaks of relevance for crystalline IND were the
carbonyl group at 1713 cm$^{-1}$ and 1690 cm$^{-1}$, whilst, three peaks at 1735, 1710 and
1684 cm$^{-1}$ were observed for amorphous IND. From the IR spectra, it can be
shown that the presence of the peak at 1682 cm$^{-1}$, corresponding to the
amorphous IND (benzoyl C=O) was evidenced in all ASD samples except in 0.7
w/w IND-EPO prepared by quench-cooled method.

The peak at 1690 cm$^{-1}$ for 0.7 w/w quench-cooled IND-EPO indicated the presence
of crystalline IND. Additionally, the presence of the amorphous IND peak (1735
cm$^{-1}$) for both extruded samples and the 0.4 w/w quench-cooled IND-EPO ASD
suggests the amorphous nature of IND (Liu et al., 2012). The absence of the dimer
formation (1710 cm$^{-1}$) for carbonyl peak at 1710$^{-1}$ cm also suggests the formation
of stronger intermolecular interactions between IND and EPO in the extruded
HDASDs (Liu et al., 2012). Similar disruption of the dimer formation at the
carbonyl peak of the drug has also been discussed for hydrogen-bonding based
ASD systems (Taylor and Zografi, 1997).

The spectra of NPX with EPO (Figure 10) showed different characteristic peaks to
the other NSAID systems, with less focus on the carbonyl regions. In comparison
of all the ASDs with crystalline NPX, an additional band at 1682 cm\(^{-1}\) relating to the carboxylic acid dimer was only recorded for 0.65 w/w NPX-EPO system prepared by quench-cooled method. The appearance of this peak indicated the lack of drug-polymer interactions between EPO and NPX (Adibkia et al., 2013; Doreth et al., 2016). An additional peak was recorded between 1200-1230 cm\(^{-1}\) for all the rest samples suggesting the formation of strong drug-polymer interaction (Figure 10b). The effects of strong drug-EPO intermolecular interactions for all three system facilitated by HME were further examined by in vitro drug release studies. The rate and extend of drug release were significantly higher for EXT samples in comparison to the QCPM samples (support information Figure S3).

### 3.5 Verification of residual crystal in extrudates

Atomic force microscopy (AFM) was further used for to determine residual crystal after extrusion. Through the use of phase contrast mode, outlining the phase differences based on the adhesion and friction on the surface of the extrudates, nanoscale and microscale domains may be differentiated. Examples of AFM phase images (10x10 μm) of the NPX-EPO HDASD at three drug loadings (0.45, 0.6, 0.7 w/w) were presented in Figure 11 (d-f) with corresponding 3D map of the surface (a-c). The root mean square surface roughness of the extrudates were also calculated based on the average of randomly selected five different samples. When the initial drug loading was close to/exceeding the predicted liquid-solid curve (Figure 6), an increase on the surface roughness was observed for both NPX-EPO and IND-EPO HDASD systems. However, it was very difficult to characterise the IBU-EPO HDASD systems using AFM due to the stick and rubbery nature of these
samples at room temperature. Nevertheless, a smooth, homogenous surface (low surface roughness, Figure 11g) with the absence of structured particles were normally observed for NPX-EPO HDASD at drug loadings of 0.45 w/w (d) and 0.6 w/w (e). In comparison, when drug loading was increased to 0.65 w/w (predicted to be crystalline in NPX-EPO system), a sudden increase on surface roughness with the appearance of structured particles can be observed by the AFM (Figure 11 c, f and g). With the calculated root mean square surface roughness for each extruded systems, it was possible to direct visualise the transitions of the system from one-phase amorphous to extrudates with residual crystals (Lauer et al., 2018).

3.6 Storage of HDASDs at high humidity conditions

Due to the ingress of water in the system at high humidity, microRaman spectroscopic analysis was employed to monitor the appearance of crystalline drug during storage. This technique has also been widely recommended to offer the sensitivity of differentiating the crystalline and amorphous nature of the drug within ASDs without the influence of moisture (Esmonde-White et al., 2017). It was also suggested that the stability of these HDASDs system may be further enhanced by the potential moisture-induced ionic interactions between weak acidic drugs and polymer EPO (Sarode et al., 2013). In this work, the storage conditions (~95% RH) were achieved by preparing a saturated salt solution of potassium nitrate at 20°C. High humidity and high drug loading (0.6 w/w) were used to accelerate the potential phase separation and crystallisation of drug from the HDASDs (Figure 12). The correlation maps were constructed based on the relative spectra correlation calculation between the freshly prepared HDASDs and the spectra of crystalline drugs (white to black rainbow colour chart was used to
represent the correlation ratio of 0.999 – 0.599). In the case of NPX, as observed in the spectra shown in Figure 12a, the key peak of interest in the NPX spectrum is at 3070 cm\(^{-1}\). This peak was observed in crystalline NPX but absent in the amorphous from attributing to the aromatic CH stretching. At 0.6 w/w NPX drug loading, the sample was shown to be amorphous both prior to and after three weeks of high humidity storage with potential aggregation and amorphous phase separation (T=3 weeks, chemical map). Similarly, IND also showed no recrystallisation after 3 weeks of storage at the same high humidity conditions (Figure 12b) indicating by the carbonyl peak at 1680 cm\(^{-1}\) in comparison to the 1700 cm\(^{-1}\) from crystalline IND. This characteristic peak of amorphous IND was recorded for 0.6 w/w IND-EPO HDASD prior to and after three weeks of storage.

Finally, in the case of 0.6 w/w IBU-EPO system where the characteristic peak at 1608 cm\(^{-1}\) in the crystalline IBU and 1613 cm\(^{-1}\) in the HDASD was also clearly observed (Rossi et al., 2009). Again, there was no apparent recrystallisation of the drug after three weeks at high humidity storage (Figure 12c), however, a shift on the correlation between amorphous and crystalline IBU was recorded with potential drug aggregation after the storage.

4. Conclusion

Flory-Huggins based thermodynamic modelling is an informative framework for the establishment of a design space of amorphous solid dispersion. Through the constructed phase diagrams for all three HDASD systems, LCST behaviours were obtained indicating the possibility of forming stable amorphous systems at high drug loadings and low temperatures. Further characterisations on the extrudates confirmed that the amorphisation of NPX, IBU and IND at these pre-defined
conditions can be achieved by one-step continuous HME process. The establishment of predictive thermodynamic model allows the interpretation and evaluation of HME process in a well-defined space, in return, ensure the quality of amorphous solid dispersions. Further work will be focused on the investigations of kinetic impacts of the HME process based on the pre-defined thermodynamics of the HDASD systems.

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Table 1 Physicochemical properties for drugs and polymer used in this study (Cai et al., 2011; Kindermann et al., 2011; Li et al., 2016; Ng et al., 2013).

<table>
<thead>
<tr>
<th>Substance</th>
<th>$T_g$ (°C)</th>
<th>$T_m$ (°C)</th>
<th>Molecular weight (g/mol)</th>
<th>Density (g/cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® E (EPO)</td>
<td>48</td>
<td>____</td>
<td>47000.00</td>
<td>0.83</td>
</tr>
<tr>
<td>Naproxen</td>
<td>6</td>
<td>152</td>
<td>230.59</td>
<td>1.29</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>-44</td>
<td>76</td>
<td>206.29</td>
<td>1.03</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>50</td>
<td>156</td>
<td>357.79</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Table 2 HME process conditions and drug loadings for EPO with drug IND, NPX and IBU

<table>
<thead>
<tr>
<th>Systems</th>
<th>Process condition, full convey (11mm, L/D 20:1)</th>
<th>Drug weight fractions (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>indomethacin - EPO</td>
<td>120 °C, 60 RPM</td>
<td>0.4; 0.6; 0.7</td>
</tr>
<tr>
<td>naproxen - EPO</td>
<td>120 °C, 60 RPM</td>
<td>0.45; 0.6; 0.65</td>
</tr>
<tr>
<td>ibuprofen - EPO</td>
<td>65°C, 60 RPM</td>
<td>0.45; 0.6; 0.7</td>
</tr>
</tbody>
</table>

Table 3 Flory-Huggins interaction parameter constants for system IND+EPO, NPX+EPO and IBU+EPO

<table>
<thead>
<tr>
<th>HDASDs</th>
<th>B</th>
<th>A</th>
<th>R$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND-EPO</td>
<td>-19601</td>
<td>42.39</td>
<td>0.93</td>
</tr>
<tr>
<td>NPX-EPO</td>
<td>-8072.5</td>
<td>17.28</td>
<td>0.94</td>
</tr>
<tr>
<td>IBU-EPO</td>
<td>-9083.2</td>
<td>24.86</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Table 4: The predicted drug-EPO solubility as function of temperatures for IND, NPX and IBU systems

<table>
<thead>
<tr>
<th>Temperatures (°C)</th>
<th>IND solubility in EPO (w/w) §</th>
<th>NPX solubility in EPO (w/w)</th>
<th>IBU solubility in EPO (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.631</td>
<td>0.473</td>
<td>0.541</td>
</tr>
<tr>
<td>30</td>
<td>0.634</td>
<td>0.480</td>
<td>0.557</td>
</tr>
<tr>
<td>50</td>
<td>0.641</td>
<td>0.495</td>
<td>0.611</td>
</tr>
<tr>
<td>70</td>
<td>0.651</td>
<td>0.516</td>
<td>0.766</td>
</tr>
<tr>
<td>90</td>
<td>0.664</td>
<td>0.544</td>
<td>1</td>
</tr>
<tr>
<td>120</td>
<td>0.699</td>
<td>0.614</td>
<td>Spinodal region</td>
</tr>
</tbody>
</table>

* data for drug solubility in polymer EPO was predicted through the constructed temperature-composition phase diagrams

§ denoted the values are not statistically significant at different temperatures

suggesting a less temperature dependent drug-polymer interaction parameters (p>0.05)

Table 5: Thermal events recorded using DSC for IBU-EPO mixtures at selected drug loadings

<table>
<thead>
<tr>
<th>Sample</th>
<th>Glass Transition (°C)</th>
<th>Melting Event (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45 IBU_PM</td>
<td>7.41 ± 0.32</td>
<td>-</td>
</tr>
<tr>
<td>0.45 IBU_EXT</td>
<td>3.62 ± 1.4</td>
<td>-</td>
</tr>
<tr>
<td>0.6 IBU_PM</td>
<td>-15.97 ± 1.6</td>
<td>65.23-81.64</td>
</tr>
<tr>
<td>0.6 IBU_EXT</td>
<td>4.67 ± 1.1</td>
<td>-</td>
</tr>
<tr>
<td>0.65 IBU_PM</td>
<td>-21.88 ± 0.91</td>
<td>58.78-84.57</td>
</tr>
<tr>
<td>0.65 IBU_EXT</td>
<td>-13.6 ± 0.81</td>
<td>-</td>
</tr>
</tbody>
</table>

* Glass transition temperatures were average value±standard deviation (n=3)

Table 6: Thermal events recorded using DSC for NPX-EPO mixtures at selected drug loadings and production methods

<table>
<thead>
<tr>
<th>Sample</th>
<th>Glass Transition (°C)</th>
<th>Melting Event (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45 NPX_BM</td>
<td>36.57 ± 0.61</td>
<td>-</td>
</tr>
<tr>
<td>0.45 NPX_EXT</td>
<td>38.1 ± 0.69</td>
<td>-</td>
</tr>
<tr>
<td>0.6 NPX_BM</td>
<td>35.58 ± 0.93</td>
<td>-</td>
</tr>
<tr>
<td>0.6 NPX_EXT</td>
<td>38.23 ± 0.45</td>
<td>-</td>
</tr>
<tr>
<td>0.65 NPX_BM</td>
<td>28.34 ± 0.11</td>
<td>133.14 ± 1.50</td>
</tr>
<tr>
<td>0.65 NPX_EXT</td>
<td>36.42 ± 0.45</td>
<td>-</td>
</tr>
</tbody>
</table>
Glass transition temperatures were average value ± standard deviation (n=3)

Table 7 Thermal events measured using DSC of IND_EPO mixes at different drug loading and production methods

<table>
<thead>
<tr>
<th>Sample</th>
<th>Glass Transition (°C)</th>
<th>Melting Event (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 IND_BM</td>
<td>53.50 ± 0.36</td>
<td>-</td>
</tr>
<tr>
<td>0.4 IND_EXT</td>
<td>54.70 ± 0.46</td>
<td>-</td>
</tr>
<tr>
<td>0.6 IND PM</td>
<td>31.10 ± 1.4</td>
<td>81.35-120.45</td>
</tr>
<tr>
<td>0.6 IND EXT</td>
<td>59.49 ± 0.67</td>
<td>-</td>
</tr>
<tr>
<td>0.7 IND PM</td>
<td>19.24</td>
<td>82.2-132.67</td>
</tr>
<tr>
<td>0.7 IND EXT</td>
<td>54.27 ± 0.77</td>
<td>126.21-147.58</td>
</tr>
</tbody>
</table>

Glass transition temperatures were average value ± standard deviation (n=3)

Table 8 The key IR absorption peaks for all drug-polymer ASDs prepared via different production methods

<table>
<thead>
<tr>
<th>Tested samples</th>
<th>Key peaks presented by IR wavenumbers (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IND_EPO</td>
</tr>
<tr>
<td></td>
<td>HME</td>
</tr>
<tr>
<td>Higher drug loadings (0.65/0.7)</td>
<td>1682</td>
</tr>
<tr>
<td></td>
<td>1735</td>
</tr>
<tr>
<td>Lower drug loadings (0.45/0.4)</td>
<td>1682</td>
</tr>
<tr>
<td></td>
<td>1735</td>
</tr>
</tbody>
</table>

Fig.1
Fig. 2

a_70%IND-EPO

b_70%NPX-EPO
Fig. 3

50%IBU-EPO, ball-milled 10 mins, 15Hz

WAXS, 60 seconds, vacuum

SAXS, 600 seconds, vacuum
Fig. 7

Graph showing the relationship between temperature and drug weight fraction (w/w) for different solubility and spinodal lines.
Fig. 8

![Graph showing transmission (%) vs. wavenumber (cm⁻¹) with various compounds and concentrations.]

Fig. 9

![Graph showing transmission (%) vs. wavenumber (cm⁻¹) with different IND preparations and concentrations.]

Fig. 10

![Graph showing transmission (%) vs. wavenumber (cm⁻¹) with EPO and NPX preparations at different concentrations.]

(a)
Fig. 11

(b)

Transmission (%)

Wavenumber cm \(^{-1}\)

EPO
45% NPX EXT
45% NPX QCPM
65% NPX EXT
65% NPX QCPM
Pure NPX

Examples of NPX-EPO EXTs

0.45 w/w 0.60 w/w 0.65 w/w

(a) (b) (c)

(d) (e) (f)

Root mean square roughness (nm)

0.45 0.6 0.65 w/w NPX

(g)

Root mean square roughness (nm)

0.4 0.6 0.7 w/w IND

(h)
Fig. 12

a. HDASD 0.6 w/w NPX-EPO

T=0

Crystalline NPX

T=3 weeks

b. HDASD 0.6 w/w IND-EPO

T=0

Crystalline IND

T=3 weeks
Figure 1 chemical structure of polymer Eudragit® EPO (a) and drug indomethacin (b) naproxen (c) ibuprofen (d), reported potential strong drug-polymer intermolecular interactions are highlighted in circles

Figure 2 Evolution of WAXS scattering profiles as a function of sample temperature for physical mixtures IND-EPO (a), NPX-EPO (b) and IBU_EPO (c) at drug loading of 0.7 w/w

Figure 3 The WAXS and SAXS scattering plots for 0.5 w/w IBU-EPO physical mixture processed via ball-milling at 15Hz for 10 minutes

Figure 4 Example of melting point depression thermograms for IND-EPO ball-milled physical mixtures, compositions from 1 to 0.75 w/w.

Figure 5 Plots of Flory-Huggins interaction parameters versus temperature for IND-EPO, NPX-EPO and IBU-EPO systems showing Lower Critical Solution Temperature behaviour with $B < 0, A > 0$ (LCST, at high temperature range)

Figure 6 the temperature-composition phase diagram for systems IND-EPO (a), NPX-EPO (b) and IBU-EPO (c) with associated errors; the calculated spinodal curves are shown in dash lines; the experimental and theoretical glass transition temperatures for these HDASDs are also included; EXT and (X) denoted the extrusion conditions
Figure 7 Schematic phase diagrams for various kinds of crystalline-amorphous polymer blends. The binodal and melting point are drawn by solid line (partially by dashed line) and spinodal curves are drawn by dotted lines; red dot illustrates the temperature and drug loading for a stable ASD from both thermodynamic and kinetic perspectives.

Figure 8 IR spectra of IBU-EPO mixtures prepared by HME (solid) and quench-cooled melt (QCPM, dashed) compared with pure crystalline drug and pure EPO polymer.

Figure 9 IR spectra of IND-EPO mixtures prepared by HME (solid) and quench-cooled method (QCPM, dashed) in comparison to the crystalline IND.

Figure 10 IR spectra of NPX and EPO mixtures prepared by HME (solid) and quench-cooled method (dashed) at the regions of carbonyl region (a) and C-N (b).

Figure 11 Atomic force microscopic images of NPX-EPO extrudates containing 0.45, 0.60 and 0.65 w/w drug loadings collected in both topography (a, b, c) and phase contrast modes (d, e, f); the root mean square surface roughness of the extrudates containing various drug loadings for systems NPX-EPO (g) and IND-EPO (h).

Figure 12 microRaman chemical maps and spectra (49x49 μm, pixel size 1.25 μm/pixel) of HDASDs containing 0.6 w/w NPX (a) 0.6 w/w IND (b) and 0.6 w/w IBU (c) before and after three-week storage at 95%RH, the spectra for crystalline drugs are highlighted using the black arrows.