European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 463–470

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Influence of polyethylene glycol/polyethylene oxide on the release characteristics of sustained-release ethylcellulose mini-matrices produced by hot-melt extrusion: in vitro and in vivo evaluations

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ARTICLE INFO

Article history:
Received 24 June 2008
Accepted in revised form 16 January 2009
Available online 25 January 2009

Keywords:
Hot-melt extrusion
Sustained-release
Multiple-unit dosage form
Matrix system
Polyethylene glycol
Polyethylene oxide
Ethylcellulose
Metoprolol tartrate

ABSTRACT

Mini-matrices with release-sustaining properties were developed by hot-melt extrusion (diameter 3 mm, height 2 mm) using metoprolol tartrate as model drug (30%, w/w) and ethylcellulose as sustained-release agent. Polyethylene glycol or polyethylene oxide was added to the formulation to increase drug release. Changing the hydrophilic polymer concentration (0%, 1%, 2.5%, 5%, 10%, 20% and 70%, w/w) and molecular weight (6000, 100,000, 1,000,000 and 7,000,000) modified the in vitro drug release: increasing concentrations yielded faster drug release (irrespective of molecular weight), whereas the influence of molecular weight depended on concentration. Smooth extrudates were obtained when processed at 40 and 70 °C for polyethylene glycol and polyethylene oxide formulations, respectively. Raman analysis revealed that metoprolol tartrate was homogeneously distributed in the mini-matrices, independent of hydrophilic polymer concentration and molecular weight. Also drug and polymer crystallinity were independent of both parameters. An oral dose of 200 mg metoprolol tartrate was administered to dogs in a randomized order either as immediate-release preparation (Lopresor® 100), as sustained-release formulation (Slow-Lopresor® 200 Divitabs®), or as experimental mini-matrices (varying in hydrophilic polymer concentration). The sustained-release effect of the experimental formulations was limited, and relative bioavailabilities of 66.2% and 148.2% were obtained for 5% and 20% PEO 1,000,000 mini-matrices, respectively.

1. Introduction

Hot-melt extrusion is a technology used in the pharmaceutical industry to produce matrix formulations where a drug is homogeneously embedded in a release-controlling polymer matrix. Since the different steps (mixing, melting, homogenizing and shaping) are continuously performed as a one-step process on a single machine, it has advantages over direct compression and granulation as conventional technique to manufacture controlled-release matrices [1–3]. Ethylcellulose, a polymer with thermoplastic properties, has been intensively investigated as drug carrier in hot-stage extrusion [4–6]. Mini-matrices could be developed by hot-melt extrusion using ethylcellulose to sustain the release of ibuprofen: the combination of ethylcellulose and a hydrophilic component (hydroxypropylmethylcellulose [7,8], xanthan gum [7–9]) offered a flexible system to tailor the in vitro as well as in vivo drug release. Due to the specific drug-matrix interaction, the low-melting ibuprofen (melting point 76 °C) was identified as a plasticizer for ethylcellulose [10]. As a consequence, the characteristics of ethylcellulose/hydrophilic polymer mini-matrices containing ibuprofen were not predictive of the extrusion and dissolution properties of ethylcellulose mini-matrices containing non-plasticizing drugs. Therefore, ibuprofen was substituted by a drug with a higher melting point (metoprolol tartrate, 123 °C) and a conventional plasticizer was added to the formulation [11].

In the present study sustained-release mini-matrices were developed by hot-melt extrusion of a metoprolol tartrate/ethylcellulose/dibutyl sebacate-mixture with the addition of polyethylene glycol or polyethylene oxide as hydrophilic polymer to tailor drug release. The aim was to examine the effect of different concentrations (0–70%, w/w) and molecular weights (polyethylene glycol 6000 and polyethylene oxide 100,000–7,000,000) of these hydrophilic polymers on drug and polyethylene glycol/polyethylene oxide release, drug homogeneity and drug and polymer crystallinity. The influence of polyethylene oxide concentration on bioavailability in dogs was also evaluated, and compared with xanthan gum mini-matrices [11].

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doi:10.1016/j.ejpb.2009.01.006

2. Materials and methods

2.1. Materials

Metoprolol tartrate (MPT) (10 μm) (Esteve Quimica, Barcelona, Spain) was selected as model drug. The matrix consisted of ethylcellulose (EC) (Ethocel® Std 10 FP Premium, particle size: 3–15 μm), kindly donated by Dow Chemical Company (Midland, USA), and a hydrophilic component: polyethylene glycol (PEG 6000) (Fagron, Waregem, Belgium), polyethylene oxide (PEO, Sentry™ Polyox™ WSR N10, N12 K and 303 having a molecular weight (MW) of 100,000, 1,000,000 and 7,000,000, respectively) (Dow Chemical Company, Midland, USA) and xanthan gum (XG) (Xantural® 75, mean particle size: 75 μm) (CP Kelco, Liverpool, UK). Dibutyl sebacate (DBS) (Sigma–Aldrich, Steinheim, Germany) was used as plasticizer for ethylcellulose. Slow-Lopresor® 200 Divitabs® and Lopresor® 100 (commercially available hydrophilic matrix tablets and immediate-release tablets containing 200 and 100 mg metoprolol tartrate, respectively) were purchased from Sankyo Pharma (Louvain-la-Neuve, Belgium). All other chemicals were of analytical grade.

2.2. Hot-melt extrusion

2.2.1. Production of mini-matrices

The MPT content was kept constant at 30% (w/w). The concentration of hydrophilic polymer varied between 0% and 70% (w/w) for all PEG/PEO types under investigation. The remaining part of the formulation consisted of EC/DBS, in a ratio of 2/1 (w/w) [11]. The concentrations of PEG, PEO and EC/DBS were varied according to Table 1.

The components were blended in a planetary mixer (15 min, 90 rpm) (Kenwood Major Classic, Hampshire, UK) and incubated overnight at room temperature to achieve sufficient interaction between EC and plasticizer. The mixture was passed through the screws of the powder feeder of the extruder and recycled into the powder reservoir to homogeneously distribute DBS in the powder prior to hot-melt extrusion. Hot-melt extrusion was performed using a laboratory-scale intermeshing co-rotating twin-screw extruder (MP19TC-25, APV Baker, Newcastle-under-Lyme, UK) having a length-to-diameter ratio of 25/1. The machine was equipped with a Brabender twin-screw powder feeder, and a screw with two mixing sections and a densification zone [9,11]. The die block (2.6 cm thickness) was fixed to the extruder barrel and the axially mounted die plate (1.9 cm thickness, with a cylindrical hole of 3 mm diameter for shaping the extrudates) was attached to the die block. The following extrusion conditions were used: a screw speed of 30 rpm, a powder feed rate of 6 g/min and a temperature of 40 and 70 °C for the five heating zones along the barrel for extrusion of PEG and PEO formulations, respectively. After cooling down to room temperature, the extruded rods (∅ = 3 mm) were manually cut, using surgical blades, into mini-matrices of 2 mm length.

The surface properties of the extrudates were visually inspected for defects (shark skinning) and evaluated for their suitability to be cut into mini-matrices (deformation due to cutting, smoothness of the cutting surfaces and the edges) using a digital camera (C3030 Olympus) linked to an image analysis system (analySIS®, Soft Imaging system, Münster, Germany) (magnification 9.5×). Drug and PEG/PEO release was evaluated by dissolution testing. Drug (and polymer) crystallinity and homogeneity was evaluated by X-ray diffraction and Raman analysis, respectively.

Table 1
Composition (%, w/w) of the mini-matrices.

MPT	30	30	30	30	30	30	30
PEG/PEO	–	1	2.5	5	10	20	70
EC	46.7	46	45	43.3	40	33.3	–
DBS	23.3	23	22.5	21.7	20	16.7	–

2.2.2. Hot-melt extruded samples

To investigate the thermal stability of the polymers (EC, PEG and PEOs) during the hot-melt extrusion process, the polymers were extruded at 100 and 200 °C, using the process parameters as described above. The samples (powder before extrusion, extruded samples at 100 and 200 °C) were analyzed by means of gel filtration chromatography with the appropriate polymer standards.

Binary mixtures (EC/DBS, EC/PEG(PEO), EC/MPT, DBS/PEG(PEO) and MPT/PEG(PEO) were extruded under the same processing conditions as described above, and evaluated for changes in glass transition temperature, melting point, crystallinity and possible interactions by modulated temperature differential scanning calorimetry (by comparing the results with the thermograms of the powder blends prior to extrusion). All types of PEG/PEO were investigated. The ratios of both components in these blends were identical to their ratio in the mini-matrices (2.5%, 10%, 20% and 70%, w/w).

2.3. In vitro drug and PEG/PEO release

Drug release from the mini-matrices (approximately 60 mg) was determined using USP apparatus 1 (baskets), in a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, New Jersey, USA). Demineralized water was used as dissolution medium. The temperature of the medium (900 ml) was kept at 37 ± 0.5 °C, while the rotational speed of the baskets was set at 100 rpm. Samples of 5 ml were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h and spectrophotometrically analyzed for MPT at 222 nm by means of a Perkin-Elmer Lambda 12 UV–VIS double beam spectrophotometer (Zaventem, Belgium). The dissolution was performed in six dissolution vessels, each vessel containing four mini-matrices.

PEG/PEO release from the mini-matrices was determined using the USP paddle method under the same conditions as described above. PEG/PEO concentrations in the samples were measured by gel filtration chromatography (GFC) (detection via refractive index). Due to the sensitivity of the GFC analysis, the sample size for dissolution testing was increased (36, 9, 5 and 2 g mini-matrices for the 2.5%, 10%, 20% and 70% PEG/PEO formulations, respectively) and the paddle method was used. The PEG/PEO release was performed in twofold. The stability of PEG/PEO following hot-melt extrusion was also determined via GFC. For PEG 6000 and PEO 100,000 analysis, a Waters 600 Controller/Waters 610 Fluid Unit pump (flow rate: 1.0 ml/min) with a Waters 410 Differential Refractometer was used. 20 μl sample (using a 100 μl Hamilton syringe) was injected on the column (TSK-gel® G 4000 PW (TosoHaas; 7.5 mm ID × 30 cm – particle size 17 μm) and TSK-gel® G 3000 PW (7.5 mm ID × 30 cm – particle size 10 μm) coupled in series). PEO 1,000,000 and 7,000,000 samples were analyzed using a Waters 515 HPLC pump (flow: 1.0 ml/min) combined with a Waters Differential Refractometer R401. 20 μl sample was injected on the column (TSK-gel® G 6000 PW (7.5 mm ID × 30 cm – particle size 17 μm) and TSK-gel® G 5000 PW (7.5 mm ID × 30 cm – particle size 10 μm) coupled in series). The chromatograms were integrated using the Millenium 2010 Chromatography Manager (Version 2.15.01). The mobile phase consisted of water (Milli-Q® Water Purification System), filtered using Durapore® membrane filters (0.45 μm – HVLP type) and degassed with helium. The PEG/PEO concentrations were calculated from a calibration curve between 0.10 and 5.00 mg/ml, using polymer standards (analytical or HPLC grade).

To determine the in vitro release properties of the formulations used during the in vivo experiments, a dissolution experiment was performed with hard-gelatin capsules (n° 000) containing 667 mg mini-matrices. Their swelling behaviour (after 4 and 24 h immersion in the dissolution medium) was also evaluated by microscopic analysis using a digital camera (C3030 Olympus) linked to an image analysis system (analySIS®, Soft Imaging system, Münster, Germany) (magnification 9.5×).

2.4. Raman analysis

MPT distribution in the mini-matrices containing different concentrations and types of PEG/PEO was evaluated by Raman spectroscopic mapping. Three areas ($2150 \times 1150\ \mu m^2$) (two at the edges and one in the middle of the mini-matrix) of each mini-matrix ($n = 3$) were scanned using a 10× long working distance objective lens (laser spot size: 50 μm) in point-by-point mapping mode with a step size of 100 μm in both the x and y directions. The resulting map provides an overview of the MPT distribution in the mapped area. The mapping system used in this study was a RamanRxn 1 Analyzer and Microprobe (Kaiser Optical Systems, Ann Arbor, USA), equipped with an air cooled CCD detector (back-illuminated deep depletion design). The laser wavelength during the experiments was the 785 nm line from a 785 nm Invictus NIR diode laser. All spectra were recorded at a resolution of 4 cm^{-1} using a laser power of 400 mW and a laser light exposure time of 20 s per collected spectrum. Before data analysis, spectra were baseline corrected. Data collection and data analysis were done using the HoloGRAMS™ data collection software package, the HoloMAP™ data analysis software and Matlab® software package (version 6.5.).

2.5. Thermal analysis

The glass transition temperature (T_g) and/or melting point (T_m) of the pure components (EC, MPT, DBS, PEG and PEO) and in binary mixtures of these materials (powder blends prior to extrusion and hot-melt extruded samples) were determined via modulated temperature differential scanning calorimetry (MTDSC).

The thermal behaviour of powders and hot-melt extruded samples was evaluated using a 2920 Modulated DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system (RCS). Dry helium at a flow rate of 40 ml/min was used as purge gas through the DSC cell and 150 ml/min nitrogen through the RCS unit. Samples (±10 mg) were run in closed aluminium pans supplied by TA Instruments; the mass of each empty sample pan was matched with the mass of the empty reference pan to ± 0.10 mg. The experimental method consisted of an initial 5 min isothermal equilibration period at 0 °C. During the subsequent heating run the following experimental parameters were used: an underlying heating rate of 2 °C/min from −70 to 200 °C, a modulation amplitude of 0.212 °C and a period of 40 s. Temperature and enthalpic calibration were performed with an indium standard, whereas calibration of the heat capacity was performed with a sapphire standard. The results were analyzed using the TA Instruments Universal Analysis Software. Measurements were performed in duplicate and the T_g values (midpoint half height) are reported.

2.6. X-ray diffraction

To investigate the crystallinity of the components in the mini-matrices, X-ray diffraction was performed (on pulverized mini-matrices). The X-ray patterns of MPT, EC, PEG, PEO and mini-matrices were determined using a D5000 Cu Kα Diffractor ($\lambda = 0.154$ nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

2.7. In vivo study

All procedures were performed in accordance with the guidelines and approval of the local Institutional Animal Experimentation Ethics Committee.

2.7.1. Subjects and study design

A group of six male mixed-breed dogs (weight 22.0–38.0 kg) was used in this study. To investigate the influence of the concentration of the hydrophilic component (PEO or XG) in the experimental mini-tablets on the bioavailability of metoprolol tartrate, the following drug formulations were administered:

F-1: hot-melt extruded mini-matrices, consisting of 30% MPT, 5% XG, 43.3% EC and 21.7% DBS (5% XG)
F-2: hot-melt extruded mini-matrices, consisting of 30% MPT, 10% XG, 40% EC and 20% DBS (10% XG)
F-3: hot-melt extruded mini-matrices, consisting of 30% MPT, 20% XG, 33.3% EC and 16.7% DBS (20% XG)
F-4: hot-melt extruded mini-matrices, consisting of 30% MPT, 5% PEO 1,000,000, 43.3% EC and 21.7% DBS (5% PEO)
F-5: hot-melt extruded mini-matrices, consisting of 30% MPT, 20% PEO 1,000,000, 33.3% EC and 16.7% DBS (20% PEO)
F-6: Lopresor® 100
F-7: Slow-Lopresor® 200 Divitabs®

The mini-matrices of the experimental formulations were filled in hard-gelatin capsules n° 000, each capsule containing 200 mg metoprolol tartrate. Lopresor® 100 (2 tablets) and Slow-Lopresor® 200 Divitabs® (1 tablet) were used as immediate- and sustained-release reference formulations, respectively. The formulations were administered in randomized order with a wash-out period of at least 8 days between different sessions. On the experimental days the dogs were fasted for 12 h prior to the study period, although water was available ad libitum. Before administration of the formulations, an intravenous cannula was placed in the lateral saphenous and a blank blood sample was obtained. The formulations were orally administered with 10 ml water. The blood samples (2 ml at each sampling) were collected in dry heparinized tubes 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 36 h after intake of the formulations. No food was administered to the dogs during the initial 24 h of the test, afterwards they resumed their usual diet. Water could be taken freely. Within 1 h after collection, blood was centrifuged for 10 min at 1450g and the plasma was immediately assayed for metoprolol tartrate.

2.7.2. Metoprolol tartrate assay

The metoprolol tartrate plasma concentrations were determined by a validated HPLC-fluorescence method. All chemicals were of analytical or HPLC grade.

A solid phase extraction (SPE) procedure was used to extract metoprolol tartrate. The SPE equipment consisted of Oasis® HLB (1 cc 30 mg) cartridges (Waters, Brussels, Belgium) and a 16-port vacuum manifold (Alltech Europe, Laarne, Belgium). Extraction cartridges were first conditioned by rinsing consecutively with methanol (1 ml), water (1 ml) and phosphate-buffered saline (PBS) (1 ml). Plasma samples (300 μl) were mixed with 20 μl alprenolol (5.625 μg/ml alprenolol in water, as internal standard) and 680 μl PBS, homogenized by 30 s vortexing, and then loaded on the column. The columns were washed with water (1 ml) and the analytes were then eluted with methanol (1 ml). The eluates were evaporated to dryness under N_2, reconstituted in 150 μl

water (30 s of vortexing) and 20 μl solution was injected in the HPLC system.

The metoprolol tartrate plasma concentrations were determined via a calibration curve. For the standard curves, spiked samples were prepared by mixing 280 μl plasma with 20 μl of a solution containing different concentrations of metoprolol tartrate in water (0.375, 0.5625, 0.75, 2.25, 5.625, 7.5, 15.0 and 22.5 μg/ml). To these spiked samples, 20 μl alprenolol (internal standard solution) and 680 μl PBS were added. These mixtures were extracted as described above.

The HPLC equipment (Merck-Hitachi, Darmstadt, Germany) consisted of a solvent pump (L-7110) set at a constant flow rate of 0.8 ml/min, a variable wavelength fluorescence detector (L-7480) set at an excitation and emission wavelength of 275 and 300 nm, respectively, a LiChrospher® 100 CN (5 μm) column (250 × 4 mm) and precolumn (4 × 4 mm), an autosampler (Gilson 234 autoinjector, Middleton, Wisconsin, USA) with a 50 μl loop (Valco Instruments, Houston, Texas, USA) and an automatic integration system (software D-7000 Multi-Manager) to collect and process the signals. The mobile phase consisted of acetonitrile/sodium dihydrogen orthophosphate buffer (2 M)/water (5/0.5/94.5, v/v/v). The mixture was adjusted to pH 3.0 with phosphoric acid.

2.7.3. Data analysis

The peak plasma concentration (C_{max}), the time to reach C_{max} (T_{max}) and the extent of absorption ($AUC_{0-36\ h}$) were calculated using the MW-Pharm Program version 3.0 (Mediware 1987–1991, Utrecht, The Netherlands). The $AUC_{0-36\ h}$ was calculated using logarithmic and linear trapezoidal rules. The relative bioavailability (F_{rel}, expressed in %) was calculated as the ratio of $AUC_{0-36\ h}$ between a test formulation and the sustained-release reference formulation (Slow-Lopresor® 200 Divitabs®). The sustained-release characteristics of a formulation were evaluated by the time span during which the plasma concentrations were at least 50% of the C_{max} value ($HVD_{t50\%Cmax}$, the width of the plasma concentration profile at 50% of C_{max}) [12,13]. The $HVD_{t50\%Cmax}$ values were determined from the individual plasma concentration-time profiles. The ratio between the $HVD_{t50\%Cmax}$ values of a test formulation and the immediate-release reference formulation (Lopresor® 100) (expressed as R_D) is indicative of the sustained-release effect: a ratio of 1.5, 2 and >3 indicating a low, intermediate and strong sustained-release effect, respectively [12].

2.7.4. Statistical analysis

The effect of metoprolol tartrate formulation on the bioavailability was assessed by repeated-measures ANOVA (univariate analysis). To further compare the effects of the different treatments, a multiple comparison among pairs of means was performed using a Bonferroni post-hoc test with $P < 0.05$ as significance level. The normality of the residuals was tested with a Kolmogorov–Smirnov test. SPSS version 16.0 was used to perform the statistical analysis.

3. Results and discussion

The drug release rate from hot-melt extruded dosage forms is mainly determined by the ratio of hydrophilic and hydrophobic polymers included in the matrix formulations [5,6,14–17]. Based on this principle polymeric hot-melt extruded mini-matrices consisting of EC (hydrophobic matrix former) and XG (hydrophilic additive to modify drug release) yielded zero-order release kinetics of freely water soluble drugs. Drug release depended on XG concentration and grade [9,11] as these factors determined the swelling behaviour and water uptake of the mini-matrices. As an alternative to XG, PEG and PEO could be used as these polymers have already been used for hot-melt extrusion. Since it is known that the swelling properties of PEO depend on their molecular weight [17–24], variable concentrations and grades of PEG/PEO were processed in combination with EC to modify drug release from these matrices.

The different formulations (Table 1) were easily processed at an extrusion temperature of 40 and 70 °C for PEG and PEO formulations, respectively, independent of PEG/PEO concentration and MW: no surface defects were detected and the extrudates having a smooth surface could be cut into high quality mini-tablets (without cracks or other irregularities at the cutting edges).

Whereas previous work by the authors [11] already confirmed that MPT is stable at these processing temperatures, the thermal stability of EC, PEG and PEOs after hot-melt extrusion at 100 and 200 °C was analyzed using GFC since polymers are subjected to mechanical, thermal and oxidative degradation during hot-melt extrusion. For all polymers, the MW profile of the samples prior to and after extrusion overlapped. As an example, the GFC chromatograms of PEO 1,000,000 are shown (Fig. 1). The retention time of PEG 6000, PEO 100,000, 1,000,000 and 7,000,000 during GFC analysis was 15, 11, 13 and 10 min, respectively. No discoloration of the polymers occurred when PEG and PEO were extruded at 200 °C, indicating that there was no degradation of PEG/PEO under these extrusion conditions. Moreover, the mini-matrices were extruded at 40 and 70 °C for formulations containing PEG and PEO, respectively, hence degradation of any component in the mini-matrices is unlikely. Other investigators reported that PEO stability in matrix tablets prepared by hot-melt extrusion depended on the storage and processing temperature, screw speed and the MW of the polymer [17,25].

An increase in PEG/PEO content significantly increased the drug release rate, irrespective of their MW due to the higher hydrophilicity of the matrix. Fig. 2 shows exemplarily the results obtained for PEO 100,000-containing mini-matrices. For all mini-matrices, the release from a formulation containing 1% and 2.5% PEG/PEO was similar, whereas the data of the 5% PEG/PEO mini-matrices coincided with the 10% PEG/PEO formulations. Interestingly the mini-matrices retained their cylindrical shape during dissolution testing and did not significantly swell, except for the 70% PEG/PEO formulations which had dissolved after approximately 1 h. Although the swelling of purely hydrophilic PEG/PEO matrices and films has been reported during dissolution [17–24], the cohesive nature of the EC matrix structure probably restricted swelling of the mini-matrices upon wetting. Formulations with 0%, 1%, 2.5%, 5% and 10% showed zero-order, but incomplete release kinetics. Complete drug release was observed at PEG/PEO concentrations of 20% and above; however, the burst release from these formula-

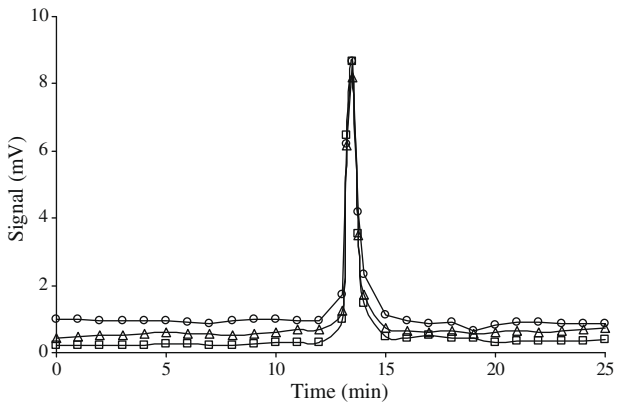

Fig. 1. Gelfiltration chromatograms of PEO 1,000,000: (□) prior to extrusion, hot-melt extruded sample at (△) 100 °C and (○) 200 °C.

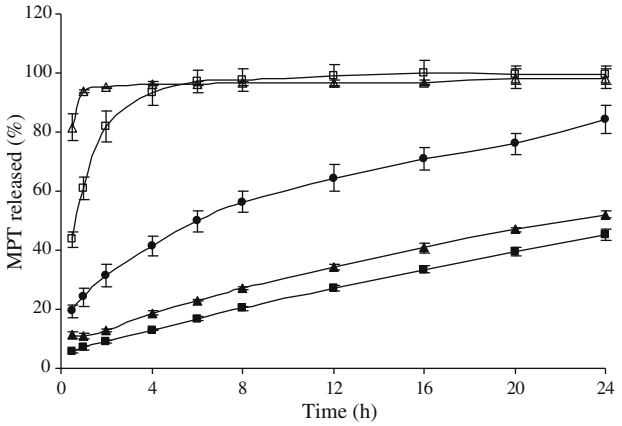

Fig. 2. Influence of PEO 100,000 concentration on the dissolution profiles (mean ± SD, $n = 6$) of mini-matrices containing 30% (w/w) MPT, EC/plasticizer (2/1, w/w) and PEO 100,000: (■) 0%, (▲) 2.5%, (●) 10%, (□) 20% and (△) 70%.

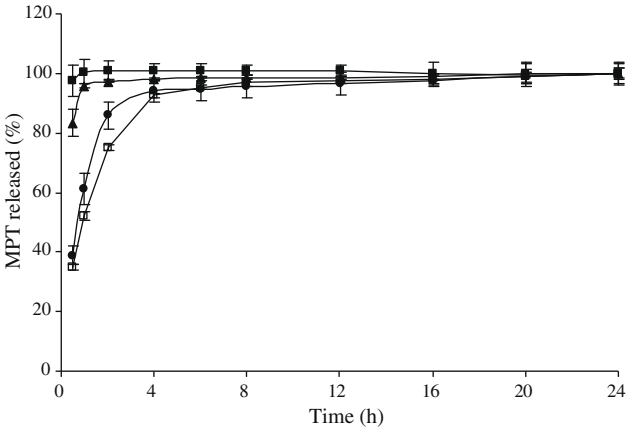

Fig. 4. Influence of PEG/PEO MW on the dissolution profiles (mean ± SD, $n = 6$) of mini-matrices containing 30% (w/w) MPT and 70% (w/w) hydrophilic polymer: (■) PEG 6000, (▲) PEO 100,000, (●) PEO 1,000,000, (□) PEO 7,000,000.

tions was significant: 43.6% and 81.6% released after 30 min (PEO 100,000).

At low PEG/PEO concentrations (1–2.5%), no effect of PEG/PEO MW on drug release was observed. Although a slower drug release is described from hydrophilic matrices containing higher MW PEO due to the increasing viscosity of the polymer [17–24,26–28] (the increased MW leads to an increase in gel strength, which tends to decrease the diffusion of the drug), drug release from matrices containing 5% and 10% PEG 6000 and PEO 100,000 was significantly slower in comparison to the PEO 1,000,000 and 7,000,000 mini-matrices (Fig. 3). This might be due to the faster release of low MW PEG/PEO from the matrix (which are released much faster in comparison with high MW PEO), resulting in molecular rearrangement of EC, thus modifying the porous network inside the matrix and hindering drug release. The dissolution conditions provided sufficient mobility for the EC polymer chains as MTDSC analysis showed that T_g of EC in combination with DBS (EC/DBS ratio: 2/1) was 40 °C. At 20% and 70% PEG/PEO, the drug release rate was slower using high MW PEO (Fig. 4), which is consistent with the data reported by other investigators [17–24,26–28], due to the increasing viscosity at higher MW since the properties of PEG/PEO became more predominant for drug release.

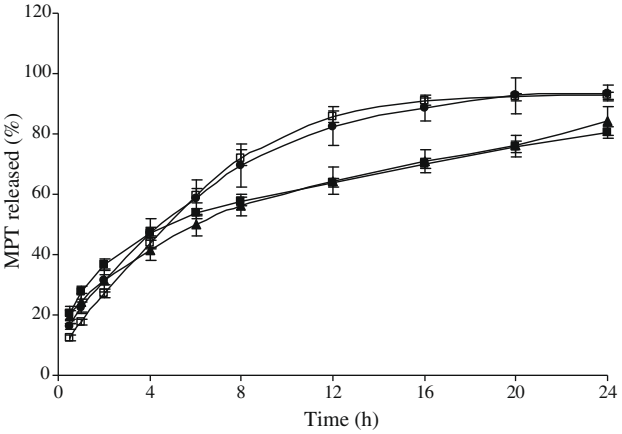

Fig. 3. Influence of PEG/PEO MW on the dissolution profiles (mean ± SD, $n = 6$) of mini-matrices containing 30% (w/w) MPT, EC/plasticizer (2/1, w/w) and 10% (w/w) hydrophilic polymer: (■) PEG 6000, (▲) PEO 100,000, (●) PEO 1,000,000, (□) PEO 7,000,000.

PEG/PEO release increased at higher PEG/PEO concentrations (irrespective of MW) as less matrix-forming polymer was present and the mini-matrices became less hydrophobic. In addition, PEG/PEO release from mini-matrices depended on the MW of the hydrophilic polymer as the viscous nature of high MW PEO reduced its mobility and consequently the release kinetics. MPT release was not in all cases correlated with PEG/PEO leaching, especially in relation to the effect of PEG/PEO MW: although a slower PEG/PEO release was observed for all formulations formulated with high MW PEO, drug release was not affected by PEO MW in case of mini-matrices containing low PEG/PEO concentrations (1–2.5%), and drug release from mini-matrices containing 5–10% PEG/PEO increased when using higher MW PEG/PEO.

The MPT distribution in the mini-matrices was monitored off-line via Raman using the 627–653 cm^{-1} spectral band as no overlap with other ingredients occurred at these wavenumbers (Fig. 5). No difference was seen between the different PEG/PEO types. Based on the intensity of the Raman signal across the scanned sections of the mini-matrices it was confirmed that MPT is homogeneously distributed in the mini-matrix irrespective of the PEG/PEO concentration and MW.

Fig. 6 shows the X-ray diffraction spectra of MPT, EC, PEO 1,000,000 and 20% PEO 1,000,000 mini-tablet. The drug and hydrophilic polymer were crystalline, while EC was amorphous. The X-ray pattern of the hot-melt extruded 20% PEO 1,000,000 mini-tablet showed only diffraction peaks corresponding to MPT and PEO 1,000,000, indicating that these products remained crystalline during extrusion. However, the diffraction peaks were smaller in comparison with the pure materials, illustrating the presence of smaller crystals. Other investigators also noticed a reduction in PEO peak intensity following thermal processing compared to the unprocessed polymer, associated with a decrease in crystallinity,

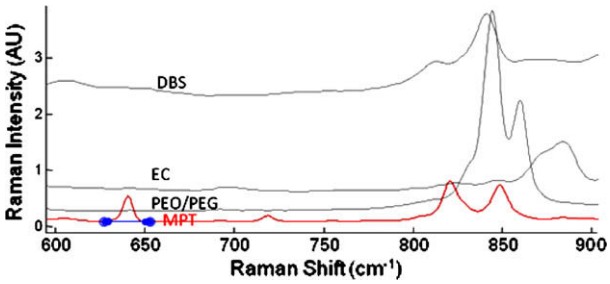

Fig. 5. Raman spectra from the compounds in the mini-matrices.

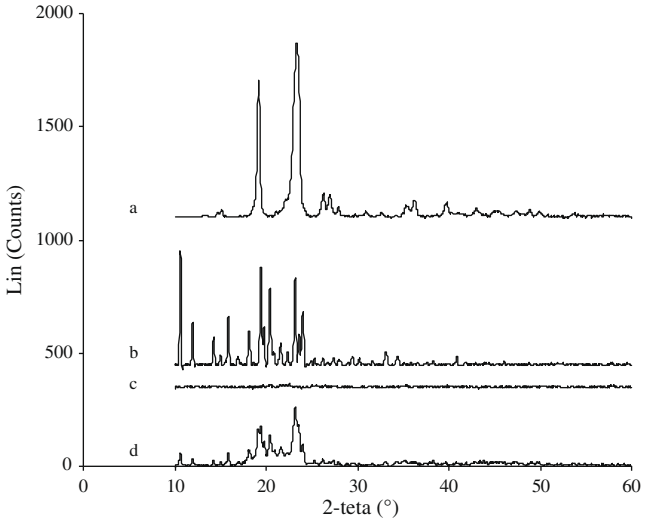

Fig. 6. X-ray diffraction pattern of (a) PEO 1,000,000, (b) MPT, (c) EC and (d) 20% PEO 1,000,000 mini-matrix.

and the PEO peaks became more broad due to a wider distribution of crystal size [29–32].

To check for changes in the thermal behaviour of the components or to identify interactions between components, MTDSC analysis was performed: the values of T_g of EC and T_m of MPT were 127.9 ± 0.2 °C and 122.6 ± 0.4 °C, respectively. The T_m of PEG 6000, PEO 100,000, PEO 1,000,000 and PEO 7,000,000 is 60.3 ± 0.0 °C, 65.4 ± 0.4 °C, 67.7 ± 0.1 °C and 69.5 ± 0.3 °C, respectively (the onset of melting and the melting point of PEO increased as the MW increased). After extrusion of PEG and PEO samples at 40 and 70 °C, respectively, (blends without PEG or PEO were processed at both temperatures) no shifts in T_g and T_m were detected in case of binary mixtures, the degree of crystallinity had not changed and the individual thermal signals were detected, indicating that no interactions between components occurred during extrusion under the processing conditions described above. However, others reported changes in drug and polymer thermal transitions when drug and PEOs were co-processed, associated with their (partially) miscibility and formation of solid dispersions and solid solutions [18,25,26,28–32,33,34]. All binary blends of EC/DBS, EC/PEG(PEO), EC/MPT and MPT/PEG(PEO) could be processed via extrusion and were subsequently analyzed via MTDSC. In contrast, only a binary mixture of PEG(PEO)/DBS in a ratio of 20/16.7 (corresponding to a formulation with 20% hydrophilic polymer) could be processed via extrusion for PEO 1,000,000 and 7,000,000, as the other PEG(PEO)/DBS ratios (Table 1) and PEG/PEO grades resulted in phase separation (due to the high liquid fraction).

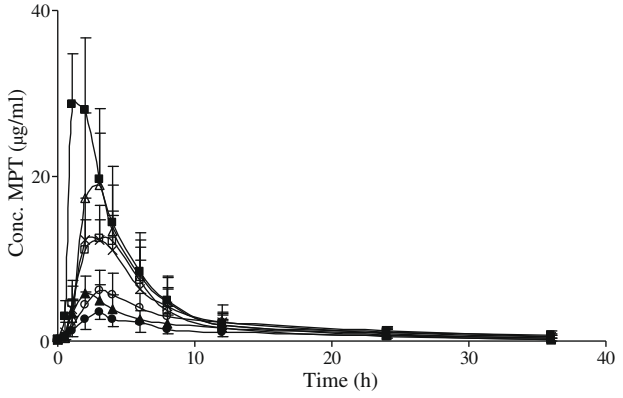

Fig. 7. Mean plasma concentration-time profiles (± SD, $n = 6$) after oral administration of 200 mg metoprolol tartrate to dogs: (■) Lopresor® 100 (2 tablets), (□) Slow-Lopresor® 200 Divitabs® (1 tablet), (●) 5% XG mini-matrices, (○) 10% XG mini-matrices, (x) 20% XG mini-matrices, (▲) 5% PEO 1,000,000 mini-matrices and (△) 20% PEO 1,000,000 mini-matrices.

MPT, a drug with high solubility and permeability, is well absorbed over a large part of the gastrointestinal tract. Its relatively short half-life (3–4 h) makes MPT a suitable candidate for an extended-release formulation [35–39]. The enhanced therapeutic efficacy of this drug through the provision of constant drug input and maintenance of steady-state blood levels is well documented, and different types of controlled-release formulations improved the clinical efficacy of MPT. Its administration in dogs is considered to be safe [40,41].

Prior to the investigation of the influence of PEG/PEO concentrations on MPT release, the authors investigated in the previous work the effect of XG concentration on in vitro drug release [11]. Based on the different swelling behaviour of the mini-matrices formulated with both hydrophilic polymers upon contact with the dissolution medium (swelling in case of XG versus no swelling for PEG/PEO mini-matrices), it is of interest to compare the bioavailability of both types of mini-tablets. Drug release from formulations without hydrophilic polymer, 1% and 2.5% (w/w) of XG [11] and PEG/PEO (Fig. 2) was not complete after 24 h, and these mini-matrices were therefore not selected for in vivo analysis. The MPT release kinetics from 5%, 10% and 20% XG mini-matrices (all resulting in complete drug release after 24 h) were significantly different [11], and these formulations were selected for the in vivo study. Only formulations with 5% and 20% PEO were administered to the dogs, as 10% PEO mini-tablets yielded similar dissolution profiles as 5% PEO mini-matrices. Mini-matrices with 70% PEG/PEO gave a burst release (Fig. 2) and were consequently not of interest as sustained-release dosage form. PEO 1,000,000 (intermediate MW) was selected as hydrophilic polymer for the in vivo analysis.

Fig. 7 shows the mean plasma concentration-time profiles after oral administration of 200 mg MPT to six dogs as Lopresor® 100 (2 tablets), Slow-Lopresor® 200 Divitabs® (1 tablet) and the experi-

Table 2
Mean pharmacokinetic parameters (± SD, $n = 6$) after oral administration of 200 mg metoprolol tartrate to dogs as 5% XG mini-matrices, 10% XG mini-matrices, 20% XG mini-matrices, 5% PEO 1,000,000 mini-matrices, 20% PEO 1,000,000 mini-matrices, Lopresor® 100 (2 tablets) and Slow-Lopresor® 200 Divitabs® (1 tablet).

	C_{max} (µg/ml)	T_{max} (h)	$AUC_{0-36\ h}$ (µg h/ml)	$HVD_{r50\%Cmax}$ (h)	F_{rel}* (%)	R_D
5% XG	3.9 ± 0.7	3.3 ± 1.4	39.2 ± 16.2	4.6 ± 1.8	51.5 ± 27.8	1.6 ± 0.4
10% XG	6.6 ± 2.3	3.5 ± 1.4	72.1 ± 22.5	5.7 ± 2.3	94.4 ± 43.2	2.2 ± 1.1
20% XG	13.9 ± 3.5	2.7 ± 0.8	100.6 ± 39.9	4.0 ± 1.6	131.5 ± 70.0	1.4 ± 0.2
5% PEO 1,000,000	5.9 ± 2.1	2.2 ± 0.4	51.5 ± 22.6	4.3 ± 1.2	66.2 ± 31.0	1.6 ± 0.5
20% PEO 1,000,000	21.3 ± 7.9	2.7 ± 0.5	113.5 ± 54.9	3.7 ± 1.0	148.2 ± 87.7	1.4 ± 0.6
Lopresor® 100 (2 tablets)	31.8 ± 4.6	1.3 ± 0.5	151.3 ± 51.4	2.9 ± 1.2	–	–
Slow-Lopresor® 200 Divitabs® (1 tablet)	13.3 ± 2.8	3.2 ± 1.0	87.8 ± 35.8	4.9 ± 1.2	–	2.0 ± 1.0

– not applicable.
* Slow-Lopresor® 200 Divitabs® (1 tablet).

mental mini-matrices. The pharmacokinetic parameters are reported in Table 2.

The in vivo behaviour of the experimental mini-matrices was reflected in their in vitro dissolution profiles (Fig. 8). An increasing XG concentration of 5–20% enhanced drug release, which was reflected in the higher $AUC_{0-36\ h}$ and F_{rel}. The same observation was valid for the PEO mini-matrices as the $AUC_{0-36\ h}$ values correlated with the in vitro release profiles. Concerning the AUC values, no hot-melt extruded formulation was significantly different when compared with the sustained-release reference formulation Slow-Lopresor® 200 Divitabs® ($P > 0.05$), although the AUC values tended to increase at higher hydrophilic polymer concentration. None of the formulations showed a strong sustained-release effect since R_D values ranged from 1.4 to 1.6, except for the 10% XG mini-matrices which showed an intermediate sustained-release effect (R_D 2.2). In comparison with the 20% XG mini-tablets, the 10% XG formulation is characterized by a higher T_{max} (2.7 and 3.5 h, respectively) and lower C_{max} (13.9 and 6.6 μg/ml, respectively), which is typical for sustained-release formulations and which is reflected in its higher $HVD_{t50\%Cmax}$ (4.0 and 5.7 h, respectively) and R_D (1.4 and 2.2, respectively). Only the C_{max} values of 5% XG (mean difference: 9.4 (95% C.I.: 1.9–16.8; $P = 0.018$)) and 5% PEO (mean difference: 7.4 (95% C.I.: 0.4–14.4; $P = 0.039$)) formulations were significantly different from Slow-Lopresor® 200 Divitabs® at the 0.05 level of significance. For all experimental formulations, T_{max} and $HVD_{t50\%Cmax}$ values showed no significant difference in comparison with the sustained-release reference formulation ($P > 0.05$). F_{rel} of the 5% and 10% XG formulations was significantly different (mean difference: 42.9 (95% C.I.: 3.6–82.3; $P = 0.035$)), whereas no significant difference between the PEO formulations was seen ($P > 0.05$). Concerning the sustained-release effect, the R_D values of the experimental formulations were not significantly different from Slow-Lopresor® 200 Divitabs®. Based on the pharmacokinetic data (Table 2), C_{max} and T_{max} of 20% XG mini-tablets (multiparticulate dosage form) and Slow-Lopresor® 200 Divitabs® (single-unit dosage form) were similar which supported the hypothesis that 20% XG mini-matrices behaved in vivo as a single-unit dosage form instead of multiparticulates. This was confirmed by the swelling behaviour of the 20% XG mini-matrices during dissolution (using a larger sample size of mini-matrices filled into a capsule, similar to the dosage form administered to the dogs): due to the rapid swelling of XG, the mini-matrices stick together and the increased diffusion path length from this plug reduced drug release, $AUC_{0-36\ h}$ and F_{rel} [9] (Fig. 9a and b). In contrast, PEO mini-matrices did not swell during dissolution testing (Fig. 9c and d). Previous work [9] had also shown

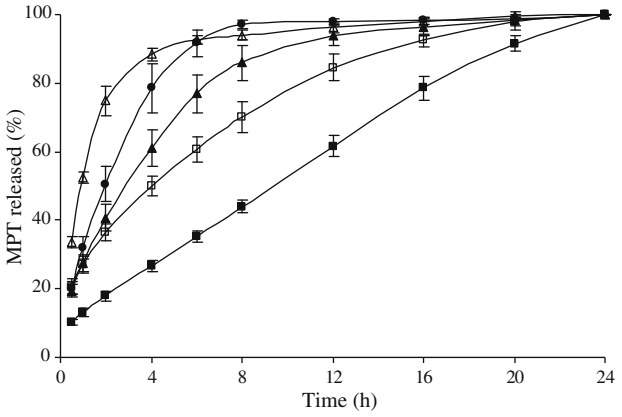

Fig. 8. Influence of XG and PEO 100,000 concentration on the dissolution profiles (mean ± SD, $n = 6$) of mini-matrices containing 30% (w/w) MPT, EC/plasticizer (2/1, w/w) and hydrophilic polymer: (■) 5% XG, (▲) 10% XG, (●) 20% XG, (□) 5% PEO 1,000,000 and (△) 20% PEO 1,000,000.

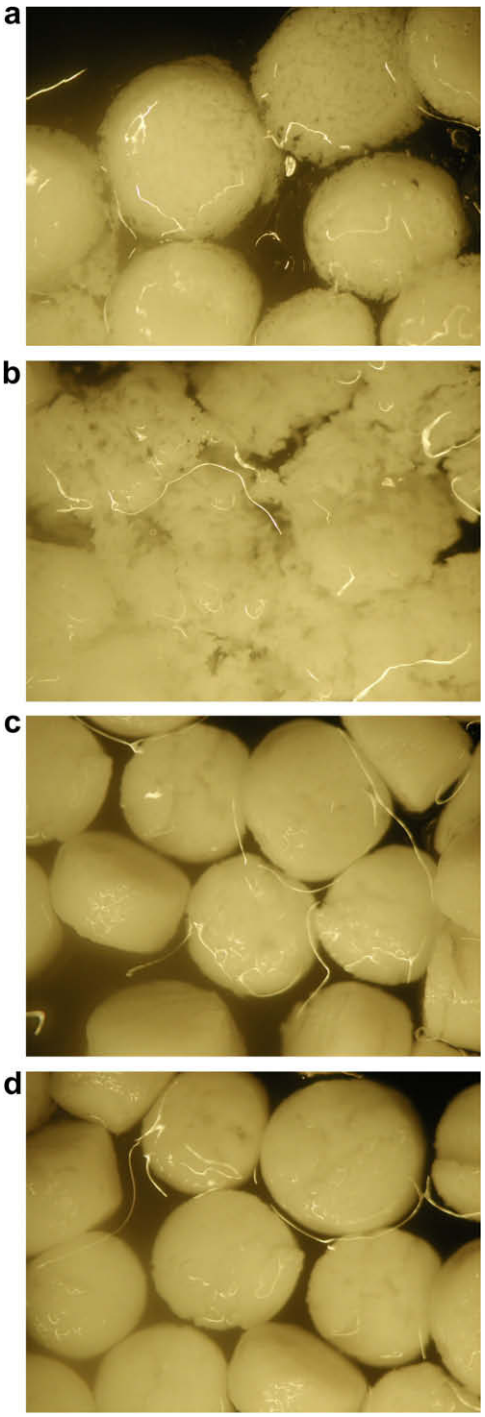

Fig. 9. Swelling behaviour of mini-matrices after immersion in the dissolution medium: (a) 20% XG – 4 h, (b) 20% XG – 24 h, (c) 20% PEO 1,000,000 – 4 h, (d) 20% PEO 1,000,000 – 24 h.

that mini-matrices with 20% and 30% XG had similar in vivo behaviour, caused by their similar swelling behaviour upon immersion with the dissolution medium. However, in this study a significant difference in pharmacokinetic parameters and plasma concentration-time profiles between 10% and 20% XG formulations was observed. This can be due to the fact that we used a drug with a high water solubility for this study (in comparison with ibuprofen, which is a BSC class II drug). In addition, it might also be explained by the different drug/XG, drug/EC and EC/XG ratios for formulations with ibuprofen and MPT: MPT which is dissolved very rapidly

might therefore be less influenced by the rapid XG swelling and consequently release kinetics from the XG mini-matrices.

4. Conclusions

This paper showed that hot-melt extrusion can be used to produce mini-matrices with controlled drug delivery: the presented ethylcellulose-polyethylene glycol/polyethylene oxide mini-matrices allow to manufacture sustained-release dosage forms with a wide range of drug release patterns. Importantly, not only the slope but also the shape of the resulting release curves can be adjusted by varying the polyethylene glycol/polyethylene oxide content and molecular weight. All components remained stable under the processing conditions. Neither drug and polymer crystallinity nor drug homogeneity was influenced by the concentration and type of hydrophilic polymer. In vivo data showed that oral administration of ethylcellulose-xanthan gum was able to sustain metoprolol tartrate plasma levels in dogs. Xanthan gum and polyethylene oxide behaved differently upon contact with the swelling medium.

Further work will be conducted in order to determine the underlying mass transport mechanism of drug and hydrophilic polymer, and experiments will be performed to predict the effects of the mini-matrix geometry on the resulting drug release kinetics and to evaluate the validity of these theoretical predictions.

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