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Article

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Fixed Dose Combination Formulations: Multi-Layered Platforms Designed for the Management of Cardiovascular Disease

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Abstract

Hyperlipidaemia is considered as one of the main risk factors associated with cardiovascular diseases (CVDs). Among different lipid-lowering agents used to manage hyperlipidaemia, statins are highly prescribed for management of hyperlipidaemia with simvastatin being one of the most common. Simvastatin is susceptible to extensive metabolism by CYP450 3A4 and 3A5 which are expressed both in the liver and the gastrointestinal tract. Nevertheless, the localization of these enzymes is site dependent with lower concentration at the distal/proximal regions of the small intestine/colon. In addition to statins, medications such as antihypertensive and anti-coagulants are introduced as adjuvants, for the treatment of cardiovascular disease. The aim of this study was to design a bi-layer delivery system capable of delivering bi-phasic release of Simvastatin and Aspirin, within a fixed dose combination. A delayed release platform based on a combination of anionic polymers prepared using hot melt extrusion was developed to delay the release of simvastatin. An optimized formulation was tested for dissolution performance clearly demonstrated an ability to delay the release of Simvastatin. In addition, an immediate release layer based on Kollidon VA64 was successfully developed to deliver Aspirin. Both formulations were then manufactured as a bi-layer drug delivery system (tablets and co-extrudates) and the release performance examined. Based on the obtained results, these formulations may be used as a platform for delivering a wide range of medications in a bi-phasic manner.

Keywords: Fixed-dose combination, hot-melt coextrusion, multilayer drug delivery, bi-phasic drug release, simvastatin, enhanced bioavailability.

Introduction

According to the world health organization (WHO), cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide ^{1,2}. The main risk factors associated with CVDs are smoking, hypertension and dyslipidaemia. Amongst them, dyslipidaemia is considered the predominant risk ³. The National Institute for Health and Care Excellence (NICE) guidelines for medicine-based CVD management following an acute myocardial infarction and/or stroke (secondary prevention) includes the use of agents such as aspirin, angiotensin converting enzyme inhibitors (ACE inhibitors), β -blockers, thiazide-like diuretics and statins. However, for patients without a prior history of cardiovascular events (primary prevention), recent trial evidence has been cited in support of the recommendation of calcium channel blockers (CCBs), as an alternative to β -antagonists. It is therefore clear that, whilst blood pressure (BP) regulators may be varied between primary and secondary prevention, low dose aspirin and a statin are consistently administered ^{4,5}.

The mechanism by which statins lower the high level of LDL is through the effective inhibition of 3-hydroxy,3-methylglutaryl coenzyme A reductase (HMG-co-A) which mediates the synthesis of cholesterol ⁶. Endogenous production of cholesterol is at its highest at night, hence, the administration time of a statin exhibiting a short half-life (e.g., simvastatin, lovastatin and fluvastatin), becomes critical, if drug concentration in the body is to match cholesterol biosynthesis in the liver ⁷. According to prescription cost analysis (PCA) for England in 2017, simvastatin represented more than 37% of all statins prescribed, at a total cost of £28.7 million ⁸. Despite this, it is interesting to note that the bioavailability of simvastatin is extremely poor (less than 5%) due to the fact that it is considered a BCS class II drug and a CYP 3A substrate ⁹. Being a Class II compound, it has poor solubility in GI fluids. Therefore, enhancing the solubility of simvastatin using enabling technologies represents an exciting means of improving the pharmacokinetics and hence bioavailability of this drug.

In addition, Simvastatin (SIM) is marketed as a prodrug in the lactone form with conversion to the active metabolite, open-chain β -hydroxyl acid, in the GI tract. Importantly, simvastatin either in the acid or lactone form are rapidly and irreversibly cleared by enzymatic oxidation. Enterocytes, which are located mainly in the villi tips of jejuna mucosa, contain virtually all types of drug-metabolising enzymes found in the liver (CYP 3A). Moreover, the localisation of CYP 3A in the gut is regional with higher levels in the jejunum, slightly

decreased levels in the duodenum, and significantly decreased levels in the ileum, caecum and colon. Protecting the drug from the hostile environment of the upper GIT may enhance therapeutic activity¹⁰. Moreover, lower statin dosing may be achievable with improved bioavailability, thus reduce the risk of adverse events.

While co-administer low-dose aspirin (ASP) with statins is highly recommended as stated previously, long-term and multiple dosage regimes, typical of CVD, often lead to poor patient compliance, reduced clinical efficacy, and, an increased risk of CVD related complications. Fixed-dose combination products (FDCs) negate the need for complex treatment regimens and are deemed preferable in long-term disease management. In this particular case where ASP and delayed release SIM are combined, ASP shows good solubility in Intestinal fluids due to its low pKa (3.5). However, given the acidic nature of aspirin, release of the drug at the same site as simvastatin may alter microenvironment pH limiting simvastatin lactone to β -hydroxyl acid hydrolysis and solubility of β -hydroxyl acid. Separating APS and SIM into different layers is, therefore, considered necessary for achieving optimal therapeutic outcome.

In respect to manufacturing multi-layered FDCs, processes must be used that produce robust drug delivery platforms that consistently deliver the required amount of drug to the patient, at the optimum rate, in order to achieve the desired therapeutic effect. Importantly, the processes used must also be capable of operating at full production scale with an associated high throughput. Undoubtedly, current processes used to manufacture multi-layer FDCs are sub-optimal and suffer from a number of significant disadvantages. Alternatively, hot melt extrusion (HME), an innovative continuous manufacturing platform, may provide a more efficient means of manufacturing complex oral dosage forms^{11–14}. Hot melt co-extrusion (HMCE), has been used to manufacture multilayer drug delivery systems^{15,16}. In reference to this emerging view of advanced pharmaceutical manufacturing, this article addresses the design, manufacture and characterization of clinically relevant FDCs using extrusion technology. Solid dosage forms containing ASP and SIM to provide FDCs that offer an immediate release of low-dose ASP, and a delayed release of SIM to where it is optimally effective, have been engineered. Moreover, by targeting the release of SIM to the distal regions of the GI tract, enzymatic metabolism in the gut may be limited, resulting in improved bioavailability (higher plasma levels). In this study, HME was used for the manufacturing of an immediate release ASP formulation and an enabling site-specific SIM formulation. As a

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proof of concept, the aforementioned formulations were also subjected to HMCE with minimal formulation variation to prepare bi-layered, bi-phasic drug delivery systems in a single-step manner.

110 **Materials and Methods**

Materials

Acetylsalicylic acid (ASP) and polyethylene glycol 200 were purchased from sigma Aldrich (U.K.) and Simvastatin (SIM) was purchased from Kemptek (U.K). Hydroxypropyl methyl cellulose acetate succinate (HPMCAS) HF and MF grades were gifts from Shin-Etsu (Japan), methyl methacrylate co-acrylic acid (Eudragit® L100), ethyl acrylate co-acrylic acid (Eudragit® L100-55), aminomethyl methacrylate (Eudragit® EPO) were kindly supplied by Evonik (Germany) and polyvinyl pyrrolidone-vinyl acetate (Kollidon® VA64) and polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) were supplied by BASF (Germany). Triethyl citrate (TEC) was purchased from Lancaster synthesis (U.K.). All other materials were of analytical grade and were used as supplied.

Methods

Thermogravimetric Analysis (TGA)

Thermal decomposition behaviour of individual materials was evaluated using thermogravimetric analysis. A Thermal Advantage model Q500 (TA instrument, Leatherhead, U.K.) was used in all analyses. Samples of 5-10 mg were loaded into aluminium pans (TA Instrument, USA) and were ramped across a temperature range from 25-300°C at heating rate of 10°C/min. Nitrogen was used as purge gas at flow rate of 60ml/min to maintain an inert atmosphere. Percent mass loss was recorded as a function of temperature during measurements and samples were analysed in triplicate.

Differential Scanning Calorimetry (DSC)

Thermal behaviour of all formulation components and extrudate was evaluated using a DSC 8000 power compensation dual furnace differential scanning calorimeter (Perkin-Elmer, Windsor, Berkshire, UK). The instrument was calibrated with indium and zinc for heat of fusion and melting point, respectively. 3-5 mg of sample was accurately weighted into DSC pans (Perkin-Elmer, Berkshire, U.K.) and crimped using aluminium lids. Samples were analysed in a heat/cool/heat procedure using a heating rate of 200°C/min across the range between -60°C and 200°C. In all cases dry helium was used as purging gas at flow rate of 40

140 ml/min. Samples were analysed in triplicate and heat flow was recorded as a function of temperature.

Powder X-ray diffraction

Prior to PXRD analysis, pelletized extrudates were milled in a ball-milling chamber for two intermittent (rest period of 20 seconds) 30s periods with a frequency of 1/25s⁻¹. Powdered samples were immediately analysed at room temperature using a MiniFlex II Desktop Powder X-ray Diffractometer (Rigaku Corporation, Kent, England) equipped with Cu K β radiation, at a voltage of 30 kV and a current of 15 mA. The powders were gently consolidated on a glass top-loading sample holder with 0.2mm depression. All samples were scanned within the angular range of 3-45° 2 θ in continuous mode with a sample width of 0.03° and a scan speed of 2.0°/min. Formulations components were individually analysed prior to extrusion using similar conditions.

Preparation of solid dispersions using HME

Preliminary assessment of polymers processability for both ASP and SIM was investigated using a co-rotating conical twin-screw extruder (HAAKE minilab, Thermo Electron Corporation, Stone, Staffordshire, UK). All formulations were processed at 50 rpm and with different temperatures ranging from 100°C to 140°C tried for processability. The physical mixtures of desirable formulations (processable at relatively low temperature and showed desired dissolution behaviour) of both ASP and SIM formulations were then extruded using a Rondol® fully-intermeshing co-rotating 10mm twin-screw extruder (Rondol Industries SAS, Strasbourg, France) equipped with a 2mm diameter cylindrical die. The screw configuration adopted contained a range of kneading (K) and conveying (C) elements, as detailed in Table 1. All formulations were extruded at a screw speed of 50rpm and the temperature profiles employed for ASP and SIM matrices, respectively, are given in Table 2.

Preparation of bilayer dosage forms

Preparation of the bi-layer co-extrudates was performed using two identical fully-intermeshing co-rotating 10mm twin-screw extruders (Rondol® Industries SAS, Strasbourg,

France) connected with an in-house designed co-extrusion die (Figure 1). Co-extrusion was performed with barrel temperature profiles directly transferred from single layer extrusion (Table 2) with the co-extrusion die substituting the original cylindrical die for each extruder. The extruders were fed manually and were operated at screw speeds of 15 rpm (core) and 2 rpm (coat), respectively. Co-extrudates were air-cooled on conveying belt with a measured total diameter of 6.6mm, a core diameter of 4.6 and coating thickness of 1mm.

In an attempt to compare the dissolution behaviour of the obtained bilayer co-extrudates with a dosage form prepared via conventional methods, bilayer tablets also were prepared using a hydraulic disc/pellet presser. Approx. 375mg of an ASP formulation (equating to 75mg of ASP) was loaded between two stainless steel discs and pressed using a pressure of 7.5 ton for a 3-minute period. The formed ASP tablet was collected and placed in between the two compression discs with approx. 440mg of a SIM formulation (offering equivalent to 20mg of SIM) placed on top and pressed using a pressure of 7.5 ton for a further 3 minutes. The obtained tablet was a laminar bilayer tablet with a theoretical total weight of 815mg.

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In-vitro dissolution test

In-vitro drug release behaviour of ASP and SIM was examined using an USP TYPE II dissolution apparatus tester Copley DIS 8000 (Copley, U.K.). The pH of human GIT increases progressively from the stomach (pH1-3 with an average of 1.8) to the terminal ileum (pH7-8 with an average of 7.5), followed by a sharp decrease to a mean of pH6.5 in the caecum, and then rises progressively again to a final mean of pH 7.0 in the distal colon¹⁷⁻¹⁹. Transit time in the small intestine is often quoted to be 3–4 h. However, in an attempt to treat the distal region where pH value increases as a separate site, 2 h was used for pH6.8 to represent the proximal small intestine. Dissolution testing for SIM was therefore carried out as follows:

- (I) 0.1N HCl (pH 1.2) for two hours;
- (II) Medium pH adjusted to 6.8 by addition of 0.2M Na₃PO₄ and the dissolution test was carried out 2 hours (total 4 hours);
- (III) pH was then adjusted to 7.5 using 2M NaOH drops and the dissolution continued for 2 hours (total 6 hours);

(IV) Further pH adjustment to 6.5 was performed with addition of 1M HCl drops and the dissolution test was continued for another 18 hours.

The temperature of the dissolution media was maintained at $37\pm0.5^{\circ}\text{C}$ using a paddle stirring speed of 75rpm. During formulation development, pelletised extrudates containing equivalent to 75mg ASP and 20mg SIM, respectively, were examined. The co-extruded pellets composed of the most promising ASP and SIM formulations, on the other hand, were examined with equivalent to 50mg ASP and 25mg SIM, respectively, in each dissolution vessel. Samples were withdrawn at predetermined time points during the four stages of dissolution. At each time point, a 2 ml aliquot was withdrawn from each dissolution vessel, filtered through a $0.22\mu\text{m}$ Millex®-GS syringe filter and replaced with 2 ml of the corresponding buffer. 1 ml of the filtered aliquot was then diluted with 0.5 ml of acetonitrile (ACN) to prevent recrystallization of SIM during HPLC analysis. For comparison purposes, the dissolution performance of pure SIM powders, Zocor (20mg SIM) and, compressed bilayer tablets were also investigated.

Determination of drug concentration using HPLC.

Determination of drug concentration was performed using an Agilent infinity series 1220 HPLC (Agilent technology, Germany). All chromatographic analyses were performed in isocratic mode. Two independent methods were developed and validated in order to quantify SIM and ASP, respectively.

Simvastatin lactone and its corresponding open-chain β -hydroxy acid form were quantified using a C18 Poroshell 300 porous silica column from Agilent ($300\text{\AA}$, $2.1\times75\text{mm}$, $5\mu\text{m}$ particle size). The mobile phase consisted of a mixture (42:58, v/v) of acetonitrile (ACN) and acetate buffer (12mM, pH 4.5 adjusted by glacial acetic acid filtered through $0.2\mu\text{m}$ cellulose nitrate membrane filter). The flow rate was set to 0.28mL/min, and the column compartment temperature to 30.0°C . The injection volume was $3\mu\text{L}$, and the detection wavelength set to 238nm. The method was validated and there was no interference from drug components or excipients.

ASP and its hydrolysis product salicylic acid (SA) were quantified using a C¹⁸ Kinetex[®] column from Phenomenex (100Å, 4.6×150mm, 5µm). The mobile phase consisted of a mixture of acetonitrile (ACN) with 0.1% TFA and phosphate buffer solution (25mM adjusted to pH 2.0 using orthophosphoric acid and filtered through 0.2µm cellulose nitrate membrane filter) at 35:65 (v/v) which was filtered and degassed prior to use. The flow rate was set to 1.0mL/min, and the column compartment temperature to 30.0°C. The injection volume was 5µL and the detection wavelength set to 276nm. The method was validated and showed no interference from simvastatin lactone or its open-chain β-hydroxy acid.

Raman Spectroscopic analysis

Raman spectroscopy was performed using a RamanMicro 300 Raman microscope (Perkin Elmer, Windsor, Berkshire, UK) coupled with an Avalon Raman station R3 model AVRS003A spectrometer (Avalon Instrument, Belfast, UK, 785 nm laser). A magnification of x20 with a total exposure time of 20s (4s x 5 exposures) was used for all samples. Data was collected from 200-3200cm⁻¹ with an automatic baseline correction and 15s photo bleaching. Additionally, drug migration was investigated using Raman mapping. Measurements were performed at a resolution of 2 cm⁻¹ using a x20 objective lens and a total exposure time of 20s (5s, x 4 exposures). A pellet cross-section was mapped using a 50µm spacing between points. Raman imaging was performed using Spectrum Image analysis software (R1.6.4.0394) using single wavenumber mode. The wavenumber selected for the APIs were: 1644 cm⁻¹ for SIM and 1039 cm⁻¹ and 932 cm⁻¹ for ASP.

Statistical analysis

Statistical tests were conducted using GraphPad Prism. A one-way analysis of variance with Tukey's multiple comparison tests was used. The confidence interval was set automatically to 95%. In all cases, at least six replicates were used for analyses and p≤0.05 denoted significance.

Results and Discussion

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ASP layer development

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ASP has a relatively poor stability profile being susceptible to ester hydrolysis in the presence of moisture. This results in the formation of two compounds, namely salicylic acid (SA) and acetic acid (AA). The ASP decomposition can be further affected by increasing pH which facilitates hydrolysis towards completion, and with elevated temperature where salicylic acid is broken down through decarboxylation process to produce phenol and CO₂²⁰. Poor stability of ASP, especially if water and/or non-ambient processing is used during manufacture, must be considered. The decomposition of ASP when exposed to high temperatures, a principal concern in this study, has been reported in the literature^{21,22}. It was therefore the main focus, in the design and process of an IR ASP formulation, to prevent ASP decomposition and SA formation..

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Herein, the two main criteria imposed for carrier selection for an ASP layer were (i) the ability of the carrier to offer compendial-acceptable immediate ASP release, and (ii) the ability to process the formulation without inducing ASP thermal degradation. Pre-formulation characterisation of ASP using thermogravimetric analysis showed that ASP started to show significant decomposition close to its melting point (onset of melting at approx. 142°C whilst peak at 150°C, thermogram not shown). It is therefore abundantly clear that the processing temperature selected for HME should be strictly controlled and ideally well below 142°C to minimise the risk of ASP degradation. Taking this into consideration, EPO, SOL and VA64 were selected for preliminary investigation. The EPO-ASP binary mixture was not extrudable below the set criteria and therefore plasticiser was incorporated. It was suggested in a previous publication that the addition of polyethylene glycol (PEG) could significantly reduce the extrusion torque and consequently reduce the melt zone temperature setting for EPO based matrices²². For PVP-VA64 matrices, plasticisers were mainly used to improve extrudates flexibility and hence downstream processability. A citrate ester plasticiser, triethyl citrate (TEC), in addition to PEG, was also studied for its suitability in such cases owing to its frequent use in polymers with vinyl groups. For extrudates consisted of Soluplus, on the other hand, Lutrol F68 (a Polyoxyethylene-polyoxypropylene block copolymer) was utilised as a

dissolution modifier since extruded SOL matrices are well-known for their compendial-unsatisfactory dissolution performance.

The extruded ASP matrices were examined for free SA content as well as the actual drug loading in each formulation where both recovered ASP and SA were taken into account (Table 3). It is clearly shown that formulations based on SOL and VA64 all yielded excellent match between theoretical and measured drug loadings with compendial-acceptable levels of SA content (<3% of the labelled ASP amount). Formulations based on EPO, on the other hand, all resulted in high free SA content and moreover, unaccounted drug loss. Such results may be indicative of ASP degradation pathways other than hydrolysis, in this case most probably, thermal decomposition. It is worth mentioning that the equal-weight blending of VA64 with EPO (formulations ASP 4-6) was originally intended to decrease the required processing temperature. Interestingly, as shown by the measured drug loading values (Table 3), such practice incidentally supports the aforementioned thermal decomposition hypothesis as the recovered drug content increased with decreasing processing temperature.

The SOL and VA64 based ASP formulations were subjected to drug release study using simulated blank gastric fluid (pH 1.2) and the dissolution profiles are illustrated in Figure 2. It was evident that the ASP-SOL matrices (formulations ASP 1 & 2) exhibited statistically similar release profiles, despite the addition of Lutrol F68 to ASP 2 as a dissolution modifier. The rate of drug release for neither ASP-SOL formulations was compendial satisfactory (at least 75% release within the first 45min according to compendial methods)^{23,24}, where only approx. 20% drug was released after 45 minutes (Table 3), and should fail as immediate release platforms. By comparison, formulations manufactured using VA64 (ASP 7 – ASP 11) all passed the compendial requirement for dissolution rate as an immediate release formulation, with ASP 7 and ASP 9 releasing $94.67 \pm 3.97\%$ and $94.08 \pm 1.56\%$ aspirin, respectively within 45min and reaching complete release at 90min, both qualifying as the most successful ASP formulation. ASP 7, however, was suboptimal due to flexibility issues after cooled to ambient temperature. The lack of flexibility is not only problematic during downstream secondary processing such as cutting/pelletizing, but can also cause surface defects when used as an exterior coating in multilayer co-extrusion. ASP 9, on the other hand, exhibited significantly improved flexibility therefore represented the best candidate to carry forward to bilayer co-extrude studies.

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SIM layer development

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As with Aspirin, pre-formulation studies involving solid state characterisation (DSC and TGA) of SIM was performed. Thermogravimetric analysis showed that SIM started to degrade at a relatively high temperature, approximately 240°C (data not shown). On the other hand, DSC thermograms showed that SIM melted at 145°C and formed an amorphous solid with a glass transition at approximately 36°C if quench cooled from its melt (Figure 3). The large gap (around 100°C) between SIM melting and its onset of degradation provided a extensive processing temperature window without inducing SIM thermal degradation. The ultimate goal of formulating SIM was to delay its release until it reaches specific sites of the GIT (distal small intestine and proximal colon) at which the expression of the oxidative enzymes, CYP450 3A4, are at a minimum ²⁵. Delaying SIM release is expected to result in an improvement in the pharmacokinetic activity of the drug as a consequence of the reduced metabolism by localized oxidative enzymes. Additionally, SIM formulation should be enabling and improve drug solubility, which in turn, might synergistically improve its bioavailability. There are a number of different polymers commonly used to target drugs to specific regions of the GIT (Table 4).

Initial studies using a broad range of enteric polymers confirmed that HPMC-AS was the most appropriate polymer for formulation. Eudgrait S100 was difficult to extrude and released drug much too slowly to be of benefit in this study. HPMC-AS was carried forward and a number of different polymer combinations were extruded based upon this base polymer (Table 5).

Melt-extruded matrices showed excellent gastric and proximal small intestinal resistance in the in-vitro simulated fluids (with less than 10% drug release in pH1.2 and pH6.8 media (Figure 4). It was found that factors such as excipient blend ratio, plasticizer loading, and addition of antioxidant, could significantly influence the release kinetics.

The effect of drug loading (Figure 4a) on the release behaviour of extruded formulations was tested at two different drug loadings (5 and 20% w/w). Dissolution testing revealed that the higher the drug loading, the lower the extent of release. This can be attributed to the fact that the concentration of the polymers, which are expected to inhibit the precipitation of SIM, is lower at high drug loading and hence decreased potency to remain supersaturated under non-sink conditions.

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3 350 In a similar manner, the amount of TEC added to the formulation inversely affected the extent
4 of SIM release (Figure 4b) which can be attributed to the fact that the concentration of the
5 polymers is lower at higher TEC concentrations. However, increased plasticizer content
6 noticeably improved extrudate flexibility. All investigated formulations showed multi-stage,
7 pH dependent dissolution behaviour. In all cases, although the delivery platforms released
8 drug that mirrored the pH step change, the release of drug was incomplete in the final phase
9 (pH 6.5). Thus, Eudragit L-100-55 was incorporated as a polymer that has a lower pH solubility
10 threshold when compared to both HPMCAS-HF and L-100. A formulation based on a higher
11 ratio of HPMCAS-HF compared to L-100 and L-100-55 (Figure 4c) showed a higher extent of
12 release when compared to those composed of an equal ratio of the three polymers. The
13 difference in the extent of SIM released was only observed at stage III and stage IV of the
14 dissolution experiment. At these stages, the pH of the media is higher than or equal to the pH
15 value at which HPMCAS-HF begins to dissolve. Thus, the higher the ratio of HPMCAS-HF the
16 higher the extent of release. The presence of HPMCAS-HF might have also played an
17 important role in retarding the precipitation of SIM as described previously. Therefore, the
18 higher the ratio, the higher the extent of inhibition and hence higher the extent of SIM
19 release. The dissolution behaviour of the extruded formulation was further improved by the
20 addition of TPGS as a dissolution modifier. The incorporation of TPGS, a water-soluble vitamin
21 E derivative, played two important roles: (I) to prevent the oxidation reaction of the carboxylic
22 acid groups in HPMCAS-HF during extrusion and (II) owing to the amphiphilic nature of the
23 compound, it was found that SIM release was significantly improved (when compared to
24 those without TPGS.

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31 365 Based on these preliminary investigations whereby binary polymeric combinations were used
32 as a platform to manufacture tailored delayed release drug delivery systems, a blend of
33 HPMCAS-HF/L-100/L100-55 was employed as a matrix for SIM dispersion. The blend was
34 loaded with 5% w/w of SIM and plasticized with TEC in order to improve processability. The
35 matrix was able to retard drug release at low pH (1.2) and started to release SIM upon
36 changing pH to 6.8. This delivery platform was able to maintain the release of SIM upon
37 further change in media pH to 7.5 with further release observed when media pH reduced
38 to 6.5. Interestingly, the solubility of SIM was improved (approximately two-fold
39 increase) when compared to pure SIM. Despite the improvement in the dissolution
40 behaviour of the extruded formulation following matrix development, the incomplete release
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of SIM over the 24-hour period was considered a major drawback of the formulation. Therefore, to drive the release to completion within the 24-hour window, the incorporation of a lower grade of HPMCAS polymer which had lower pH solubility threshold was considered. Subsequently, HPMCAS-HF was substituted with a lower grade HPMCAS-MF which has a lower threshold of pH solubility (0.5 pH units than HF). Formulations based on different ratios of HPMCAS-HF:HPMCAS-MF were extruded using the conditions described previously. Solid state characterisation of the obtained extrudates revealed a single glass transition temperature at 53°C which is an intermediate temperature between that of the drug and the excipient mixture, indicative of an amorphous miscible system (Figure 5). Amorphization of SIM in these formulations was also evident with complete loss of crystalline characteristics (halo like PXRD pattern, Figure 6) when compared with the physical mixture of the formulations. Figure 7 depicts the dissolution behaviour of the formulations based on 100% HPMCAS-HF, 50:50 HPMCAS-HF: HPMCAS-MF and 100% HPMCAS-MF. Substituting 50% of HPMCAS-HF resulted in no significant improvement in both dissolution rate and extent in simulated ileum fluid (Figure 7, pH 7.5) which can be explained by the fact that neither of the polymers is dominant and hence there was no impact upon release of the drug. As the pH of the dissolution was altered to 6.5, a significant difference in the extent of dissolution was observed which can be attributed to the presence of HPMCAS-MF which has a pH threshold below the pH of the media. Despite the improvement in SIM release, complete release was not achieved for either formulation. Complete substitution of HF grade with the MF grade, interestingly, resulted in a significant improvement in SIM release in the dissolution media. This was particularly evident in regions mimicking the GI fluid of the duodenum-proximal colon, with greater release at pH 7.5, representing the ileum/proximal colonic region of the GIT. The ability of this combination of polymer to retard the release at low pH and to completely release SIM at high pH is attributed to the presence of polymers that have relatively high pH threshold to bypass the low pH media of the stomach but low enough to release SIM as the media pH increases. The pH of the buffer at the last three stages of the dissolution test was above the pH-solubility threshold of all the polymers included in the formulation thus facilitating matrix dissolution and hence a significant improvement in SIM release. The ability of this formulation to behave in a similar manner when tested *in-vivo* is highly desirable as the oxidative enzymes associated with the degradation of SIM are highly concentrated in the proximal part of the GI tract and is known to be less expressed at the

distal part of the GI tract. Based on the desirable dissolution behaviour obtained with formulation SIM 6, it was later used as the core layer of the co-extruded bi-layer release platform.

Preparation of multilayer drug delivery system based on optimised ASP and SIM formulations.

Co-extrusion

Formulations of both ASP (ASP 9) and SIM (SIM 6) were manually fed into the extruders to manufacture co-extrudates that combine two different drug delivery platforms. The resulted co-extrudates (Figure 8) showed a clear formation of the coat-and-core structure with a core of 6.6mm diameter covered by a 1mm thick coat.

Obtained co-extrudates were subsequently cut into pellets with a length of 6mm (equal to the overall diameter of the co-extrudates) and were used for dissolution testing. The drug contents in the pelletised bilayer co-extrudates were determined. Figure 9 illustrates the dissolution behaviour of the obtained co-extrudates. Both layers showed a dissolution behaviour matching their corresponding monolithic extrudates. More specifically, the coat layer released 90% of ASP in 45 minutes and completely released ASP within the first two hours. On the other hand, the core layer desirably retarded the release of SIM in the first two hours (average residence time in the stomach) and started to release SIM upon increasing the pH of the dissolution media to a pH mimicking the hostile environment in the middle part of the small intestine (jejunum). Further release of SIM was observed with increasing the pH of the dissolution media to 7.5 at which >80% of SIM was released.

Spectroscopic analysis using Raman spectroscopy (Raman mapping) showed a clear separation between the core and coat layer (Figure 10). The spectra from both the core and the coat layers showed good agreement with those of the monolithic systems. The coat layer spectrum (Figure 11) showed a peak at 1039 cm^{-1} corresponding to ASP with complete absence of the peaks associated with SA confirmed the stability of ASP during co-extrusion. With respect to the core layer, the characteristic peak of SIM at 1646 cm^{-1} was shifted to 1644 cm^{-1} in the spectrum of the core layer (Figure 11) suggesting an interaction between SIM and the polymeric mixture of the core layer. Tracking ASP and SIM migration (using single

wavenumber analysis) during co-extrusion showed that both SIM and ASP was distributed in the core/coat layers with no sign of migration, immediately following extrusion. The red spots found in the core layers upon tracking ASP migration using a wavenumber of 1039 cm^{-1} was attributed to overlapping between the spectra of the core with that of the coat at this wavenumber due to the noise in the baseline. However, using another distinct wavenumber (932 cm^{-1} , limited overlap with the coat spectrum) to track ASP distribution, removed this issue (Figure 10).

Multilayer tablet

In an attempt to compare the dissolution behaviour of multilayer drug delivery systems manufactured using advanced and conventional manufacturing techniques, optimised ASP and SIM formulations (ASP 9 and SIM 6, respectively) were also manufactured into a multilayer tablet using standard compression. The obtained extrudates were milled and compressed into bilayer tablets as described previously. It is worth noting that the dissolution behaviour of the co-extruded pellets showed no significant difference when compared to milled extrudates. Despite this, the *in-vitro* dissolution behaviour of the bi-layer tablet (Figure 12) was significantly different to the co-extrudate. In particular, ASP in the immediate release layer achieved 40 percent ASP release within the first 45 minutes, whereas co-extrudate ASP release levels met compendial standards. This may be due to variations in the disintegration of the ASP layer, as the result of secondary processing (compression) and change of layer thickness. The fact that the ASP layer requires burst release as an IR platform emphasises the role of disintegration. Interestingly, there was no difference in the release of simvastatin in the extruded matrix and the bilayer tablet.

Conclusion

In this study, HME was successfully employed to manufacture two different drug delivery systems exhibiting immediate and delayed release of ASP and SIM, respectively. The data obtained shows the importance of using a combination of polymers to attain better control of a site-specific drug release. A blend of the anionic polymers was able to retard SIM release in the low-pH media (pH 1.2) and release SIM upon transition to higher pH media (>6.8).

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3 Manipulation of formulation components such as plasticizer concentration, drug loading and
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5 475 polymer ratio clearly impact the release kinetics and the extent of SIM release. Substituting
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7 high pH threshold polymers with low pH threshold polymers was associated with a higher
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9 extent of release. Manufacture of multilayer drug delivery systems was successfully
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11 performed using two different manufacturing techniques (co-extrusion and conventional
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13 compression). The release of ASP was significantly different between these two dosage forms,
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15 480 with the co-extruded bi-layer drug delivery systems outperforming the bi-layer tablet. It may
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17 be interesting to examine the performance of multilayer mini-tablets (exhibiting a greater
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19 surface area) using conventional manufacturing methods and compare to co-extruded
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21 pellets. As a proof of concept, this paper has shown potential of Hot Melt Co-extrusion as a
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23 viable continuous manufacturing method capable of producing advanced bi-layer
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25 485 combination drug delivery systems for CVD management.
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List of Figures

Figure 1. In-house designed co-extrusion die used in the preparation of concentrated bi-layer co-extrudates.

Figure 2 Dissolution profiles of ASP extrudates based on SOL, EPO and VA64, respectively, as polymeric carriers. Dissolution testing was performed in 0.1N HCl. (±S.D., n=3)

Figure 3. DSC thermogram for SIM obtained by sequential heat/cool/heat procedure using high speed DSC.

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Figure 4 In-vitro dissolution profiles of melt-extruded SIM formulations showing (a) the influence of SIM loading, (b) TEC content and, (c) blend ratio amongst three anionic matrix polymers as well as the addition of an anti-oxidant TPGS, respectively.

Figure 5: DSC thermogram for SIM formulations based on different ratios of HPMCAS-HF and HPMCAS-MF obtained using Hyper DSC. A glass transition temperature event was evident during heating at 200°C/min from ambient to 100°C.

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Figure 6: PXRD patterns for the physical mixtures and extruded matrices of the of the formulation based on different ratios of HPMCAS-HF and HPMCAS-MF. Measurements were performed between 3-45 2θ at scan speed of 2.0°/min.

Figure 7: Dissolution behaviour of extrudates shows the effect of changing HPMCAS grades on the extent of SIM release. Values represent the average $\pm$ SD (N=3).

Figure 8: Representative micro-photos of the co-extrudates produced using the prompted formulations showing the diameter of the co-extrudates and the core layer.

Figure 9: Dissolution behaviour of the co-extrudates combining an immediate release ASP and a delayed release SIM. Values represent the average $\pm$ SD ($N=3$).

Figure 10 False colour map of the co-extrudates showing the clear separation between the core and the coat layers. Average intensity (top left), SIM distribution (top right), ASP distribution (1039 cm^{-1} , bottom left) and ASP distribution (932 cm^{-1} , bottom right). Measurements were performed at resolution of 2 cm^{-1} and total exposure time of 20 s/point and using a co-extrudate immediately after production.

Figure 11 Raman spectra of (from bottom to top): ASP (blue), SA (orange), SIM (grey), core layer (yellow) and the coat layer (light blue). Measurement were performed at resolution of 2 cm⁻¹ and total exposure time of 20s.

Figure 12: Dissolution behaviour of bi-layer tablet combining an immediate release ASP and a delayed release SIM. Values represent the average $\pm$ SD (N=3).

List of tables

Table 1: Screw configuration used for extrusion processing of simvastatin and aspirin optimized formulations.

SIMVASTATIN		ASPIRIN	
No. of Elements	Element Type	No. of Elements	Element Type
5	Forward conveying	8	Forward conveying
2	60° kneading	1	60° kneading
2	90° kneading	1	90° kneading
1	60° kneading	1	60° kneading
2	Forward conveying	3	Forward conveying
1	60° kneading	1	60° kneading
1	90° kneading	1	90° kneading
1	60° kneading	3	Forward conveying
4	Forward conveying	1	End unit
1	End unit		Screw tip
	Screw tip		

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Table 2: Barrel temperatures for the extruders used to manufacture the core (SIM) and the coat (ASP) layers.

	Zone 1 (°C)	Zone 2 (°C)	Zone 3 (°C)	Zone 4 (°C)	Die (°C)
SIM (core)	80	150	140	130	120
ASP (coat)	60	120	120	120	120
Extrusion direction

Table 3: List of ASP formulations used for preliminary investigation of the processability of selected polymers. Formulations were processed using a co-rotating twin screw extruder operated at 50 rpm.

Formulation	Aspirin	Soluplus®	Eudragit® EPO	PVP- VA64	TEC	Lutrol F68	PEG200	HME Temperature	Measured drug loading*	Free SA content as % of declared ASP**	% ASP Release on declared ASP @ 45min
No.	g	g	g	g	g	g	g	°C	wt%	wt%	%
ASP 1	2.000	8.000	-	-	-	-	-	120	20.57±1.38	0.21±0.07	17.31±4.31
ASP 2	2.000	6.400	-	-	-	1.600	-	120	20.99±1.04	0.29±0.05	20.62±2.88
ASP 3	2.000	-	7.200	-	-	-	0.800	140	15.49±0.65	40.81±1.15	-
ASP 4	2.000	-	3.600	3.600	-	-	0.800	140	15.37±0.96	33.17±2.64	-
ASP 5	2.000	-	3.600	3.600	-	-	0.800	120	18.18±0.39	39.37±1.79	-
ASP 6	2.000	-	3.600	3.600	-	-	0.800	100	19.82±0.34	31.91±0.64	-
ASP 7	2.000	-	-	8.000	-	-	-	120	21.00±0.83	0.59±0.25	94.67±3.97
ASP 8	2.000	-	-	7.600	-	-	0.400	120	21.28±1.23	1.43±0.22	91.42±2.45
ASP 9	2.000	-	-	7.200	-	-	0.800	100	21.62±0.81	0.85±0.69	94.08±1.56
ASP 10	2.000	-	-	7.600	0.400	-	-	120	20.72±1.37	1.62±0.54	85.24±0.13
ASP 11	2.000	-	-	7.200	0.800	-	-	100	19.32±3.62	0.29±0.11	77.81±3.17

*The “measured drug loading” takes into account both ASP and SA recovered from content uniformity test.

**Free SA assessment – The compendial acceptable level of SA content in a ASP formulation should be <3% of the declared ASP content.

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695 *Table 4: Commonly used polymers in delayed release drug delivery systems with pH threshold and GIT site of delivery* ^{26,27}.

Polymer	pH threshold for dissolution	Targeted site for GI delivery
Eudragit® L100-55	5.5	Duodenum
HPMC phthalate 55	5.5	Duodenum
HPMC-AS LF	5.5	Duodenum
HPMC-AS MF	6	Jejunum
Eudragit® L100	6	Jejunum
HPMC-AS HF	6.8	Ileum & Colon
Eudragit® S100	7	Colon

Table 5: List of SIM formulations investigated for the processability of selected polymers. Formulations were processed at 50 rpm.

Formulation No.	SIM g	HPMC-AS (HF) g	L-100 g	L-100-55 g	TEC g	TPGS g
SIM 1	0.500	4.275	4.275	-	0.950	-
SIM 2	1.000	4.050	4.050	-	0.900	-
SIM 3	2.000	3.600	3.600	-	0.800	-
SIM 4	0.500	3.800	3.800	-	1.900	-
SIM 5	0.500	4.275	2.1375	2.1375	0.950	-
SIM 6	0.500	4.275	2.1375	2.1375	0.950	1.000
SIM 7	0.500	2.850	2.850	2.850	0.950	-
SIM 8	0.500	2.850	2.850	2.850	0.950	1.000

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Co-extrusion Die, Co-extrudate Fixed Dose Combination and Release Profile

338x190mm (54 x 54 DPI)