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European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 312–319
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Influence of formulation and process parameters on the release characteristics of ethylcellulose sustained-release mini-matrices produced by hot-melt extrusion

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Received 30 August 2007; accepted in revised form 8 October 2007
Available online 15 October 2007

Abstract

Mini-matrices (multiple unit dosage form) with release-sustaining properties were developed by hot-melt extrusion (cylindrical die: 3 mm) using metoprolol tartrate as model drug and ethylcellulose as sustained-release agent. Dibutyl sebacate was selected as plasticizer and its concentration was optimized to 50% (w/w) of the ethylcellulose concentration. Xanthan gum, a hydrophilic polymer, was added to the formulation to increase drug release. Changing the xanthan gum concentration modified the in vitro drug release: increasing xanthan gum concentrations (1%, 2.5%, 5%, 10% and 20%, w/w) yielded a faster drug release. Zero-order drug release was obtained at 5% (w/w) xanthan gum. Using kneading paddles, smooth extrudates were obtained when processed at 60 °C. At least one mixing zone was required to obtain smooth and homogeneous extrudates. The mixing efficacy and drug release were not affected by the number of mixing zones or their position along the extruder barrel. Raman analysis revealed that metoprolol tartrate was homogeneously distributed in the mini-matrices, independent of screw design and processing conditions. Simultaneously changing the powder feed rate (6–25–50 g/min) and screw speed (30–100–200 rpm) did not alter extrudate quality or dissolution properties.

Keywords: Hot-melt extrusion; Sustained-release; Multiple-unit dosage form; Matrix system; Xanthan gum

1. Introduction

Hot-melt extrusion is a technology used in the pharmaceutical industry to produce matrix formulations into which a drug is homogeneously embedded. Its major advantage over conventional techniques for manufacturing sustained-release matrices is the continuity of the production process as the different steps (mixing, melting, homogenizing and shaping) are carried out on a single machine [1–3]. The excellent feasibility of ethylcellulose, a polymer with thermoplastic properties, for hot-stage extrusion has been established in a variety of applications [4–6]. Previous work has shown that hot-melt extrusion is an appropriate technique to develop mini-matrices using ethylcellulose to sustain the release of ibuprofen: the combination of ethylcellulose and a hydrophilic component (hydroxypropyl-methylcellulose [7–9], xanthan gum [7–10]) 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 [11]. Consequently, the characteristics of ethylcellulose/hydrophilic polymer mini-matrices containing ibuprofen are 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

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doi:10.1016/j.ejpb.2007.10.007

tartrate, 123 °C) and a conventional plasticizer was added to the formulation.

In the present study sustained-release mini-matrices were developed by hot-melt extrusion of a metoprolol tartrate/ethylcellulose-mixture with the addition of xanthan gum to tailor drug release. The aim was to examine the effect of different plasticizers on the extrusion behaviour and extrudate quality. After optimization of the formulation (type and concentration of plasticizer, xanthan gum concentration) to obtain zero-order drug release, the effect of extrusion process parameters (screw design, powder feed rate and screw speed) on the quality and drug release properties of the mini-matrices was evaluated.

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 of 3–15 μm), kindly donated by the Dow Chemical Company (Midland, USA), and a hydrophilic component: xanthan gum (XG) (Xantural® 75, mean particle size of 75 μm) supplied by CP Kelco (Liverpool, UK). Dibutyl sebacate (DBS), diethyl phthalate (DEP), triethyl citrate (TEC) and triacetin (TA) (Sigma–Aldrich, Steinheim, Germany) were tested as potential plasticizers for ethylcellulose. All other chemicals were of analytical grade.

2.2. Preparation of co-evaporates and hot-melt extruded samples

The glass transition temperature (T_g) of EC in EC/plasticizer co-evaporates (containing 0%, 10%, 20% and 30% (w/w) DBS, DEP, TEC or TA), in hot-melt extruded EC/DBS mixtures (ratio: 95/5, 80/20 and 66/33 (w/w)) and in hot-melt extruded MPT/EC/plasticizer (30/50/20, w/w/w) mixtures was determined via differential scanning calorimetry (DSC).

2.2.1. Co-evaporates

Co-evaporates were prepared by dissolving the plasticizer and EC in ethanol. The polymer solution (total solid content: 0.5 g in 150 ml) was transferred into a Teflon flask and a rotavapor (Büchi Rotavapor R-200, Flawil, Switzerland) was used to remove the solvent under reduced pressure at 70 °C. The films were peeled from the perfluoroalkoxy surface of the flask and stored in an oven at 70 °C for 2 days to ensure complete removal of ethanol. Subsequently the films were pulverized in a mortar using liquid nitrogen, further dried and stored at 40 °C before subjecting the samples to thermal analysis.

2.2.2. Hot-melt extruded samples

Hot-melt extruded EC/DBS samples were prepared at a powder feed rate at 6 g/min, screw speed of 30 rpm, using the standard screw configuration and different extrusion temperatures (range: 50–200 °C with 25 °C intervals). Hot-melt extruded MPT/EC/plasticizer mixtures were processed at 65 °C. Additionally, the influence of MPT on the T_g of EC is measured in an extruded sample having an EC/MPT ratio of 33.3/30 (w/w) (i.e. the lowest EC/MPT ratio in the formulations tested thus offering the highest interaction possible).

2.3. Optimization of plasticizer

To select a suitable plasticizer EC was combined with different plasticizers (DBS, DEP, TEC and TA) in a ratio of 2.5/1 (w/w). The MPT content of these formulations was 30% (w/w). 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 grind the MPT/EC/plasticizer mixture 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, a screw with two mixing sections and a densification zone (the geometry of the screws is illustrated in Fig. 1). The die block (2.6 cm thickness) was fixed to the extruder barrel, and additionally, an axially mounted die plate (1.9 cm thickness) was attached to the die block, with a cylindrical hole of 3 mm diameter for shaping the extrudates. The following extrusion conditions were used: a screw speed of 30 rpm, a powder feed rate of 6 g/min and a temperature of 65 °C for the five heating zones along the barrel. After cooling down to room temperature, the extruded rods ($\varnothing = 3$ mm) were manually cut, using surgical blades, into mini-matrix of 2 mm length. The influence of the plasticizer type on drug release was evaluated via in vitro dissolution testing.

To optimize the extrudate quality and mini-matrices properties, formulations with variable DBS concentrations were processed (EC/DBS ratio: 5/1, 3/1, 2/1 and 1.4/1, w/w). The MPT and XG content were 30% and 10% (w/w), respectively. The mini-matrices were manufactured using the same process as described above, except for the temperature: the initial extrusion temperature was set at 80 °C and was lowered in steps of 10 °C until shark skinning of the extrudate occurred. The surface properties of the extrudates were visually inspected for any defects 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×).

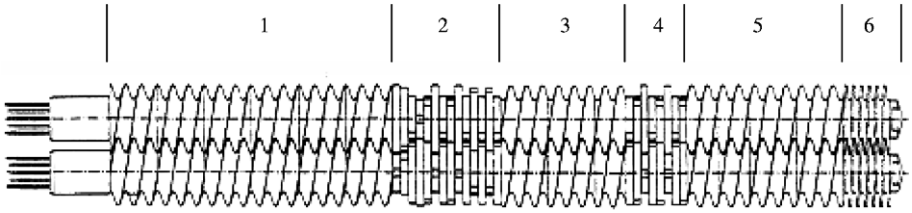

Fig. 1. Configuration of the intermeshing co-rotating screws. Standard screw configuration with two kneading blocks: transport zone (1), mixing zone (2), transport zone (3), mixing zone (4), transport zone (5) and densification zone (6).

2.4. Influence of xanthan gum

To modify the drug release and obtain zero-order release kinetics from the EC mini-matrices, XG was added to the formulation in concentrations of 0%, 1%, 2.5%, 5%, 10% and 20% (w/w). The MPT content was 30% (w/w), the EC/DBS ratio 2/1 (w/w). The formulations were processed via hot-melt extrusion: screw speed of 30 rpm, powder feed rate of 6 g/min, extrusion temperature of 60 °C, using the standard screw profile described above. In vitro dissolution testing and swelling properties of the mini-matrices were evaluated via microscopic analysis after 4 h immersion in the dissolution medium.

2.5. Influence of the extrusion process parameters

The influence of process parameters (screw design, powder feed rate and screw speed) on the extrusion process, extrudate quality and drug release properties of an optimized formulation (MPT/XG/EC/DBS ratio: 30/5/43.3/21.7, w/w/w/w) was evaluated.

The standard configuration (Fig. 1) of the screw (length: 47.5 cm, diameter: 1.9 cm) consisted of transport elements (forwarding elements that serve as drivers to provide forwarding pressure to transport the material through the extruder), two kneading blocks and a discharge element (densification zone). The conveying sections built out of transport elements have a double helix and a pitch of 9.5 mm. The kneading blocks consist of disks (4.75 mm thickness, mixing elements) which ensure a good blending of the powder mixture. The first kneading block (at 26.6 cm from the discharge end) consists of 10 disks with increasing staggering angle (4 disks at 30°, 4 disks at 60° and 2 disks at 90°). The second kneading block (at 15.2 cm from the discharge end) has 6 disks with a staggering angle of 60°. The discharge element is placed at the end of the screw and has a length of 2.8 cm and a pitch of 5.0 mm. Next to the standard screw design experiments were also performed with a screw having only one kneading block (the first or second mixing zone, the kneading paddles of the other mixing zone were replaced by transport elements) and without kneading block (the screw consisted of only transport elements and the discharge zone). The extrusion was carried out at a powder feed rate of 6 g/min, screw speed of 30 rpm and a processing temperature of 60 °C.

The effect of production rate (depending on powder feed rate and screw speed) was determined by manufacturing mini-matrices at the following conditions: standard screw configuration, processing temperature of 60 °C and variable powder feed rate and screw speed: 6 g/min in combination with 30 rpm, 25 g/min with 100 rpm, and 50 g/min with 200 rpm.

Extrudate quality and mini-matrix properties were visually evaluated (microscopic analysis) and via in vitro dissolution testing.

Using the standard extrusion settings (standard screw configuration, processing temperature of 60 °C, powder feed rate of 6 g/min and screw speed of 30 rpm), the reproducibility of the extrusion process was evaluated by processing three batches on three consecutive days, and the equilibration time of the production process was determined by collecting extrudate samples at several time points (5, 10, 15, 20 and 25 min after start-up). In vitro dissolution testing was used as evaluation method to differentiate between samples collected at different days and at different sampling points.

MPT distribution in the mini-matrices prepared via different extrusion processes (using 0, 1 or 2 kneading blocks) 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 (spot size laser of 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 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.).

2.6. Thermal analysis

The thermal behaviour of powders, co-evaporates 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 the purge gas through the DSC cell and 150 ml/min of nitrogen through the RCS unit. Samples (±10 mg) were run in closed aluminium pans supplied by TA Instruments (Leatherhead, UK); 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 0 to 200 °C, a modulation amplitude of 0.212 °C and a period of 40 s. Temperature and enthalpic calibration was 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 (Leatherhead, UK). Measurements were performed in duplicate and the T_g values (midpoint half height) are reported.

2.7. In vitro drug release

The mini-matrices (approximately 60 mg) were introduced in a basket (USP 27, dissolution apparatus 1). The dissolution was performed in a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, NJ, USA). Demineralised water was used as the 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). Due to interference of DEP in the absorption spectrum of MPT, dissolution samples of mini-matrices containing DEP were analyzed using a validated HPLC-UV method. The HPLC equipment consisted of a solvent pump (L-7100, Merck–Hitachi, Darmstadt, Germany) set at a constant flow rate of 1.0 ml/min, a variable wavelength UV-detector (L-7400, Merck–Hitachi, Darmstadt, Germany) set at 222 nm, a reversed-phase column and precolumn (LiChroCART® 250-4 and 4-4, LiChrospher® 100 RP-18 (5 μm); Merck, Darmstadt, Germany), an auto-sampler (L-7200, Merck–Hitachi, Darmstadt, Germany) with a 100 μl loop (Valco Instruments Corporation, Houston, TX, USA) equipped with an automatic integration system (software D-7000 Multi-Manager, Merck, Darmstadt, Germany). The mobile phase consisted of 0.01 M KH_2PO_4/acetonitrile/methanol (55/22.5/22.5, v/v/v). For both spectrophotometric methods, the MPT concentrations were calculated from a calibration curve between 0 and 50 μg/ml.

The dissolution was simultaneously performed in six dissolution vessels, each vessel containing four mini-matrices.

3. Results and discussion

3.1. Optimization of plasticizer

Previous work [11] identified ibuprofen (melting point 76 °C) as a plasticizer for EC, and therefore the characteristics of ibuprofen/EC mini-matrices are not predictive of the extrusion and dissolution properties of EC mini-matrices containing non-plasticizing drugs. The aim of this work was to substitute ibuprofen by MPT: due to its higher melting point (123 °C), a specific drug-matrix interaction (due to melting of the drug) is unlikely in case that extrusion is performed at a temperature below the drug melting point. Therefore, the effect of MPT on the polymer T_g was examined. Analyzing the thermal behaviour of an EC/MPT (33.3/30, w/w) hot-melt extruded sample (extrusion temperature: 65 °C) only revealed the melting endotherm of MPT (T_m 122.6 °C ± 0.4), whereas no T_g of EC was detected. Since the T_g of EC powder was determined 127.9 °C ± 0.2, one can assume that the T_g of EC in the melt-extruded samples is masked by the melting endotherm of MPT (peak ranging from 108.5 to 126.0 °C). Although a slight decrease in T_g of EC could be overwhelmed by the melting signal of MPT, any interaction occurring during extrusion between MPT and EC is limited (since no T_g of EC was detected at a temperature below the melting endotherm of MPT) and the incorporation of a conventional plasticizer is required to lower the extrusion temperature in order to reduce thermal degradation and improve extrudate quality.

The effect of plasticizer type and concentration is shown in Fig. 2 ($n = 3$). T_g of EC decreased at higher plasticizer concentrations, although an increase from 20% to 30% (w/w) did not induce a further drop of T_g. Despite the different polarity of the plasticizers (hydrophilic: TEC, TA/lipophilic: DBS, DEP) the efficiency of all plasticizers was similar.

Using co-evaporates it was not possible to select a specific plasticizer. However, co-evaporates could overesti-

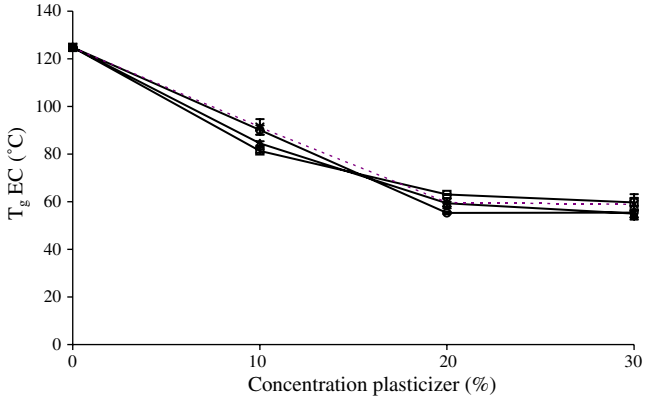

Fig. 2. Influence of plasticizer concentration and type on the T_g of EC (mean ± SD, $n = 3$) for co-evaporates. (□) DBS, (△) DEP, (○) TEC, (*) TA.

mate the plasticizing efficacy since ideal solid dispersions were manufactured, maximizing plasticizer/polymer interactions. Therefore, hot-melt extruded samples (MPT/EC/plasticizer in a ratio of 30/50/20 (w/w/w)) were processed to select the optimal plasticizer. Neither the extrusion process nor the extrudate quality was influenced by the plasticizer type since the pressure and torque were similar when extruding with the different plasticizers (extrusion temperature: 65 °C). For all hot-melt extruded samples, the T_g of EC was detected in the temperature range of 55–60 °C. Comparing these results with the T_g shifts of the co-evaporates showed that the plasticizing efficiency of the four plasticizer types was similar in both methods, indicating that intense intermolecular mixing also occurred during the hot-melt extrusion process, ensuring complete miscibility of plasticizers and EC. In contrast, Aitken-Nichol and co-workers [12] suggested that intermolecular mixing was better in a solution-cast film compared to a highly viscous melt: lidocaine HCl being a more effective plasticizer in solution cast films than in the extruded films.

Drug release in function of plasticizer type is shown in Fig. 3: the release rate was affected, indicating that the chemical nature of the plasticizer plays a major role for the underlying drug release mechanism. DBS and DEP provided a linear release of MPT, however, not all drug was released within 24 h. On the other hand, complete release was noticed for TEC- and TA-containing mini-matrices, but the burst effect was significant probably due to the hydrophilicity of these plasticizers. Other investigators [13,14] already described a similar effect of water solubility of the plasticizer on the drug release mechanism. Lecomte and co-workers [15] compared a lipophilic (dibutyl sebacate) and hydrophilic (triethyl citrate) plasticizer and reported that triethyl citrate rapidly leached from a polymer coat affecting film permeability and drug diffusion. In contrast dibutyl sebacate remained in the polymer layer, reducing the drug release rate. Due to the burst effect of the hydrophilic plasticizers, DBS was selected for MPT/EC formulations, since this combination seemed able to provide zero-order drug release from the mini-matrices.

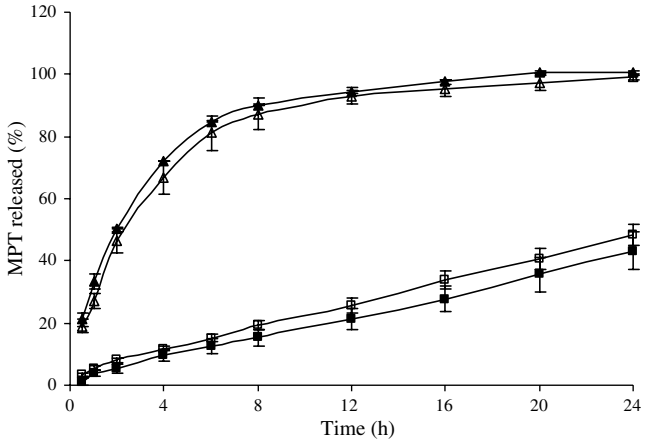

Fig. 3. Influence of plasticizer type on the dissolution profiles (mean ± SD, $n = 6$) of mini-matrices containing 30% (w/w) MPT and EC/plasticizer (2.5/1, w/w). (■) DBS, (□) DEP, (▲) TEC and (△) TA.

Depending on the DBS concentration in the formulation and the processing temperature, the pressure and torque during production varied (Table 1): both parameters increased with decreasing processing temperatures (irrespective of the DBS content) due to the higher viscosity of the material at these production conditions. Processing was also easier at higher DBS levels as T_g of EC was lowered to about 100.1, 43.8 and 38.8 °C after extrusion (at 125 °C) of binary EC/DBS mixtures containing 5%, 20% and 33% (w/w) DBS, respectively. The minimum extrusion temperature allowing processing also confirmed the efficiency of DBS during extrusion of EC: a 66/33 (w/w) and 80/20 (w/w) EC/DBS mixture could be processed at 50 and 75 °C, respectively, whereas a 95/5 (w/w) mixture already blocked the extruder at an extrusion temperature of 100 °C. At higher DBS concentration it was possible to process the extrudates at lower temperature before surface defects were observed (Table 1): at 40 °C the extrudate with an EC/DBS ratio of 2/1 (w/w) showed shark skinning, whereas at the same processing temperature the extrudate showed only a rough surface when an EC/DBS ratio of 1.4/1 (w/w) was used. For all formulations, the extrudates were sticky and had droplets (mainly DBS) on their surface when extruded at 80 °C. Since mini-matrices with cracks (Fig. 4a) are excluded from further optimization and evaluation (drug release from these mini-matrices would be difficult to control), an EC/DBS ratio of at least 2/1 (w/w) is required to produce mini-matrices with good

Table 1
Pressure (bar) and torque (%) during production of mini-matrices using different EC/DBS ratios (w/w) at different processing temperatures. The MPT and XG content were 30% and 10% (w/w), respectively

EC/DBS ratio (w/w)	Processing temperature (°C)	Pressure (bar)	Torque (%)	Extrudate	Mini-matrices
5/1	80	0	8	Sticky	–
	70	4	12	Smooth	Cracks
	60	66	93	Shark skinning	–
3/1	80	0	16	Sticky	–
	70	1	20	Smooth	Cracks
	60	6	31	Smooth	Cracks
	50	26	43	Shark skinning	–
2/1	80	0	18	Sticky	–
	70	1	26	Smooth	Smooth
	60	4	35	Smooth	Smooth
	50	10	45	Rough	–
	40	39	78	Shark skinning	–
1.4/1	80	0	19	Sticky	–
	70	0	22	Smooth	Smooth
	60	2	29	Smooth	Smooth
	50	4	38	Smooth	Smooth
	40	9	59	Rough	–

–, not applicable.

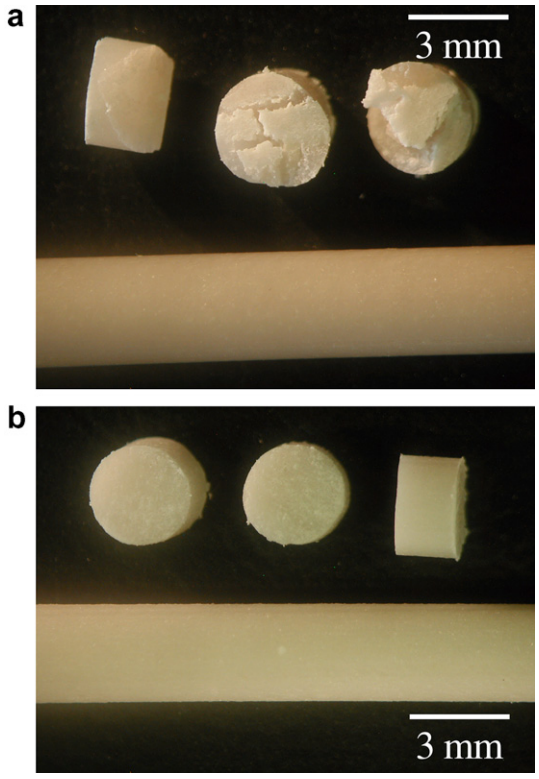

Fig. 4. Extrudates and mini-matrices consisting of (a) MPT/XG/EC/DBS (30/10/50/10, w/w/w/w) produced at 70 °C and (b) MPT/XG/EC/DBS (30/10/40/20, w/w/w/w) produced at 60 °C.

quality (without cracks) (Fig. 4b). Since it is preferential to use the lowest plasticizer concentration possible, an EC/DBS ratio of 2/1 (w/w) is selected for further experiments.

3.2. Influence of xanthan gum concentration

The drug release rate from hot-melt extruded dosage forms is highly dependent upon the characteristics of the carrier material. Most of the materials used in hot-melt extruded dosage forms are water insoluble [5,6,16,17] or have slow hydration or gelation rates [18,19]. To improve or modulate drug release from these systems, various excipients with different physicochemical properties can be

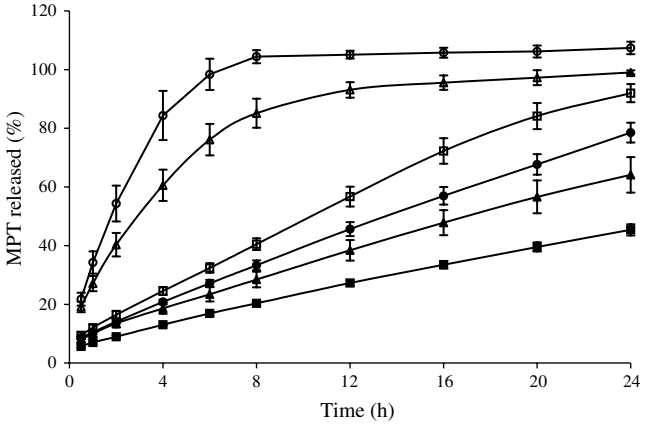

Fig. 5. Influence of XG concentration on the dissolution profiles (mean ± SD, $n = 6$) of mini-matrices containing 30% (w/w) MPT, XG, EC and DBS (EC/DBS 2/1, w/w). XG concentration (w/w): (■) 0%, (▲) 1%, (●) 2.5%, (□) 5%, (△) 10% and (○) 20%.

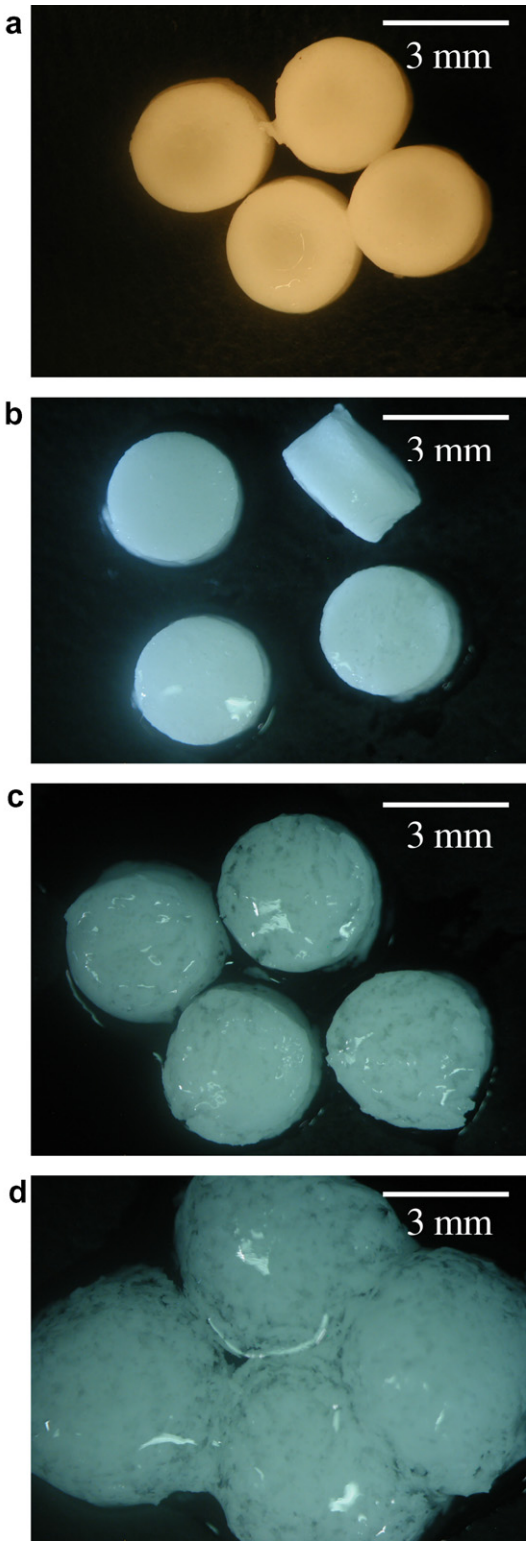

Fig. 6. Mini-matrices containing 30% (w/w) MPT, XG, EC and DBS (EC/DBS 2/1, w/w) after 4 h immersion in the dissolution medium. XG concentration (w/w): (a) 0%, (b) 5%, (c) 10% and (d) 20%.

added. In this study XG was incorporated in the formulation to increase the drug release rate by increasing the hydrophilicity and porosity of the dosage form during dissolution [10].

The different formulations were easily processed, independent of XG concentration: the pressure and torque varied between 1 and 5 bar, and 30% and 35%, respectively. All formulations were produced at 60 °C except for the 20% (w/w) XG formulation when a barrel temperature of 65 °C was required to produce smooth extrudates. Increasing XG concentrations yielded a faster drug release and a zero-order drug release was only obtained at ⩽5% (w/w) XG (Fig. 5). The 5% XG formulation was selected as reference, since incomplete drug release and burst effect were seen at lower and higher XG concentrations, respectively. Similar to EC/XG matrices containing ibuprofen [10], swelling of the mini-matrices containing 10 and 20% (w/w) XG was responsible for their faster MPT release (Fig. 6).

3.3. Reproducibility and equilibration of the production process

The extrusion process did not vary between the production of three batches on consecutive days: the pressure and torque varied between 3 and 5 bar, and 30% and 32%, respectively. The production of the 5% (w/w) XG extrudates was reproducible since the drug release profiles coincided, revealing the robustness of the production method.

After an equilibration time of 5 min extrudates of constant quality were obtained since no influence on the extrudate quality and release characteristics was seen for different extrusion times.

3.4. Influence of the extrusion process parameters

Modifications of the screw configuration allow to alter the production method as the different screw elements (feed, metering, mixing, transition, discharge) can be optimized to suit a particular application [3,20]. Literature reports described a significant influence of the screw design on the efficiency of a hot-melt extrusion process [4] and the physicochemical properties (crystallinity and dissolution properties) of extruded material [21,22].

In our study, the pressure and torque were neither influenced by the number nor the position of the mixing zones: 3, 7 and 3 bar, and 30%, 36% and 33% when using both mixing zones, only the first mixing zone and only the second mixing zone, respectively.

Independent of the screw design, smooth extrudates were obtained, yielding mini-matrices of good quality. In case of extrusion (at 60 °C) without kneading paddles (pressure: 2 bar, torque: 14%) the extrudates had a rough surface with powder spots (which Raman identified as MPT) confirming that kneading paddle elements are required for intensive mixing which was also reported by others [21,22].

The distribution of MPT in the mini-matrices was monitored via Raman using the 627–653 cm^{-1} spectral band as no overlap with other ingredients occurred at these wavenumbers (Fig. 7). Based on the intensity of the Raman signal across the scanned section of the mini-matrices it was confirmed that MPT is homogeneously distributed in the mini-matrix. Similar results were obtained for all mapped areas from all analyzed mini-matrices, irrespective of the production process, as long as kneading paddles were present in the screw.

To evaluate the effect of production rate on the extrusion process and extrudate quality, the powder feed rate and screw speed were adjusted simultaneously to ensure a constant fill level of the extrusion chamber. Smooth extrudates were obtained at all processing conditions. A pressure of 3, 2 and 2 bar, and a torque of 30%, 46% and 42% were recorded at a powder feed rate and screw speed of 6 g/min and 30 rpm, 25 g/min and 100 rpm, 50 g/min and 200 rpm, respectively. Using a high powder feed rate (25 and 50 g/min) in combination with a high screw speed (100 and 200 rpm), a lower barrel temperature was installed (50 °C) to compensate for the heat generated due to the friction [4,20]. The extrudate quality was independent of the powder feed rate and screw speed. The production rate did not alter the drug release characteristics of the mini-matrices, although other investigators reported a decreasing drug release with increasing powder feed rate and screw speed [23]. Nakamichi and coworkers reported that the extrudate quality and properties were not influenced by the screw revolution speed, in case kneading paddle elements were used [21].

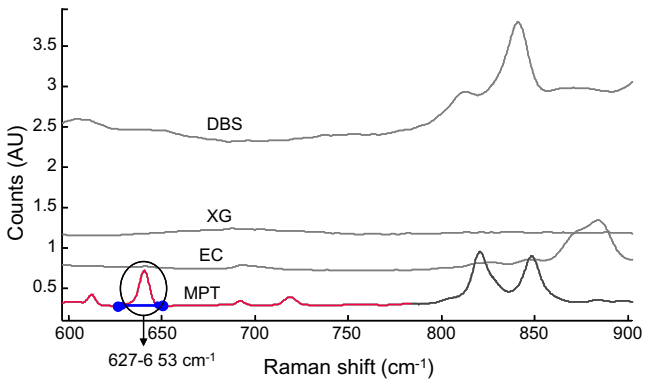

Fig. 7. Raman spectra from the compounds in the mini-matrices.

4. Conclusions

This paper showed that hot-melt extrusion can be used to produce ethylcellulose/xanthan gum mini-matrices with controlled drug delivery. Dibutyl sebacate was found to be a suitable plasticizer to obtain smooth extrudates and mini-matrices. Using xanthan gum, zero-order release kinetics with almost complete drug release could be obtained. Modifications of process parameters (screw design, powder feed

rate and screw speed) had no influence on the extrusion process or on the extrudate quality, drug homogeneity and release characteristics, confirming the robustness of the process. However, a drawback of this robustness is the fact that it offers limited flexibility for optimization of drug release. Further experiments are ongoing in order to use polyethylene oxides as an alternative for xanthan gum.

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