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Co-extrusion as manufacturing technique for fixed-dose combination mini-matrices

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Abstract

The aim of this study was to develop a multilayer (core/coat) dosage form via co-extrusion, the core providing sustained drug release and the coat immediate drug release. In this study polymers were selected which can be combined in a co-extruded dosage form. Several thermoplastic polymers were hot-melt extruded and evaluated for processability and macroscopic properties (surface smoothness, die swell). Metoprolol tartrate (MPT) and hydrochlorothiazide (HCT) were incorporated as sustained and immediate release model drugs, respectively. Based on the polymer screening experiments a combination of polycaprolactone (core) and polyethylene oxide (coat) was selected for co-extrusion trials, taking into account their drug release profiles and extrusion temperature (70°C). This combination (containing 10% HCT in the coat and 45% MPT in the core) was successfully co-extruded (diameter core: 3mm / thickness coat: 0.5mm). Adhesion between the two polymer layers was good. HCT release from the coat was complete within 30 minutes, while MPT release was sustained over 24h (55, 70, 85 and 100% after 4, 8, 12 and 24h, respectively). DSC, XRD and Raman spectroscopy revealed that MPT remained crystalline during extrusion, whereas HCT was dissolved in the polyethylene oxide matrix. The in vivo study revealed no significant differences between the experimental formulation and the reference formulation (Zok-Zid® tablet). Fixed-dose combination mini-tablets with good in vitro and in vivo performance were successfully developed by means of co-extrusion, using a combination of polycaprolactone and polyethylene oxide.

KEY WORDS: co-extrusion; hot-melt extrusion; multiple-unit dosage form; polycaprolactone; polyethylene oxide; sustained release; immediate release

Graphical abstract
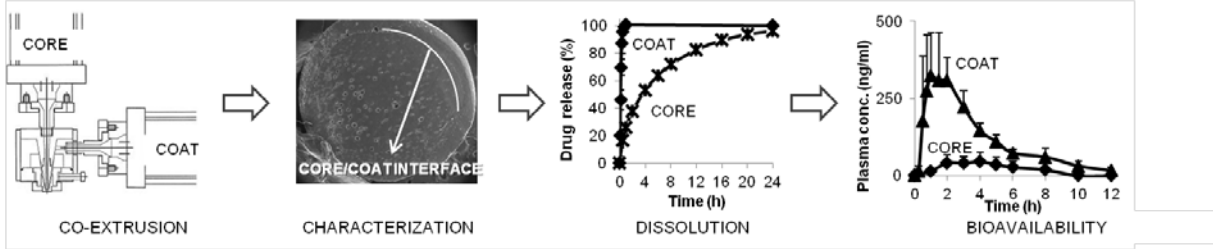
1. Introduction

Hot-melt extrusion (HME) is a technology used in the pharmaceutical industry to produce matrix formulations into which a drug is homogeneously embedded. Its major advantages over conventional techniques are the continuity of the production process, fewer processing steps, no use of organic solvents/water, decreased environmental implications, no requirements for compressibility and the possibility of improving drug solubility or sustain drug release. Co-extrusion is defined as the simultaneous extrusion of two or more materials creating a multi-layered extrudate [1]. Co-extrusion of polymers is widely applied in the plastic processing industry (e.g. packaging industry). However, this technique has been barely applied in the pharmaceutical industry. The only two co-extruded dosage forms available on the market until now are Nuvaring®, a contraceptive vaginal ring, and Implanon®, a contraceptive implant [2]. The production of oral drug delivery systems via co-extrusion offers the opportunity to combine different drugs with different release profiles, to modulate drug release (either by loading the different layers with different amounts of drug or by incorporating the drug in different matrices) and to enable the simultaneous administration of non-compatible drugs (formulated in separate layers). So far, there are no co-extruded dosage forms for oral use on the market and hardly any research has been done in this field [1, 3-5]. The biggest challenge of the co-extrusion process is to find good polymer combinations, taking into account the pharmaceutical aspects (e.g. good drug release characteristics) as well as some technical considerations (e.g. similar extrusion temperature, melt viscosity, adhesion between layers,…).

The aim of the present study was to evaluate the potential of co-extrusion as manufacturing technique for the production of multiparticulate fixed-dose combination (FDC) dosage forms for oral application. Multiparticulates are less dependent on gastric emptying rate, have a lower tendency for local irritation and have a reduced

risk of dose dumping [6]. The greatest advantage of multiparticulate systems is the ease of dose adjustment without any formulation or process change. Because the dose can be adjusted by increasing or decreasing the number of individual particles in the dosage form, the surface area and consequently the drug release profile are not affected. This reduces the extra time and cost used for bioequivalence studies [7]. In addition, the use of FDC dosage forms is likely to increase in the future because they improve patient adherence [8]. A well known application is the combination of a beta-blocker and a diuretic for the treatment of cardiovascular disease [9]. Therefore, in this study hydrochlorothiazide (HCT, a diuretic) and metoprolol tartrate (MPT, a beta-blocker) were incorporated as immediate and sustained release model drugs, respectively. Via proper selection of polymers, a core/coat dosage form was developed via co-extrusion, the core providing sustained drug release (SR) and the coat immediate drug release (IR).

2. Materials and methods

2.1. Materials

The polymers tested were: Soluplus® (BASF, Ludwigshafen, Germany), Eudragit® E and RS PO (Evonik, Darmstadt, Germany), Kollidon® VA and SR (BASF, Ludwigshafen, Germany), Ethocel® std 10 (ethylcellulose, DOW Chemical Company, Midland, USA), Sentry™ Polyox® WSR N10 (polyethylene oxide (PEO) (MW: 100,000 g/mol), Colorcon, Dartford Kent, United Kingdom), polyethylene glycol (PEG (MW: 4,000 g/mol), Fagron, Waregem, Belgium) and CAPA® 6506 (polycaprolactone (MW: 50,000 g/mol), Perstorp, Warrington, United Kingdom). Colloidal silicium dioxide (Fagron, Waregem, Belgium) was added to CAPA® to improve the flow properties. Pluronic® F68, triethyl citrate (TEC) and dibutyl sebacate (DBS) (Sigma-Aldrich, Bornem, Belgium) were used as plasticizers. Hydrochlorothiazide (HCT) (UTAG, Amsterdam, the Netherlands) and metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) were incorporated as immediate release and sustained release model drugs, 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 (surface smoothness, die swell) and in vitro drug release. Polymers were mixed with different amounts of drug (2.5-30% HCT; 10-50% MPT) and hot-melt extruded using a Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruder (ThermoFisher Scientific, Germany). The extrusion temperature varied according to the polymer, but all five heating segments of the extruder were set at the same

temperature. The appropriate extrusion temperature was defined as the lowest temperature at which the extruder torque was below 80% motor load. A strand die with a diameter of 3 mm was mounted at the end of the extruder. The machine was equipped with a gravimetric Brabender powder feeder (Duisburg, Germany). The screw speed and feed rate were kept constant at 60 rpm and 250 g/h.

2.3.   Production of co-extrudates

Polymer and drug were premixed in a tumbling mixer (Turbula® T2A, W.A. Bachofen, Basel, Switzerland) for 30 min. Co-extrusion was performed using two Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruders (ThermoFisher Scientific, Germany). A co-extrusion die (Guill, West Warwick, USA) was connected to both extruders. In the die, the two melts were combined to form two concentric layers, a core and a coat. All five heating segments of both extruders as well as the co-extrusion die were heated to 70°C. Both premixes were fed into the corresponding extruders by two Brabender Flexwall® (loss-in-weight) powder feeders (Duisburg, Germany) at a feed rate of 150 g/h for the coat and 250 g/h for the core material. A screw speed of 60 rpm was used in both extruders. The core of the co-extrudate had a diameter of 3 mm, surrounded by a coat of 0.5 mm thickness, resulting in a total extrudate 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.   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). The vessels were filled with 900 ml dissolution medium. The mini-matrices (six tablets of 2 mm length)

were exposed to a 0.1 M solution of hydrochloric acid (pH=1) for 1 hour to mimic the pH of the stomach and were then transferred to 900 ml of demineralized water (pH=±7) for the next 23 hours to mimic the pH of the intestine. Sink conditions were maintained during the experiments. The bath temperature 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 and 60 minutes for HCT, and at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24 hours for MPT. They were spectrophotometrically assessed for metoprolol tartrate and hydrochlorothiazide concentration at a wavelength of 222 nm and 272 nm, respectively, using a Perkin-Elmer Lambda 12 UV-VIS double beam spectrophotometer (Zaventem, Belgium). Since the drugs showed interference at their respective wavelengths the release of the MPT was determined using a placebo coat and vice versa.

2.5. Solid state characterization

2.5.1. Differential scanning calorimetry

Differential scanning calorimetry was used to study the crystallinity of the drug in the matrix. 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 aluminium pans. They were cooled to -50°C followed by heating to 150°C at a linear heating rate of 10°C/min.

2.5.2. Raman analysis

Raman spectroscopy was applied to detect changes in solid-state properties of the model drugs. Raman spectra of drug, polymer, physical mixtures and

extrudates were collected with a Raman RXn1 spectrometer (Kaiser Optical Systems, Ann Arbor, USA) equipped with an air-cooled CCD detector. The laser wavelength was the 785 nm line from a 785 nm Invictus NIR diode laser. The spectra were recorded at a resolution of $4cm^{-1}$ and an exposure time of 10 s, using a laser power of 400 mW. Data collection and data transfer were automated using the HoloGRAMS[TM] data collection software, the HoloREACT[TM] reaction analysis and profiling software, the Matlab software (version 7.1, The MathWorks Inc., Natick, MA) and SIMCA-P+ (version 12.0.1.0, Umetrics, Umeå, Sweden) was used for data analysis . The analyzed spectral region was $0 - 1800$ cm^{-1}, since this region contained all useful drug and polymer information.

2.5.3. X-ray diffraction

X-ray diffraction was performed to investigate the crystallinity of the drug in the mini-matrices. X-ray patterns of drug, polymer, physical mixtures, coat and core material of the co-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).

2.6. SEM

Scanning electron microscopy was used to study the interface between both layers and to compare the surface of the mini-matrices before and after administration to dogs. Tablets 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).

2.7. Adhesion

The adhesion between core and coat was measured using a tensile tester (LF Plus, Lloyd Instruments, West Sussex, UK). The capacity of the load cell was 100 N. The co-extrudates were cut into slices of 1 mm height prior to testing. The slices were placed on a holding device with a central opening of 3.3 mm. They were positioned in such a way that only the coat was supported by the device, while the core was placed over the central opening. Using a probe (diameter: 2 mm, preload: 1 N, extension rate: 100 mm/min), which applied a downward force on the core, the maximum force needed to separate the core from the coat was measured. The test was done in 20-fold.

2.8. In vivo study

2.8.1. Subjects and study design

A group of six male mixed-breed dogs (weight 23.5–39.0 kg) was used in this study. An oral dose of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide was administered to the dogs, either as experimental co-extruded mini-matrices or as reference formulation (Zok-Zid®, Pfizer, Brussels, Belgium). The core of the co-extrudate was formulated with 45% MPT, 54% polycaprolactone and 1% colloidal silicium dioxide, while the coat contained 10% HCT, 45% PEO and 45% PEG.

The mini-matrices of the experimental formulation were filled in hard-gelatin capsules, whereas the reference formulation was given as a tablet. The

formulations were administered in randomized order with a wash-out period of at least 1 week between sessions. On the experimental day the dogs were fasted for 12 h prior to the study period, although water was available. Before administration of a formulation, a blank blood sample was taken. The formulations were orally administered with 20 ml water. The blood samples were collected in dry heparinized tubes at fixed time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after intake of the formulations. No food was administered to the dogs during the entire test period. Within 1 h after collection, blood was centrifuged for 10 min at 1500g. The plasma was separated and kept frozen at -20°C until analysis.

2.8.2. Metoprolol tartrate and hydrochlorothiazide assay

Metoprolol tartrate and hydrochlorothiazide plasma concentrations were determined using two different HPLC methods. For MPT, a validated HPLC-fluorescence method was used [10]. Bisoprolol was used as internal standard. A solid phase extraction (SPE) procedure was used to extract metoprolol tartrate. Hydrochlorothiazide was determined using a validated HPLC-UV method [11]. The drug was extracted from the plasma samples by means of liquid-liquid extraction with hydroflumethiazide as internal standard. Since no interfering peaks of MPT and HCT were observed during the determination of HCT and MPT, respectively, the specificity of the methods was secured. An automatic integration system (software D-7000 Multi-Manager) was used for integration of the chromatographic peaks.

2.8.3. Data analysis

The peak plasma concentration (C_{max}), the extent of absorption (AUC_{0-12h}) and the time to reach C_{max} (T_{max}) were calculated. The relative bioavailability (F_{rel}, expressed in %) was calculated as the ratio of AUC_{0-12h} between a test formulation and the reference formulation. Data were statistically analysed using SPSS 17 (SPSS, Chicago, USA). To compare the effects of the different treatments, a paired samples t-test was performed with a significance level of α = 0.05.

3. Results and discussion

A successful co-extrusion process requires that both polymer melts can be processed at similar temperatures because they need to flow through the co-extrusion die under the same temperature conditions. Pure polymers and polymer-drug mixtures (in different ratios) were hot-melt extruded and evaluated for processability and macroscopic properties (surface smoothness, die swell). The appropriate extrusion temperature range for each of the polymers was established in order to investigate which polymers were combinable in terms of extrusion temperature. Several thermoplastic polymers were assessed for their utility in co-extrusion as immediate release coat (Soluplus®, Eudragit® E PO, Polyox® WSR N10 (PEO), Kollidon® VA) and sustained release core (CAPA® 6506, Eudragit® RS PO, Ethocel® std 10, Kollidon® SR). By adjusting the extrusion parameters all selected polymers were processable via hot melt extrusion and yielded smooth extrudates, except for Kollidon® VA and SR. Extrusion around 160 and 140°C of Kollidon® VA and SR, respectively, yielded extrudates with an irregular shape. Pure Soluplus® was extrudable in a temperature range between 140 and 180°C, while the addition of 10% Pluronic® F68 lowered the extrusion torque, which made it possible to lower the extrusion temperature to 110°C. Extrudates with a drug load up to 5% were transparent, while the ones containing 10% HCT were slightly opaque. For the processing of pure Eudragit® E PO a temperature of at least 130°C was required, but the addition of 5 and 10% of triethyl citrate lowered the extrusion temperature to 120 and 110°C, respectively. Extrudates composed of only the polymer and triethyl citrate were transparent, whereas the ones containing HCT were all white. The minimal extrusion temperature for PEO was 75°C, but extrusion at higher temperatures (130°C) was also possible. At 75°C, all PEO/HCT extrudates were brigthly yellow and transparent. Nevertheless, they became opaque after cooling down to room temperature due to the recrystallization of the

PEO. The addition of 50% of PEG 4000 to PEO resulted in lower torque values. Polycaprolactone was already processable at a temperature of 70°C without the use of any plasticizer, whereas the extrusion of Eudragit® RS PO without plasticizer was impossible. The temperature required to extrude pure Eudragit® RS PO approached the degradation temperature of the polymer (140-150°C). Hence the addition of 10% triethyl citrate was required to reduce the extrusion temperature to 120°C. Polycaprolactone yielded white extrudates at all tested MPT concentrations since the extrusion temperature was far below the melting point of MPT, whereas using Eudragit® RS PO as a carrier the extrudates were all transparent. Extrusion of ethylcellulose also required a plasticizer. The addition of 20% dibutyl sebacate allowed extrusion at 120°C. The obtained extrudates were not transparent. These above mentioned data showed that some polymers could be extruded at relatively low temperatures (polycaprolactone, PEO), while others required higher temperatures (Soluplus®, Eudragit® E & RS PO, ethylcellulose, PEO).

The polymers that yielded good quality extrudates were further tested for in vitro drug release. The dissolution profiles are shown in Fig. 1. The release of HCT from Eudragit® E PO was already complete in 30 minutes, whereas it took 1 hour for HCT to be released from PEO. In contact with the acidic dissolution medium, Eudragit® E PO became ionized and dissolved in the medium hereby releasing the drug. The solubility of PEO was pH independent and it took more time for this coat to dissolve. Nevertheless, the addition of 50% polyethylene glycol 4000 (PEG) to PEO resulted in a considerable increase in release rate (100% release in <30 min). HCT release from Soluplus® was incomplete after 1 h. Very low drug concentrations (2,5% HCT) were released relatively fast from Soluplus®, but with an increasing drug load (5% or more) the release rate dropped considerably (only 20% release after 1 h). Whereas the extrudates with 2,5% HCT had completely dissolved after 1 h, the ones with 5% HCT were swollen. Polycaprolactone and

ethylcellulose provided sustained release of MPT. The extent of the release sustaining effect from these matrices depended on drug load: a lower drug concentration resulted in a slower release rate. Eudragit® RS showed a limited release retarding effect and it was impossible to sustain MPT release over 24 h with this polymer.

Taking into account the processability and the in vitro drug release data four polymers were selected: Eudragit® E PO and PEO (with 50% PEG) for immediate release, and polycaprolactone and ethylcellulose for sustained release. Based on the extrusion temperature data, two polymer combinations were considered for co-extrusion: ethylcellulose core with Eudragit® E PO coat (both extrudable around 120°C) and polycaprolactone core with PEO coat (both extrudable around 70°C). The polycaprolactone/PEO combination was finally selected for co-extrusion trials as these polymers could be processed at a low extrusion temperature (70°C).

All co-extruded formulations consisted of a polycaprolactone-core and a PEO/PEG-coat but contained different drug concentrations of drug (10, 20, 30, 35, 40, 45, 50% MPT in the core and 10, 20, 30% HCT in the coat). Due to the poor flow properties of the polycaprolactone-MPT mixtures in the feeder 1% (w/w) colloidal silicium dioxide was added to the formulation. Polycaprolactone, a biodegradable polyester, possesses excellent thermoplastic properties and has a melting point of 58-60°C. Formulations composed of unplasticized polycaprolactone were hot-melt extruded at temperatures between 70 and 80°C. Below 70°C, the melt viscosity was too high resulting in a high torque and an inadequate flow from the extruder, while above 80°C thinner extrudates with a rough surface were obtained.

PEO (100,000 g/mol), a crystalline non-ionic hydrophilic polymer which has previously been studied for hot-melt applications [12, 13], has a melting point of 65-70°C, whereas the lower molecular weight PEG (4,000 g/mol) exhibits a melting point of 50-58°C. The ratio PEO/PEG in all coating formulations was 1/1.

Preliminary studies indicated that at higher PEG content, the drug release rate increased while the extrudates tended to be more brittle. The addition of 50% (w/w) PEG resulted in a 100% drug release in less than 60 min and good co-extrudate quality. The different formulations were easily processed at an extrusion temperature of 70°C. No surface defects were detected and the extrudates having a smooth surface were cut into high quality mini-tablets.

After extrusion, the core and coat of the co-extrudates were physico-chemically characterized. The X-ray diffractogram of metoprolol tartrate showed distinct crystalline peaks at 2θ of 19.4 and 23.1 and a series of smaller peaks at 10.6, 15.8, 20.4 and 24.0 (Fig. 2a). Those peaks were also present in the diffractogram of the core, indicating the crystalline state of MPT in the core of the co-extrudate. The DSC thermogram of MPT (Fig. 3) showed a melting peak at 124.25°C, the enthalpy of fusion indicated that the entire drug fraction remained crystalline. According to literature [14], the amorphous content of polycaprolactone remains relatively unchanged after hot-melt extrusion regardless of cooling rate. A higher amorphous content typically results in higher drug solubility, as drug molecules are soluble in the amorphous regions of the polymer. In this case, the extrusion process did not cause a considerable decrease in crystalline fraction of polycaprolactone as indicated by the enthalpy of fusion (Fig. 3). The diffraction pattern of pure HCT revealed crystalline peaks which were also detected in the physical mixture (Fig. 2b). The absence of these peaks in the diffractogram of the coat revealed that there were no drug crystals left in the coat of the co-extrudate. Since the melting point of HCT (274°C) was never reached during the extrusion process, this indicated that HCT had dissolved in the PEO/PEG-matrix. These results were confirmed with Raman spectroscopy. Other investigators already described the solubilization of drugs in PEO during extrusion [12, 13], which could be useful for solubility enhancement.The SEM picture (Fig. 4a) clearly showed the two layers in the mini-tablets and indicated that core and

coat were well attached to each other. The adhesion force between both layers was measured. For the formulation that contained 45% (w/w) MPT in the core and 10% (w/w) HCT in the coat the average force needed to separate core from coat was 10.5 ± 3.1 N.

Immediate and sustained drug release was observed from the coat and core respectively (Fig. 5a & 5b). Fig. 5a shows the influence of drug load on the release of HCT from the coat. Formulations with drug loads up to 20% (w/w) provided a release of 100% in 30 min. Although HCT was completely dissolved in formulations with a drug load of 30% (w/w), a slower drug release was observed (100% released in 1 hr) due to the slower dissolution of the coat compared to formulations containing a higher PEG/PEO fraction. The dissolution rate of MPT from the core is controlled by the drug/carrier ratio (Fig. 5b): the release rate increased at higher MPT content in the core of the formulation. At higher MPT concentration (45 and 50%) full drug release was observed after 24 h. There was no significant effect of the extrusion temperature on the release rate from the core when increasing the temperature from 70 to 80°C. However, an extrusion temperature of 90°C resulted in a significant faster release, which (after visual inspection) could be attributed to the smaller diameter of the samples extruded below 90°C. The drug release characteristics of the coat were not influenced by the extrusion temperature. Based on the dissolution results, a formulation containing 45% MPT in the core and 10% HCT in the coat was selected for in vivo testing. The MPT/HCT ratio in this system was similar to the reference formulation (Zok-Zid®).

Fig. 6 shows the mean plasma concentration-time profiles after oral administration of 200 mg MPT and 25 mg HCT as experimental mini-matrices and Zok-Zid® (2 tablets). Although Zok-Zid® is administered as a tablet, in contact with fluids, it immediately disintegrated into pellets, creating a multiparticulate system. According to the dissolution data, both test and reference formulation provided

immediate release (less than 30 min) of HCT and sustained MPT release over 24 h. However, the in vitro MPT release from the reference formulation was considerably slower, which was also reflected in the in vivo behaviour. The pharmacokinetic parameters of MPT and HCT are reported in table 1. Fig. 7 represents the AUC values of each dog separately after administration of the experimental and the reference formulation. The bioavailability data of HCT (C_{max}, T_{max} & AUC) of both formulations were comparable, without a statistical significant difference between the test and reference formulations ($p > 0.05$). Although there was a trend that the MPT bioavailability of the test formulation for each dog was higher than the reference (Fig. 7A), the difference was statistically not significant. Besides that,,the variability in AUC values for MPT was higher after administration of the experimental formulation than for the reference formulation. While the coat of the co-extrudates dissolved during gastro-intestinal passage, intact cores (which still contained 6.6 ± 0.4% of the initial MPT dose) were recovered from the faeces of the dogs. As no swelling or erosion was observed while the pore size increased (Fig. 4b), release from the caprolactone core was diffusion-controlled.

4. Conclusions

This study showed that co-extrusion seems a promising technique to produce fixed-dose combination mini-matrices. A core/coat dosage form was developed, wherein the core and coat exhibited sustained and immediate release properties, using a combination of polycaprolactone (core) and PEO/PEG (coat). There was good adhesion between the two layers. The solid state characterization revealed that MPT maintained its crystalline form whereas HCT was molecularly dispersed in the coat of the co-extrudates. The differences in in vivo performance between a reference formulation and the test formulation were statistically not significant.

Figures

Figure 1: Influence of drug load on the release of HCT (A-C) and MPT (D-F) from different polymers after extrusion. Mean dissolution profiles (±S.D.) of formulations composed of A: Soluplus® and (▲) 2.5%, (♦) 5%, (■) 10% HCT; B: Eudragit® E PO and (♦) 10%, (■) 20%, (▲) 30% HCT; C: Polyox®, 10% HCT and (♦) 0%, (▲) 50% PEG 4000; D: Polycaprolactone and (♦) 20%, (■) 30%, (✳) 35%, (▲) 40%, (✗) 50% MPT; E: Eudragit® RS PO and (♦) 10%, (▲) 20%, (✗) 30% MPT; F: Ethylcellulose and (▲) 20%, (■) 30% MPT.

Figure 2a: X-ray diffraction pattern of (A) MPT, (B) polycaprolactone, (C) colloidal silicium dioxide, (D) physical mixture and (E) extrudate composed of 40/1/59% MPT/CSD/polycaprolactone.

Figure 2b: X-ray diffraction pattern of (A) HCT, (B) PEO/PEG (1/1), (C) physical mixture and (D) extrudate composed of 10/45/45% HCT/PEO/PEG.

Figure 3: Differential scanning calorimetry profiles. From the top to the bottom: metoprolol tartrate, polycaprolactone, colloidal silicium dioxide, physical mixture and core of co-extruded tablet composed of 40/1/59% MPT/CSD/polycaprolactone.

Figure 4: SEM images of co-extrudate with a core composed of 45/55% MPT/polycaprolactone and a coat composed of 10/45/45% HCT/PEO/PEG. (A) Immediately after production (magnification 60x), (B) After faecal recovery (70x).

Figure 5a: Influence of drug load on HCT release from the coat of co-extruded mini-matrices. The coat was composed of PEO/PEG (1/1) and variable HCT concentrations: (◊) 10%, (□) 20%, (Δ) 30%, (---) reference formulation (Zok-Zid®).

Figure 5b: Influence of drug load on MPT release from the core of co-extruded mini-matrices. The core was composed of. polycaprolactone and variable MPT concentrations: (Δ) 30%, (✳) 40%, (◊) 45%, (✗) 50%, (---) reference formulation (Zok-Zid®).

Figure 6: Mean MPT (■) and HCT (▲) plasma concentration-time profiles (± SD, n = 6) after oral administration of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide to dogs: Zok-Zid® (2 tablets) (dotted line), experimental co-extruded mini-matrices with a core consisting of 45% (w/w) MPT and a coat consisting of 10% (w/w) HCT (full line).

Figure 7: Comparison of AUC level of MPT (A) and HCT (B) after oral administration of experimental co-extruded and reference formulation to dogs.

Tables

Table 1:   Mean pharmacokinetic parameters (±S.D.) of MPT and HCT after oral administration of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide to dogs (n=6), as experimental co-extruded mini-matrices (with a core consisting of 45% (w/w) MPT and a coat consisting of 10% (w/w) HCT) or as reference formulation (Zok-Zid®).

Figure 1: Influence of drug load on the release of HCT (A-C) and MPT (D-F) from different polymers after extrusion. Mean dissolution profiles (±S.D.) of formulations composed of A: Soluplus® and (▲) 2.5%, (♦) 5%, (■) 10% HCT; B: Eudragit® E PO and (♦) 10%, (■) 20%, (▲) 30% HCT; C: Polyox®, 10% HCT and (♦) 0%, (▲) 50% PEG 4000; D: Polycaprolactone and (♦) 20%, (■) 30%, (✱) 35%, (▲) 40%, (✕) 50% MPT; E: Eudragit® RS PO and (♦) 10%, (▲) 20%, (✕) 30% MPT; F: Ethylcellulose and (▲) 20%, (■) 30% MPT.

Figure 2a: X-ray diffraction pattern of (A) MPT, (B) polycaprolactone, (C) colloidal silicium dioxide, (D) physical mixture and (E) extrudate composed of 40/1/59% MPT/CSD/polycaprolactone.

Figure 2b: X-ray diffraction pattern of (A) HCT, (B) PEO/PEG (1/1), (C) physical mixture and (D) extrudate composed of 10/45/45% HCT/PEO/PEG.
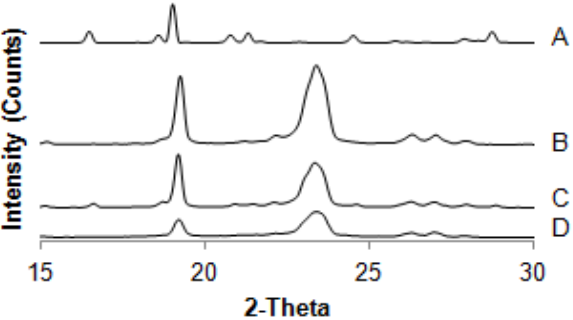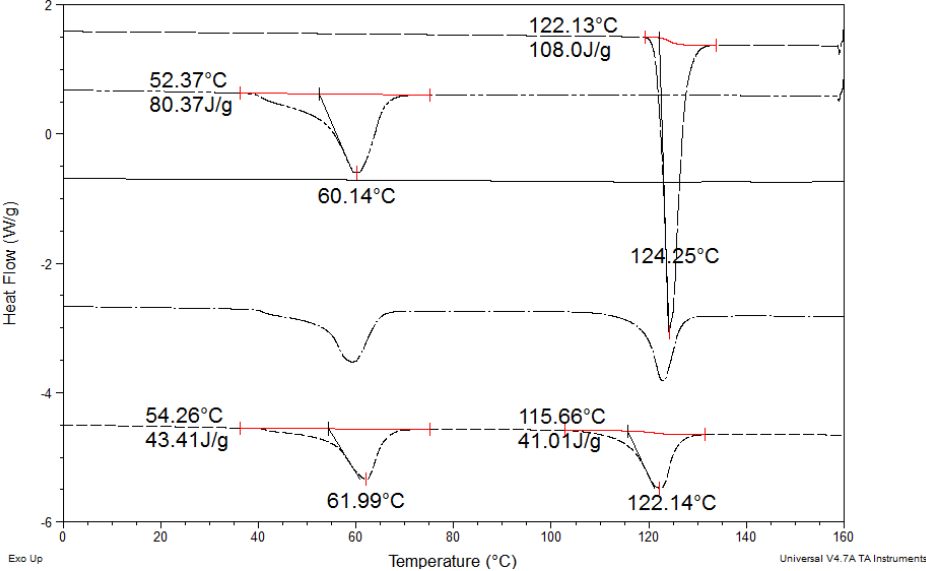
Figure 3: Differential scanning calorimetry profiles. From the top to the bottom: metoprolol tartrate, polycaprolactone, colloidal silicium dioxide, physical mixture and core of co-extruded tablet composed of 40/1/59% MPT/CSD/polycaprolactone.

Figure 4:   SEM images of co-extrudate with a core composed of 45/55% MPT/polycaprolactone and a coat composed of 10/45/45% HCT/PEO/PEG. (A) Immediately after production (magnification 60x), (B) After faecal recovery (70x).
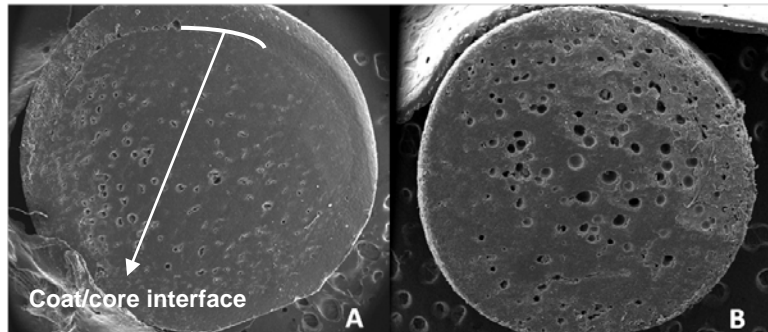
Figure 5a: Influence of drug load on HCT release from the coat of co-extruded mini-matrices. The coat was composed of PEO/PEG (1/1) and variable HCT concentrations: (◊) 10%, (□) 20%, (Δ) 30%, (---) reference formulation (Zok-Zid®).
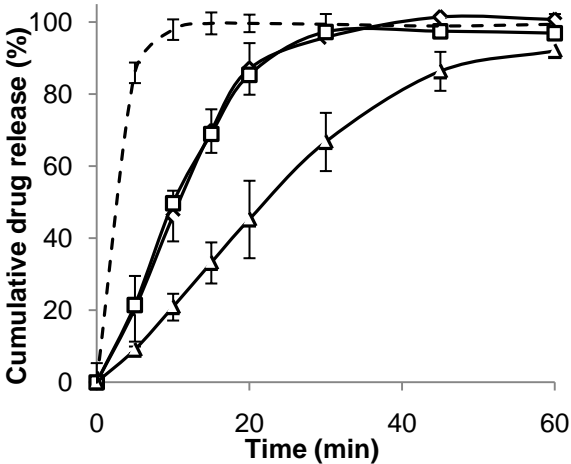

Figure 5b: Influence of drug load on MPT release from the core of co-extruded mini-matrices. The core was composed of polycaprolactone and variable MPT concentrations: (Δ) 30%, (✷) 40%, (◊) 45%, (✗) 50%, (---) reference formulation (Zok-Zid®).
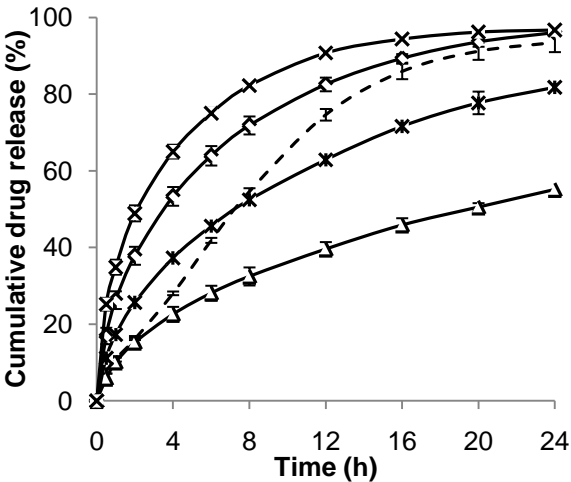
Figure 6: Mean MPT (■) and HCT (▲) plasma concentration-time profiles (± SD, n = 6) after oral administration of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide to dogs: Zok-Zid® (2 tablets) (dotted line), experimental co-extruded mini-matrices with a core consisting of 45% (w/w) MPT and a coat consisting of 10% (w/w) HCT (full line).
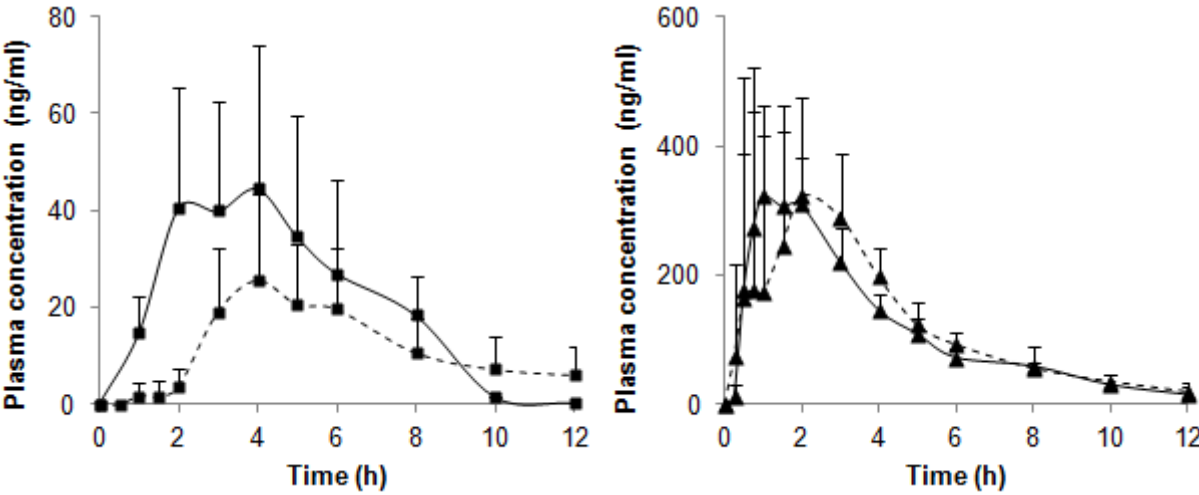
Figure 7: Comparison of AUC level of MPT (A) and HCT (B) after oral administration of experimental co-extruded and reference formulation to dogs.
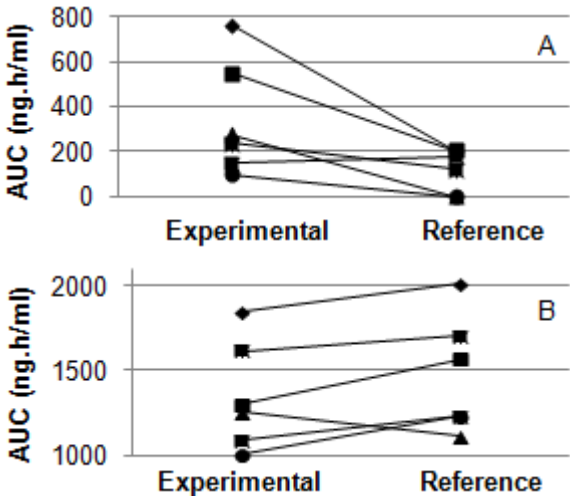
Table 1:   Mean pharmacokinetic parameters (±S.D.) of MPT and HCT after oral administration of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide to dogs (n=6), as experimental co-extruded mini-matrices (with a core consisting of 45% (w/w) MPT and a coat consisting of 10% (w/w) HCT) or as reference formulation (Zok-Zid®).

	MPT			HCT		
	C_{max} (ng/ml)	T_{max} (h)	AUC (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)	AUC (ng.h/ml)
Exp	73.6 ± 46.9	2.8 ± 0.7	345.2 ± 257.9	371.6 ± 126.0	1.6 ± 0.5	1353.8 ± 320.3
Ref	23.5 ± 19.7	4.2 ± 1.2	117.1 ± 95.6	459.9 ± 227.0	2.5 ± 1.1	1479.3 ± 346.5

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