Co-extruded solid solutions as immediate release fixed-dose combinations.

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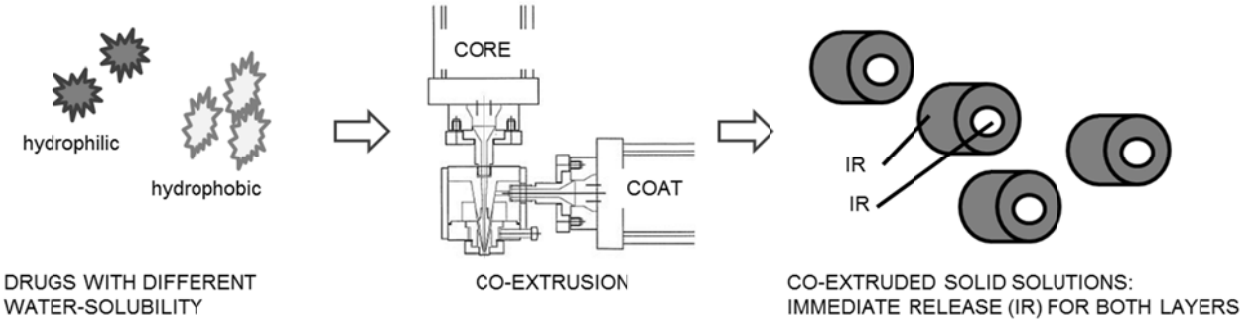
Abstract

The aim of this study was to develop by means of co-extrusion a multilayer fixed-dose combination solid dosage form for oral application characterized by immediate release for both layers, the layers containing different drugs with different water-solubility. In this study polymers were selected which can be combined in a co-extruded dosage form. Several polymers were screened on the basis of their processability via hot-melt extrusion, macroscopic properties, ASA decomposition and in vitro drug release. Acetylsalicylic acid (ASA) and fenofibrate (FF) were incorporated as hydrophilic and hydrophobic model drugs, respectively. Based on the polymer screening experiments Kollidon® PF 12 and Kollidon® VA 64 were identified as useful ASA carriers (core), while Soluplus®, Kollidon® VA 64 and Kollidon® 30 were applicable as FF carriers (coat). The combination of Kollidon® 30 (coat) with Kollidon® PF 12 or Kollidon® VA 64 (core) failed in terms of processability via co-extrusion. All other combinations (containing 20% ASA in the core and 20% FF in the coat) were successfully co-extruded (diameter core: 2 mm / thickness coat: 1 mm). All formulations showed good adhesion between core and coat. ASA release from the core was complete within 15-30 min (Kollidon® PF 12) or 30-60 min (Kollidon® VA 64), while FF release was complete within 20-30 min (Kollidon® VA 64) or 60 min (Soluplus®). DSC and XRD revealed that both drugs were molecularly dispersed in the carriers. Raman mapping exposed very little intermigration of both drugs at the interface. Fixed-dose combinations with good in vitro performance were successfully developed by means of co-extrusion, both layers providing immediate release.

KEY WORDS: hot-melt co-extrusion, fixed-dose combination product, drugs with different water-solubility, immediate release, solid solutions

Graphical abstract



1. Introduction

Hot-melt extrusion (HME) technology for pharmaceutical applications has gained significant interest in recent years. Even though this technique has been used for decades in the plastics and food industry, it is relatively new in the pharmaceutical industry. HME shows numerous benefits over traditional methods including the continuity of the production process, environmental advantages due to elimination of solvents and the possibility of improving drug solubility. The latter has drawn attention because large numbers of new chemical entities under development exhibit very poor solubility and bioavailability. Formulation of solid solutions via HME can be an efficient approach in the delivery of poorly water-soluble drugs. Co-extrusion is defined as the simultaneous extrusion of two or more materials through a single die, creating a multi-layered extrudate [1]. The final co-extruded product may offer several advantages due to material and composition characteristics imparted by the individual polymer layers. These dosage forms allow to modulate drug release from the different layers [2, 3] and to simultaneously administer non-compatible drugs (formulated in separate layers). Up until now, no co-extruded oral dosage forms are available on the market and only a few papers concerning co-extrusion as a manufacturing technique for oral drug delivery systems have been published [1-6]. Co-extrusion is gaining importance for the production of oral drug products as combination therapy is becoming increasingly important as fixed-dose combination (FDC) products offer therapeutic (improved patient adherence) and economic (lower manufacturing costs) benefits. Such “polypills” are being used in the treatment of e.g. cardiovascular disease, diabetes, hyperlipidemia, HIV, tuberculosis and malaria. In this study acetylsalicylic acid (ASA, an anticoagulant) and fenofibrate (FF, a lipid regulating drug) were incorporated as hydrophilic and hydrophobic model drugs, respectively. While ASA is slightly soluble in water and has relatively high oral bioavailability, FF is poorly water-soluble and has a low bioavailability after oral administration. Due to their biopharmaceutical and pharmacological properties, immediate release of both drugs is required. The aim of this study is to design a core/coat dosage form

suitable for co-extrusion, whereby the core and coat formulation provide immediate drug release (IR) of both drugs (ASA and FF). Several research groups have already investigated the feasibility of HME to produce immediate release FF dosage forms. Kollidon® VA 64 [7, 8], Eudragit® E PO [8], Soluplus® [9] and blends of PVPVA 64, HPMC and Soluplus® [10] were reported.

2. Materials and methods

2.1. Materials

The following polymers were used during the polymer selection procedure: Eudragit® E PO (Evonik, Darmstadt, Germany), Sentry™ Polyox® WSR N10 (polyethylene oxide, PEO 100,000 g/mol, Colorcon, Dartford Kent, United Kingdom), Soluplus®, Kollidon® VA 64, PF 12 and 30 (BASF, Ludwigshafen, Germany). Polyethylene glycol (PEG 4000 g/mol, Fagron, Waregem, Belgium) and Pluronic® F-68 (PLUR, Sigma–Aldrich, Steinheim, Germany) were used as plasticizers. Fenofibrate (FF, Roig-Farma, Barcelona, Spain) and acetylsalicylic acid (ASA, Utag, Amsterdam, The Netherlands) were incorporated as hydrophobic and hydrophilic model drug, respectively. All other chemicals were of analytical grade.

2.2. Polymer selection

For the selection procedure several thermoplastic polymers were hot-melt extruded and evaluated for processability, macroscopic properties (visual inspection of surface, die swell quantification using marking gauge), salicylic acid content (ASA formulations) and in vitro drug release. Polymers/plasticizer were mixed (with mortar and pestle) with FF and ASA (concentration range: 20-40%, w/w) and hot-melt extruded using a co-rotating, fully intermeshing twin screw extruder (Prism Eurolab 16, ThermoFisher Scientific, Germany) having a length-to-diameter ratio of 25/1. The co-rotating screws consisted of three mixing sections and a densification zone (Fig. 1). A co-extrusion die (Guill, West Warwick, USA) was connected at the end of the extruder. The extrusion temperature varied according to the polymer, but all five heating segments of the extruder were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. The premixes were fed into the extruder using a loss-in-weight powder feeder (Brabender flexwall®, Duisburg, Germany). The screw speed was kept constant at 120 rpm and 180 rpm for extrusion of ASA and FF formulations, respectively. ASA formulations were

extruded through the core orifice of the co-extrusion die, yielding extrudates with a diameter of 2 mm. FF formulations were extruded through the coat orifice (1mm coat thickness) yielding hollow cylindrical tubes with an outer and inner diameter of 4 and 2 mm, respectively. After cooling down to room temperature, the cylindrical extrudates were manually cut into mini-matrices of 2 mm length.

2.3. Production of co-extrudates

Polymer/plasticizer and drug were premixed in a tumbling mixer (Turbula® T2A, W.A. Bachofen, Basel, Switzerland) for 20 min. Co-extrusion was performed using two co-rotating, fully intermeshing twin screw extruders (Prism Eurolab 16, ThermoFisher Scientific, Germany). The co-extrusion die (Guill, West Warwick, USA) was connected to both extruders. Both melts were combined in the die to form two concentric layers, a core and a coat. All five heating segments of both extruders were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. The premixes were fed into the corresponding extruders using loss-in-weight powder feeders (Brabender Flexwall®, Duisburg, Germany). The screw speed was kept constant at 120 rpm (core) and 180 rpm (coat). The co-extrusion die was designed with a core diameter of 2 mm and a coat thickness of 1 mm, resulting in a total die diameter of 4 mm. After cooling down to room temperature, the cylindrical co-extrudates were manually cut into mini-matrices of 2 mm length.

2.4. Determination of free salicylic acid

The salicylic acid (SA) content in the extrudates was assessed according to the USP 32 monograph for aspirin tablets.

2.5. In vitro drug release

Dissolution studies were performed using USP apparatus 1 (baskets). The equipment consisted of a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, NJ, USA). Acetate buffer pH 4.5 containing 0.05 M sodium lauryl sulfate was used as dissolution medium [11, 12]. Sink conditions were maintained during the experiments. The temperature of the dissolution medium (900 ml) was kept constant at 37 ± 0.5 °C. The rotational speed of the baskets was set to 100 rpm. Samples (5 ml) were withdrawn at 5, 10, 15, 20, 30, 45, 60 (and 90) min.

ASA and FF concentrations were determined using a validated HPLC method. The HPLC equipment (Merck-Hitachi, Darmstadt, Germany) consisted of a gradient solvent pump set at a constant flow rate of 1 ml/min, an autosampler, a reversed-phase C-18 column (LiChrospher® 100 RP-18 (5 µm)) (250 x 4 mm) and guard column (4 x 4 mm) and a UV detector set at 285 nm. The injection volume was 20 µl. An automatic integration system (software D-7000 Multi-Manager) was used for peak integration. The mobile phase consisted of mixtures of buffer solution pH 2.9 [12] and methanol: initially using a 57:43-ratio (to elute ASA and SA, while FF was retained on the column). After 14.5 min the ratio of the mobile phase was rapidly changed to 10:90 (to elute the hydrophobic FF from the column), after 22.0 min the ratio between the aqueous and organic phase was again set at 57:43 and the column was equilibrated until 31.0 min prior to the following analysis.

2.6. X-ray diffraction

X-ray diffraction (XRD) was performed to investigate the crystallinity of the drugs in the mini-matrices. X-ray patterns of drug, polymer, physical mixtures and extrudates were obtained using a D5000 Cu Kα Diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany). The angular range (2θ) varied from 10° to 60° (step width = 0.02°, counting time = 1 s/step).

2.7. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to study the solid state properties of the extrudates. The thermal behavior of the individual components, physical mixtures and extrudates was evaluated using a Q2000 DSC (TA Instruments, Leatherhead, UK). The system was equipped with a refrigerated cooling system. Samples (5-10 mg) were accurately weighed and hermetically sealed in aluminum pans (TA Instruments, Leatherhead, UK).They were cooled to -70 °C, followed by heating to 170 °C at a linear heating rate of 10 °C/min.

2.8. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to visualize the interface between both co-extruded layers. Samples were coated with platinum by means of a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan). Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan).

2.9. Raman spectroscopy

The distribution of the different components in the coat and core of the co-extrudates was evaluated with Raman microscopic mapping using a Raman Rxn1 Microprobe (Kaiser Optical Systems Inc., Ann Arbor, MI, USA), equipped with an air-cooled CCD detector. The laser wavelength employed was 785 nm from a Invictus NIR diode laser (Kaiser Optical Systems Inc., Ann Arbor, MI, USA). All spectra were recorded with a resolution of 4 cm^{-1} and an exposure time of 7 s, using a laser power of 400 mW. Cross sections of co-extrudates were scanned by a 50× short working distance objective lens (spot size 10 μm) in point-by-point mapping mode using a step size of 10 μm in both the x and y directions. The resulting images provide information about the distribution of different components in the co-

extrudates. Data collection and data transfer were automated using the HoloGRAMS™ data collection software (version 2.3.5, Kaiser Optical Systems Inc., Ann Arbor, MI, USA). The analysis of the spectra was done using HoloMAP™ data analysis software (version 2.3.5, Kaiser Optical Systems Inc., Ann Arbor, MI, USA) and Matlab® software (version 7.1, The MathWorks Inc., Natick, MA, USA). All spectra were baseline corrected using the Pearsons method. To visualize the distribution of the drug within the co-extrudate, a specific peak of each drug was shown relatively to a specific peak of the polymer. In order to attribute specific Raman peaks in the spectra to the different components in the formulations, Raman spectra were collected from the pure components and the separate layers. All spectra were recorded with a resolution of 4 cm^{-1} and an exposure time of 10s. Standard normal variate (SNV) pre-processing was applied on the collected spectra prior to analysis, to correct for the variation in path length/sampling distance between probe and sample.

2.10. Karl Fisher titration

The moisture content of the polymers and plasticizers at ambient conditions was determined by volumetric Karl Fischer titration using a V30 volumetric KF titrator (Mettler Toledo, USA). The experiments were performed in triplicate.

3. Results and discussion

3.1. Polymer selection

The aim of this work was to develop a formulation providing immediate release from a co-extruded dosage form, containing ASA as hydrophilic model drug and FF as hydrophobic model drug. Several thermoplastic polymers were therefore hot-melt extruded in combination with ASA and FF, and evaluated for processability (torque and die pressure), macroscopic properties (surface, transparency, consistency and die swell), ASA decomposition (via SA content determination) and in vitro drug release. Polymers that failed one criterion, i.e. were not processable below 140 °C with a torque value of <80% motor load and a die pressure of <100 bar, exhibited unfavorable macroscopic properties (irregular surface, sticky, irregular dimensions), contained >3% SA or did not release 80% of the drug in approximately 45 min, were rejected.

3.1.1. ASA

Five polymers (PEO, Eudragit® E PO, Soluplus®, Kollidon® VA 64 and Kollidon® PF 12) were tested during ASA-polymer screening. Table 1 presents the composition, extrusion temperature, SA content and in vitro drug release of the screened formulations. All polymers were processable via hot melt extrusion at the specified temperatures. All PEO/ASA extrudates (extruded at 75 °C) were smooth, slightly yellow and transparent. However, they became opaque after cooling down to room temperature as PEO recrystallized. Process monitoring revealed that the addition of PEG 4000 as a plasticizer resulted in lower die pressures and torque values. Unplasticized Eudragit® E PO/ASA mixtures had a minimum extrusion temperature of 140 °C. The incorporation of PEG 4000 improved processing by lowering the extruder torque and die pressure. The addition of 25% PEG allowed extrusion at 120 °C. Eudragit® E PO/ASA extrudates were slightly yellow but transparent. They exhibited unfavorable macroscopic properties as they were very flexible and sticky. Extrusion of pure Soluplus® requires a temperature of 120-200 °C [13]. Soluplus®/ASA mixtures were

processable at a minimum temperature of 110 °C and good quality extrudates (smooth, clear, rigid, not sticky) were obtained, but with a slight pink discoloration. This discoloration was probably due to the formation of complexes between salicylic acid (ASA degradation) and free iron ions originating from the extrusion screws or barrel due to shear [14]. The addition of 1% sodium EDTA eliminated the pink discoloration, which supported our hypothesis. For the processing of Kollidon® VA 64/ASA extrudates a temperature of at least 130 °C was required. The extrudates were clear and smooth but the same pink discoloration as seen with Soluplus® appeared. Again, the problem was solved by adding 1% sodium EDTA. Kollidon® PF 12 was processable at a temperature of 110 °C. The quality of all Kollidon® PF 12/ASA extrudates was good (clear, rigid) and no discoloration was noticed. It was found in literature that Kollidon® forms complexes in solution with salicylic acid, which could be a possible explanation for the absence of the pink discoloration [15]. No significant die swell was observed for any of the tested polymers.

ASA undergoes thermal decomposition as is starts to decompose upon melting (140 °C) [16], while in the presence of water hydrolysis of ASA results in the formation of SA and acetic acid. Therefore the polymers that yielded good quality extrudates (PEO, Soluplus®, Kollidon® VA 64 and Kollidon® PF 12), were further tested for salicylic acid content (Table 1). The USP SA limits [11] for ASA tablets (≤0,3%) or coated ASA tablets (≤3%) were used as reference values, although solid dispersions do not comply with either dosage forms. For all PEO/ASA formulations a large amount of SA was formed during extrusion. No correlation between moisture content and SA concentration could be demonstrated. It was found that the SA content decreased (26.6, 17.8, 12.0% SA) with increasing PEG concentration (0, 25, 50% PEG) and decreasing torque (60, 30, 15% motor load) and die pressure (55, 30, 13 bar). Breitenbach [17] stated that high shear forces can lead to a local temperature increase within the extrusion barrel. In addition, Breitenbach identified the residence time and die pressure as factors with a significant impact on the impurity profile. These findings support our hypothesis that the extruder torque and die pressure may play a role in ASA degradation

during extrusion. The degree of decomposition in extrudates with Soluplus® as carrier was lower in comparison with PEO formulations, as it was possible to approach the USP limit of ≤3%. Nevertheless, the only two polymers that complied with the SA limit were Kollidon® VA 64 and Kollidon® PF 12, containing 2.4 and 1.5% SA respectively. Kollidon® VA 64 and Kollidon® PF 12, the polymers that complied with the criteria of processability and ASA stability, were tested for in vitro drug release. The ASA release from Kollidon® VA 64 was complete in 20 min, whereas the release from Kollidon® PF 12 was already complete in 10 min.

3.1.2. FF

Five polymers (PEO, Soluplus®, Eudragit® E PO, Kollidon® VA 64 and Kollidon® 30) were tested as FF carriers. Due to the plasticizing properties of FF, Kollidon® PF 12 (used during ASA polymer screening) was replaced by Kollidon® 30 exhibiting a higher T_g (149 °C instead of 90 °C). Table 2 presents the composition, extrusion temperature and in vitro drug release of the screened formulations. All polymers were processable via hot-melt extrusion at the specified temperatures. Unplasticized PEO/FF mixtures had a minimum extrusion temperature of 100 °C as the die pressure exceeded 100 bar at lower process temperatures. PEO/PEG/FF mixtures could be extruded at 75 °C, although torque and die pressure increased at lower PEG concentration. Soluplus® (loaded with 20-30% FF) was processable at a temperature of 100 °C. Apparently, an increase in FF concentration (20-30% FF) improved the ease of processing by lowering the T_g (from 30.0 to 15.0 °C). FF melted during processing since the process temperature (100 °C) exceeded its melting point (80 °C). All Soluplus® extrudates exhibited a smooth surface. All extrudates up to 30% FF were transparent. Eudragit® E PO (loaded with 20% FF) was processable at a temperature of 120 °C without the addition of a plasticizer. Increasing FF concentrations improved the ease of processing by lowering the extruder torque and die pressure. Consequently the extrusion

temperature of mixtures containing 30% and 40% FF was lowered to 110°C and 100°C, respectively. All Eudragit® E PO/FF extrudates were transparent when they emerged from the die. However, the extrudates had unfavorable properties as they were sticky and collapsed after cooling down to room temperature. Kollidon® VA 64/FF mixtures (20-40% FF) were processable between 100 and 130 °C. As observed for Soluplus® and Eudragit® E PO, the ease of processing enhanced at increasing FF loads. Clear extrudates with good quality (no die swell, thin, smooth, clear and rigid) were obtained. Kollidon® 30 loaded with 30% FF was extrudable at 150 °C. Increasing the drug load to 40% slightly enhanced the processability. However, the minimal extrusion temperature remained 150 °C as the die pressure increased sharply at lower temperature. All extrudates were clear during extrusion and remained clear after cooling down to room temperature. Good quality extrudates (no die swell, rigid, clear and a smooth surface) were obtained.

The polymers that yielded good quality extrudates were further tested for in vitro drug release (data not shown). The time required for complete FF release from the different formulations is shown in Table 2. FF release from PEO extrudates was incomplete after 1 h. Although the addition of PEG to PEO resulted in a considerable increase in release rate, the drug release rate remained too low. FF release from Soluplus® extrudates was nearly complete after 1 h. A higher drug load did not influence the release rate significantly. Although Soluplus® offers the particular advantage that precipitation and crystallization of drugs during dissolution is prevented as a result of its micellar character [13], the FF release rate was lower than expected. Hughey et al. described that Soluplus® tended to form a strong gel (in vitro) and that dissolution occured through erosion of the matrix [18]. Recently, Soluplus® was also found to tailor (delay) the release of another hydrophilic drug (acetaminophen) [19]. Complete FF release from all formulations formulated with Kollidon® VA 64 and Kollidon® 30 was achieved within 20 min.

3.2. Co-extrusion

A successful co-extrusion process requires that both melts flow through the co-extrusion die under the same temperature conditions. Based on the polymer screening data, the following formulations were identified as potentially useful for co-extrusion: Soluplus®, Kollidon® VA 64 and Kollidon® 30 as FF carriers (coat) in combination with Kollidon® VA 64 or Kollidon® PF 12 as ASA carriers (core). The ASA:FF ratio in all formulations was 35:65, which complied with the ratio of 80 mg ASA and 145 mg FF (usual daily dose). As the coat had a total volume of ±19 mm^3 versus ±6 mm^3 for the core, FF was formulated in the core. The content of ASA and FF in the co-extrudates was ensured by setting correct combinations of feed rate and drug load in both processes.

The combination of Kollidon® 30 as carrier for FF with Kollidon® VA 64 or Kollidon® PF 12 as carriers for ASA failed in terms of processability. Using the minimum possible die temperature for Kollidon® 30 (125 °C) the core formulations with Kollidon® VA 64 and Kollidon® PF 12 were too liquid as they left the die resulting in collapse during cooling down to room temperature. The co-extrusion trials showed that Kollidon® VA 64 and Kollidon® PF 12 as carrier for ASA were compatible with Kollidon® VA 64 and Soluplus® as carrier for FF in terms of extrusion temperature. The composition as well as the extrusion conditions used for each formulation are shown in Table 3. The core and coat of co-extrudate F_2 were processable at the same temperature (barrel: 130 °C, die: 105 °C). As the core and coat of F_1, F_3 and F_4 had different extrusion temperatures (cfr. polymer selection), temperature adjustments were required to enable the co-extrusion of these formulations. Nevertheless, all four formulations had good macroscopic properties as they were transparent and exhibited no die swell. Furthermore, both layers adhered firmly as no delamination was observed (Fig. 2). In addition, the thickness of the coat and core was uniform, as confirmed with a marking gauge. After extrusion, the core and coat of the co-extrudates were physico-chemically characterized. The thermogram of all coat formulations revealed that there was no crystalline FF present in formulation F_1, F_2 (Fig. 3A), F_3 and F_4 (Fig. 3B). For all formulations, a single

glass transition temperature (44.80 °C (F_1 and F_2), 32.73 °C (F_3 and F_4)) was detected, lying in between the individual glass transitions of FF (-21 °C) and Kollidon® VA 64 (101 °C) or Soluplus® (70 °C). This indicated the presence of a molecular dispersion. The DSC thermogram of ASA showed a melting peak at 144.18 °C (Fig. 4). This peak was absent in the thermogram of all core formulations, indicating the loss of crystallinity of ASA in the core of the co-extrudates. Since the melting point of ASA was never reached during the extrusion process, this indicated that ASA had dissolved in the matrices. A single glass transition temperature (30.15 °C (F_1 and F_3), 39.71 °C (F_2 and F_4)) was detected, lying in between the individual glass transitions of FF (-21 °C) and Kollidon® PF 12 (90 °C) or Kollidon® VA 64 (101 °C). These results were confirmed with XRD (data not shown). The SA content in all core formulations 1.7 ± 0.12 for F_1 and F_3 and 2.3 ± 0.29 for F_2 and F_4 was in agreement with those found during the polymer screening tests (Table 1).

To evaluate the drug distribution in core and coat, Raman microscopic mapping was performed. The peak intensity of the Raman band of ASA in the 745-760 cm^{-1} region was monitored to map the ASA distribution in the core and to check if migration of ASA to the coat of the co-extrudates had occurred during co-extrusion. Likewise, the FF distribution in coat and core was mapped by monitoring the peak intensity of the Raman band of FF in the 760-778 cm^{-1} region. Fig. 5 shows the distribution of ASA throughout co-extruded formulation F_1. A red color corresponds to a high peak intensity, indicating a high ASA concentration, while a blue color corresponds to a low ASA concentration. The ASA band in the 745-760 cm^{-1} region showed an intense peak in the core. A very low peak intensity was found in the coat at the interface with the core (light blue), indicating very little migration of ASA to the coat. Comparing the Raman spectra of the light blue area with those of the individual drugs (Fig. 6), it was demonstrated that the light blue area contained both drugs. The FF band in the 760-778 cm^{-1} region showed an intense peak in the coat and not in the core. However, a low FF peak intensity was found in the core at the interface with the coat (yellow), indicating very little migration of FF in the core. Comparing the Raman spectra of

the yellow area with those of the individual drugs (Fig. 6), it was demonstrated that the yellow area contains both drugs. The mapping results of all other formulations were similar (data not shown). Core and coat were clearly distinguished from one another, with a small region (10 µm) of intermigration in between.

The FF release from F_1, F_2, F_3 and F_4 was complete in 20, 30, 60 and 60 min, respectively (Fig. 7) and was not considered significantly different from the dissolution of the individual coat formulations during screening. Furthermore, the Kollidon® VA 64-based coat of F_1 and F_2 did not influence ASA release from the cores. ASA release from the Kollidon® VA 64 core (F_4) was clearly hindered by the Soluplus® coat. In comparison with the ASA release observed during the polymer screening (individual core), the ASA release rate from co-extrudate F_4 was significantly decreased (complete release after ± 60 min instead of 20 min). It was hypothesized that the Soluplus®-based coat partially covered the core surface during dissolution, thereby hindering ASA release.

4. Conclusions

This study identified co-extrusion as a promising technique to produce a multilayer FDC solid dosage form for oral application characterized by immediate release from both layers. Extrusion of ASA was challenging as in some carriers degradation to SA was observed, despite of the absence of water during thermal processing. However, core/coat dosage forms were successfully developed using four different polymer combinations: Kollidon® PF 12/Kollidon® VA 64, Kollidon® PF 12/Soluplus®, Kollidon® VA 64/Kollidon® VA 64 and Kollidon® VA 64/Soluplus®. All combinations showed good processability via co-extrusion, and the adhesion between core and coat was good. The solid state characterization revealed that both ASA and FF were molecularly dispersed in the co-extrudates. Raman mapping exposed very little intermigration of both drugs at the

interface. Further investigation will be required to evaluate the stability of the co-extruded solid solutions.

Acknowledgements

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Figures

Tables

Figures

Fig 1: Configuration of the intermeshing co-rotating screws. Standard screw configuration with three kneading blocks: transport zone (a), mixing zone (b) and densification zone (c).

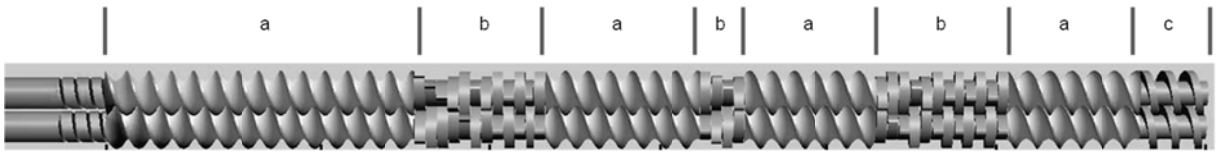


Fig. 2: SEM images of co-extruded formulations (Table 3). Core/coat interface is marked by the white arrow.

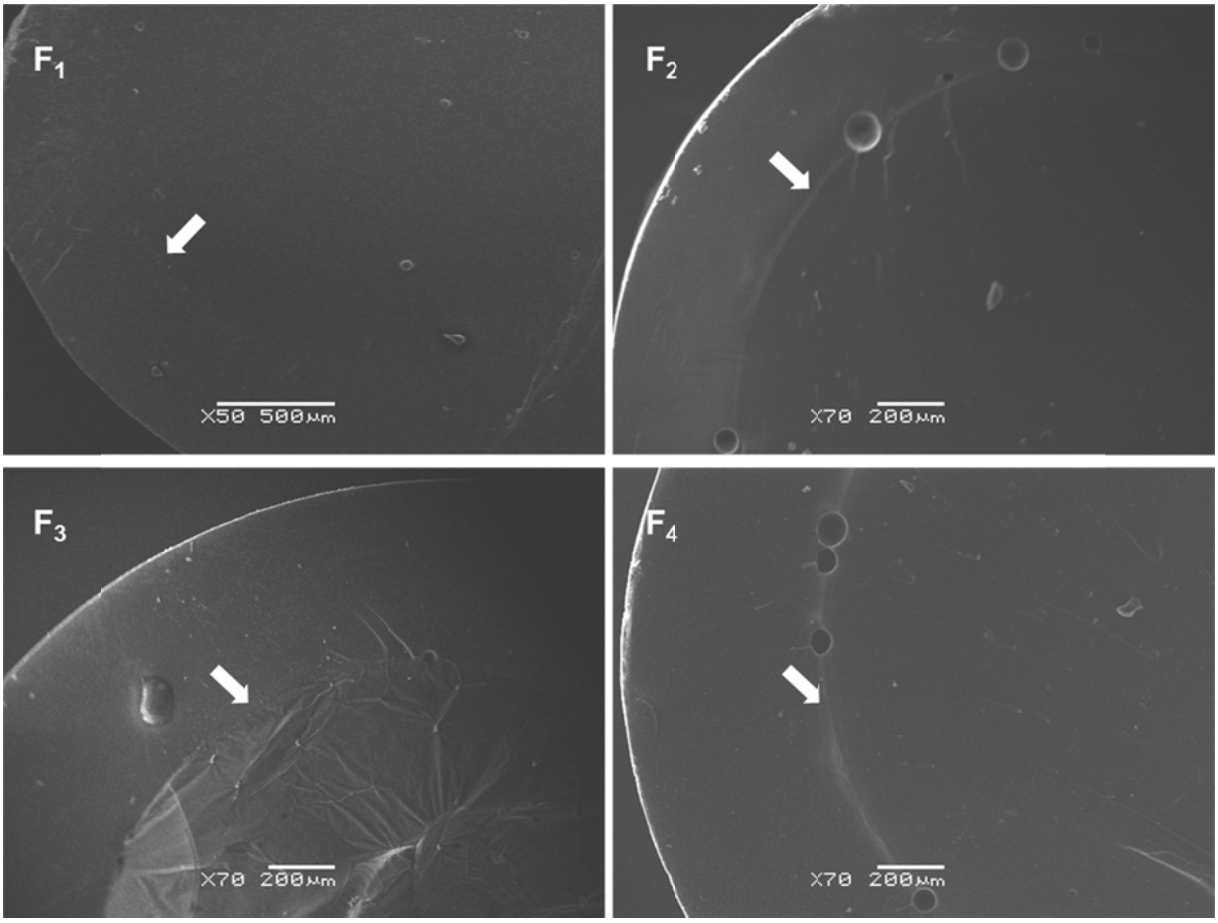
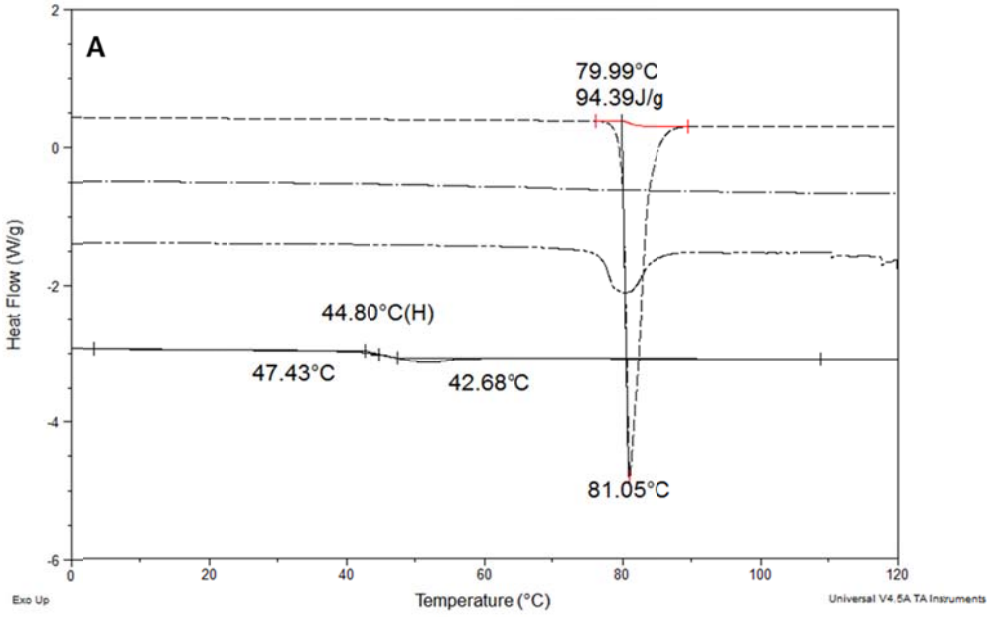


Fig. 3: Solid state characterization (DSC) of coat of co-extrudated formulations: (A) 20% FF in Kollidon® VA 64 (F_1, F_2) and (B) 20% FF in Soluplus® (F_3 ,F_4). Within each figure from top to bottom: FF, carrier (Kollidon® VA 64 (A), Soluplus® (B)), physical mixture and extruded coat formulation.



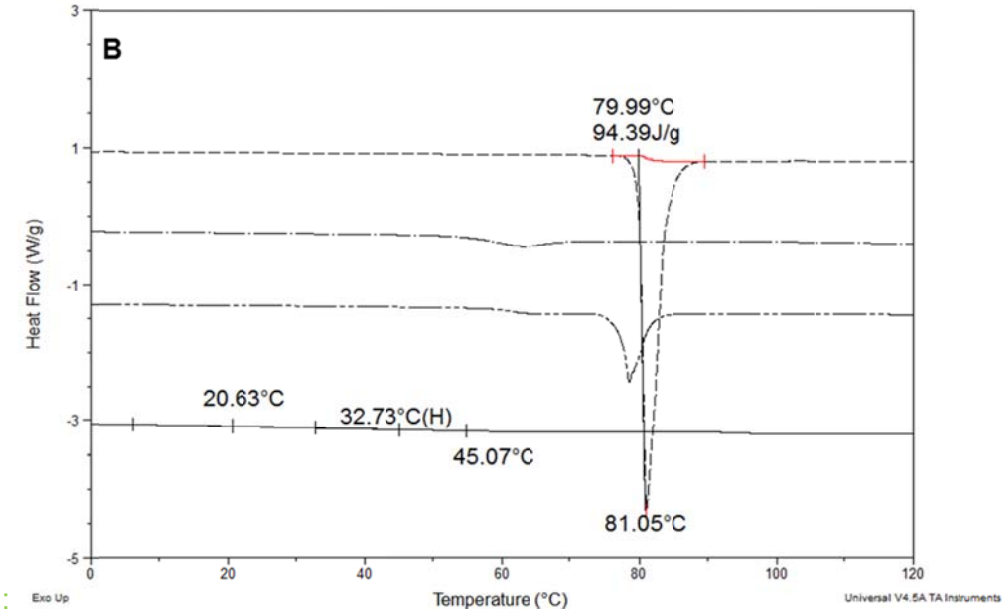


Fig. 4: Solid state characterization (DSC) of core of co-extrudated formulations: (A) 20% ASA in Kollidon® PF 12 (F_1, F_3) and (B) 20% ASA in Kollidon® VA 64 (F_2 ,F_4). Within each figure from top to bottom: ASA, carrier (Kollidon® PF 12 (A), Kollidon® VA 64 (B)), physical mixture and extruded core formulation.

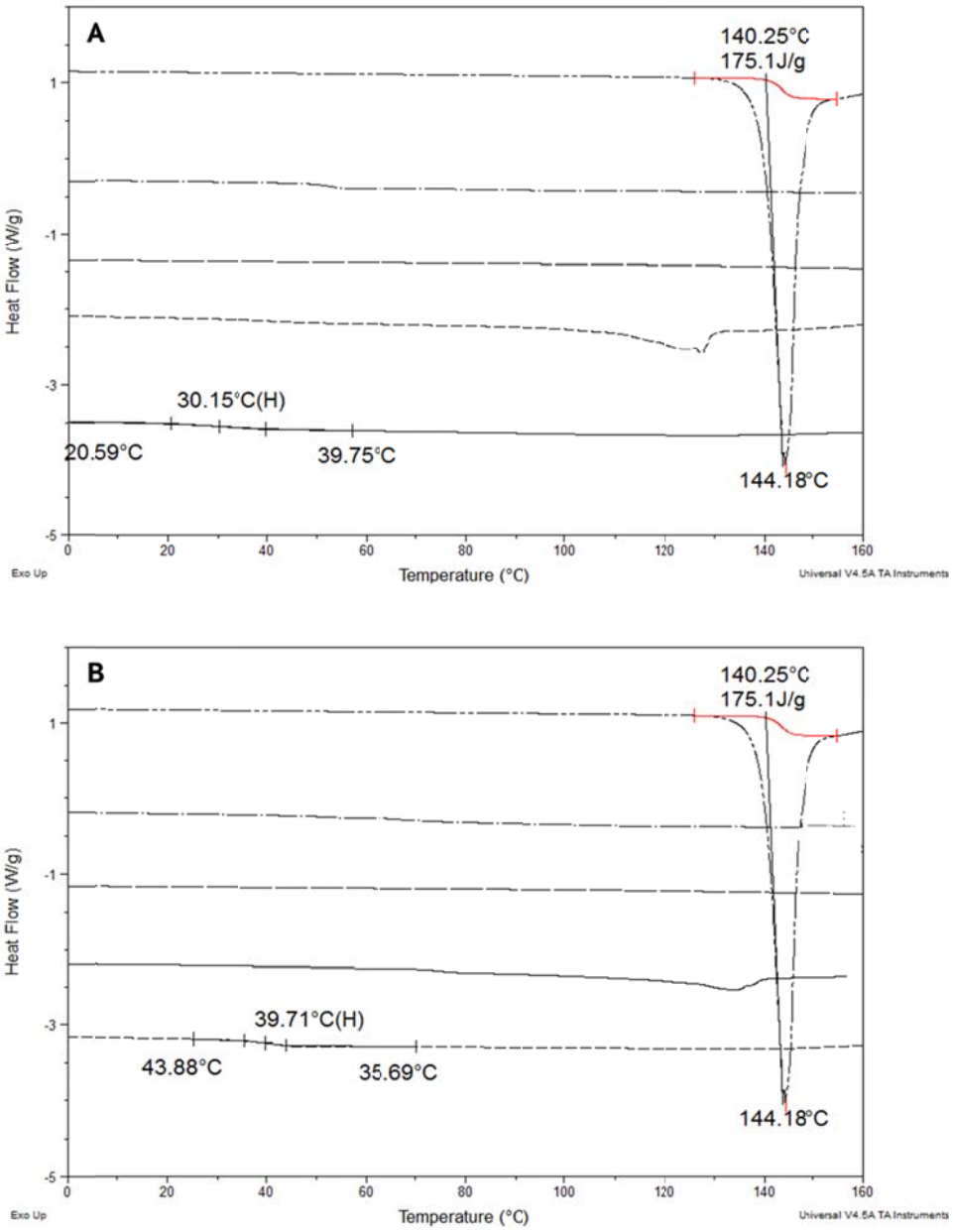


Fig. 5. Raman mapping of ASA in co-extrudate F_1. A red color corresponds to a high peak intensity in the 745-760 cm^{-1} region, indicating the presence of ASA in the core. A blue color corresponds to a very low peak intensity, indicating absence of ASA in the coat. A very low peak intensity was found in the coat at the interface with the core (light blue), indicating very little migration of ASA to the coat. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

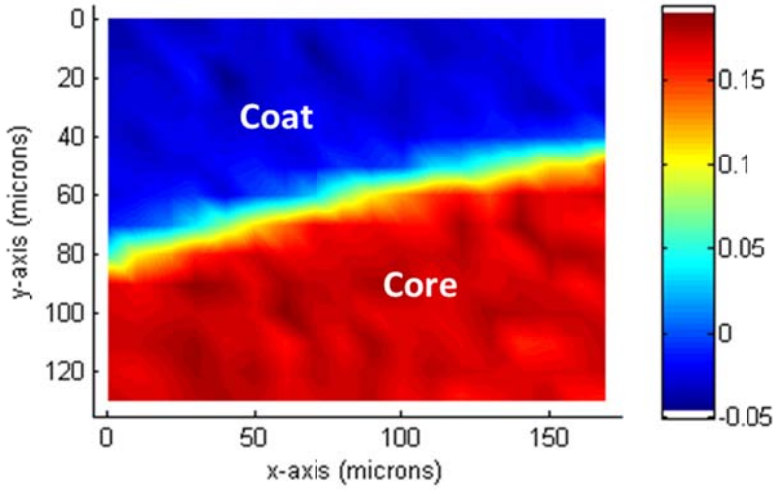


Fig. 6. Selected region of the Raman spectra of FF, light blue area (Fig. 5), yellow area (Fig. 5), ASA.

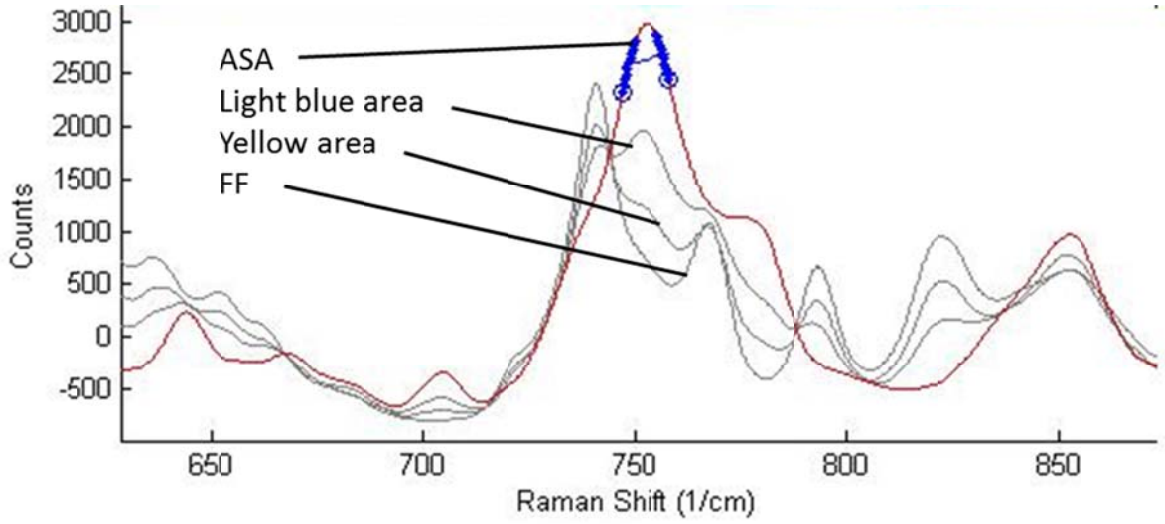
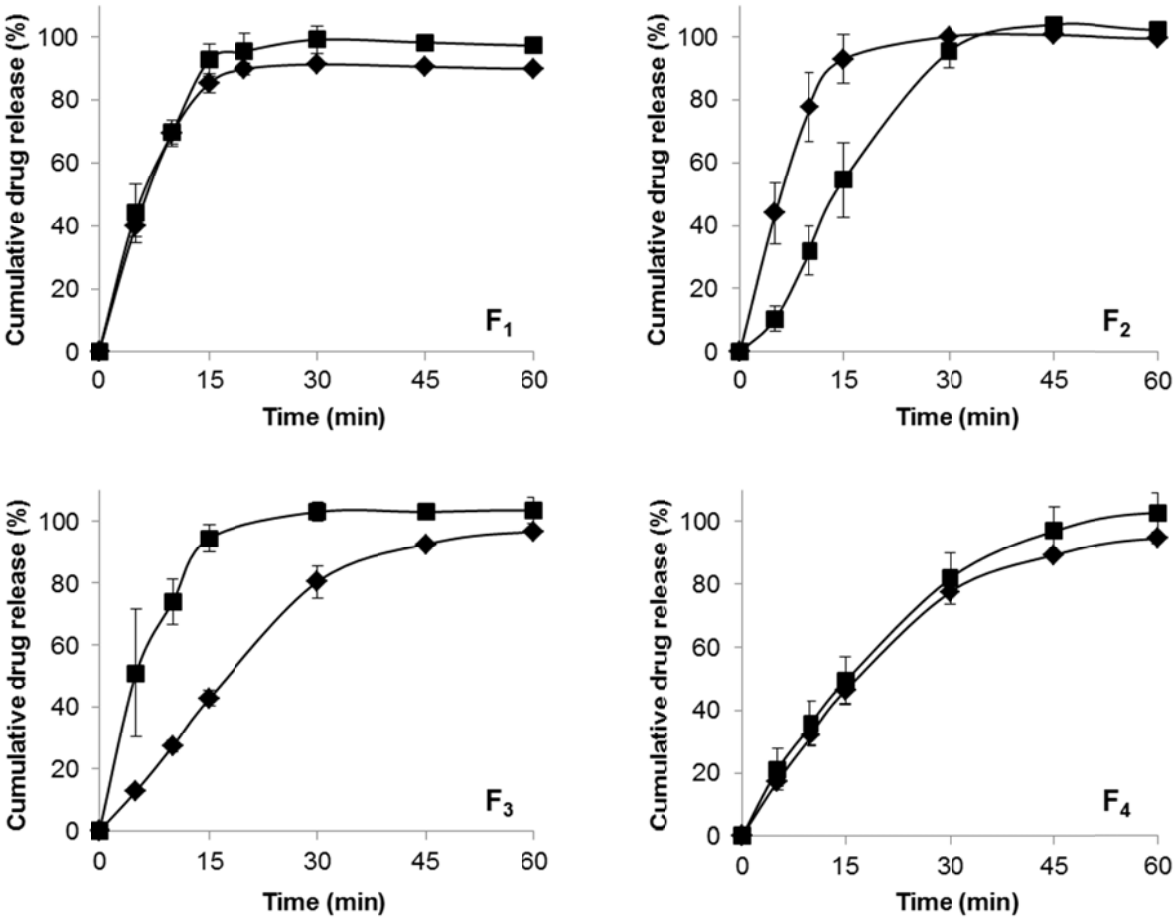


Fig. 7: Mean FF (♦) and ASA (■) dissolution profiles (±S.D.) (n = 3) of co-extruded formulations (Table 3).



Tables

Table 1: Overview of polymer screening results for ASA.

Carrier	ASA (%)	T_{die} - $T_{extrusion}$*	SA content (%)	Complete release (min)
PEO (0-50 % PEG)	20	75 - 75	26.6 (± 0.17) -12.0 (± 0.23)	not tested***
Eudragit® E PO (0-25% PEG)	20	120 - 140-120	not tested**	not tested**
Soluplus®	20	95 - 110	4.7 (± 0.21)	not tested***
Kollidon® VA 64	20	105 - 130	2.4 (± 0.11)	20
Kollidon® PF 12	20	95 - 110	1.5 (± 0.16)	10

*: lowest extrusion temperature usable resulting in a torque value of <80% motor load and a pressure of <100 bar.
**: too sticky and highly flexible
***: SA content >3%

Table 2: Overview of polymer screening results for FF.

Carrier	FF (%)	T_{die}-$T_{extrusion}$ (°C)*	Complete release (min)
PEO (0-50 % PEG)	20	75 - 100-75	>60
Soluplus®	20-30	100 - 100	±60
Eudragit® E PO	20-40	100 - 120-100	not tested**
Kollidon® VA 64	20	105 - 130	20
	30-40	100 - 100	20
Kollidon® 30	30-40	125 - 150	20

*: lowest extrusion temperature usable resulting in a torque value of <80% motor load and a pressure of <100 bar.
**: too sticky and highly flexible

Table 3: Composition and extrusion parameters of co-extruded formulations.

	Carrier		Drug concentration (%)		Extrusion temperature (°C)			Feed rate (g/h)	
	Core	Coat	Core (ASA)	Coat (FF)	Core	Coat	Die	Core	Coat
F_1	Kollidon® PF 12	Kollidon® VA 64	20	20	120	130	95	300	545
F_2	Kollidon® VA 64	Kollidon® VA 64	20	20	130	130	105	300	545
F_3	Kollidon® PF 12	Soluplus®	20	20	120	100	95	300	545
F_4	Kollidon® VA 64	Soluplus®	20	20	130	105	105	300	545

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