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ORIGINAL ARTICLE

Development and evaluation of injection-molded sustained-release tablets containing ethylcellulose and polyethylene oxide

T. Quinten[1], T. De Beer[1], A. Almeida[1], J. Vlassenbroeck[2], L. Van Hoorebeke[2], J.P. Remon[1] and C. Vervaet[1]

[1]*Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium and* [2]*Department for Subatomic and Radiation Physics, Ghent University, Ghent, Belgium*

Abstract

Purpose: It was the aim of the present study to develop sustained-release matrix tablets by means of injection molding of ethylcellulose (EC) and polyethylene oxide (PEO) mixtures and to evaluate the influence of process temperature, matrix composition, and viscosity grade of EC and PEO on processability and drug release. *Methods*: Formulations consisting of metoprolol tartrate (MPT, concentration: 30%), EC plasticized by dibutyl sebacate, and PEO were extruded and consequently injection molded into tablets. The influence of process temperature (120°C and 140°C), matrix composition, viscosity grade of EC (4, 10, 20, 45, and 100 mPa·s) and PEO (7×10^6, 1×10^6, and 1×10^5 Mw) on processability and drug release was determined. *Results*: Formulations consisting of 70% EC and 30% MPT showed incomplete drug release, whereas drug release was too fast for formulations without EC. Higher PEO concentrations increased drug release. Formulations containing 30% metoprolol, EC, and different concentrations of PEO showed first-order release rates with limited burst release. Drug release from direct compressed tablets showed faster drug release rates compared to injection-molded formulations. There was no clear relationship between the molecular weight of EC and drug release. The melting endotherm (113.9°C) of MPT observed in the differential scanning calorimeter thermogram of the tablets indicated that a solid dispersion was formed which was confirmed by X-ray diffractogram. X-ray tomography demonstrated a difference in pore structure between tablets processed at 120°C and 140°C. *Conclusion*: It was concluded that injection molding can be applied successfully to develop sustained-release PEO/EC matrix tablets.

Key words: Ethylcellulose, injection molding, matrix tablet, melt extrusion, metoprolol tartrate, polyethylene oxide, solid dispersion, sustained release, viscosity grade

Introduction

Hot melt extrusion (HME) and injection molding (IM) are major plastic processing technologies for converting thermoplastic materials with the aid of heat and pressure. Extrusion is a process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions[1]. During IM, the molten polymer is extruded and subsequently injected into a cavity mold at high pressure. After a cooling step, whereby the material solidifies in the mold, it is opened to recover the article. As a consequence, no additional time-consuming step is required to process the extrudates into the final dosage form, because IM allows direct manufacture of matrix tablets. Recently, HME has been introduced as a pharmaceutical production technique to manufacture solid dosage forms such as matrix (mini)-tablets[2], pellets[3], implants[4], transdermal[5], and transmucosal[6] drug delivery systems. For pharmaceutical applications, HME offers many advantages over traditional processing techniques. Furthermore, HME can be applied to sustain drug release via the homogeneous embedding of drug particles in release-controlling polymers[7]. The development of sustained-release

Address for correspondence: Prof. Dr. Chris Vervaet, Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium. Tel: +32(0)9 264 8069. E-mail: chris.vervaet@UGent.be

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Table 1. Composition of the different formulations with injection molding temperatures.

Formulation	Drug load (%)	EC viscosity grade (mPa·s)	EC content (%)	PEO content (%)	PEO viscosity grade (mPa·s)	Injection molding temperature (°C)
Influence of PEO concentration and production temperature						
1	30	4	70	–	7×10^6	120–140
2	30	4	60	10	7×10^6	120–140
3	30	4	50	20	7×10^6	120–140
4	30	4	35	35	7×10^6	120–140
5	30	4	–	70	7×10^6	120–140
Influence of PEO viscosity grade						
4	30	4	35	35	7×10^6	120
6	30	4	35	35	1×10^6	120
7	30	4	35	35	1×10^5	120
Influence of EC viscosity grade						
4	30	4	35	35	7×10^6	120
8	30	10	35	35	7×10^6	120
9	30	20	35	35	7×10^6	120
10	30	45	35	35	7×10^6	120
11	30	100	35	35	7×10^6	120

formulations offers many benefits over conventional dosage forms: controlled administration of a therapeutic dose at the desired delivery rate, constant blood levels of the drug, reduction of side effects, minimization of dosing frequency, and enhancement of patient compliance[8]. Ethylcellulose (EC) is an inert, hydrophobic polymer with excellent thermoplastic properties that has been studied for its application as a matrix-forming material[9,10]. Polymer choice is a critical factor to obtain desired drug release profiles during formulation development. Previous work has demonstrated that the combination of EC and a hydrophilic component such as hydroxypropylmethylcellulose (HPMC) offered a flexible system to tailor drug release by changing the viscosity, substitution type, and concentration of HPMC[11]. In addition, IM was applied successfully to sustain drug release from matrix tablets composed of EC and low-substituted hydroxypropylcellulose (L-HPC)[12]. HPMC and L-HPC were both chosen as matrix fillers to overcome time-dependent drug release profiles characteristic for matrix drug delivery systems. These systems promoted drug release by opening the matrix structure from IM matrix tablets. Although these matrix systems offered a flexible system to tailor drug release, constant drug release rates were not obtained. The objectives of this study were to investigate the influence of polyethylene oxide (PEO) as release-modifying agent to tailor drug release from EC-based matrix tablets, whereby the influence of matrix composition, molecular weight of EC and PEO, and process temperature was assessed on processability and drug release. PEO is a hydrophilic polymer, which is an ideal candidate for HME because of its broad processing window and is commonly used to prepare sustained-release drug delivery systems[13]. The influence of processing technique was studied as IM tablets were compared with direct compressed tablets. Furthermore, the drug kinetics and release mechanism were determined and the tablets were physicochemically characterized. An overview of the different studied formulations is given in Table 1.

Material and methods

Materials

Metoprolol tartrate (MPT) (EQ Esteve, Barcelona, Spain) was selected as model drug. Different viscosity grades of EC (Ethocel Std. Premium FP, kindly donated by the Dow Chemical Company, Horgen, Switzerland) with an ethoxyl content of 48.0–49.5% (w/w) were used: EC Std. 4, EC Std. 7, EC Std. 10, EC Std. 20, EC Std. 45, and EC Std. 100 with a respective viscosity of 3–5.5, 6–8, 9–11, 18–22, 41–49, and 90–110 mPa·s [5% solution, in toluene:ethanol (ratio 80:20, measured at 25°C)]. PEO (Polyox WSR-N10 NF, WSR-N12K NF, and WSR-303 NF with molecular weights of 1×10^5, 1×10^6, and 7×10^6, respectively, kindly donated by the Dow Chemical Company) was added to the formulation. The hydrophobic plasticizer dibutyl sebacate (DBS) was purchased from Sigma (St. Louis, MO, USA).

Production of injection-molded and directly compressed tablets

DBS was added to EC and mixed with mortar and pestle. This mixture was stored overnight to allow the plasticizer to migrate into the polymer. PEO and MPT were added to the plasticized EC blend, followed by mixing for 15 minutes in a tumbling mixer (batch size 100 g) prior to melt processing. The physical mixtures were extruded at different processing temperatures (120°C and 140°C) using a co-rotating twin-screw mini-extruder (HAAKE MiniLab II Micro Compounder, Thermo Electron Corporation, Karlsruhe, Germany) at a screw speed of

90 rpm. This machine was equipped with a pneumatic feeder, two Archimedes screws, and a cylindrical die of 2 mm. The hot extrudates were collected in a heated reservoir and immediately molded into tablets using a lab-scale injection molder (HAAKE MiniJet System, Thermo Electron Corporation) operating at the same temperature as the extruder to guarantee a constant processing temperature. An injection pressure of 400 bar during 10 seconds in combination with an after pressure of 200 bar for 5 seconds was used to prepare the matrix tablets. The temperature of the mold was set at 20°C. After cooling, biconvex tablets (diameter: 10 mm; height: 5 mm) with a mass of 373.5 ± 0.84 mg were obtained. For the production of directly compressed tablets, 375 mg of the physical mixture prepared as described above was accurately weighted and compacted by means of an eccentric tablet press equipped with a flat-faced double punch of 10 mm (Korsch type EKO, Berlin, Germany). The tablet properties were determined at a compression pressure of 14.7 kN.

In vitro drug release

The dissolution testing was performed using Apparatus 2 (USP27) on a VanKel VK7010 dissolution tester combined with a VK 8000 automatic sampling station (VanKel Inc., Cary, NC, USA). Sink conditions were maintained. Tablets were weighed and placed in the dissolution medium, consisting of 900 mL demineralized water. The rotational speed of the paddles was set at 50 rpm, whereas the temperature of the medium was maintained at 37 ± 0.5°C. Samples of 5 mL were withdrawn at specific time points (0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours without media replacement) and spectrophotometrically assessed for MPT concentration at a wavelength of 222 nm by means of a double-beam spectrophotometer (UV-1650PC, Shinmadzu Benelux, Antwerpen, Belgium). The MPT content in the samples was determined by linear regression using a calibration curve between 0 and 0.1 g/L. Each formulation was tested in triplicate, each dissolution vessel containing one tablet.

To investigate the drug release kinetics, several mathematical models were applied describing the kinetic behavior of drug release from matrix tablets. The drug release kinetics were determined by finding the best fit between the experimental data (amount of drug released versus time) and several kinetic models: zero-order (Equation 1) and first-order (Equation 2) release models:

$$Q_t = Q_0 + k_0 t \tag{1}$$

with Q_t the amount of drug released at time t, Q_0 the initial amount of drug released at time 0 (usually $Q_0 = 0$), and k_0 the zero-order release constant:

$$Q_t = Q_\infty (1 - e^{-k_1 t}) \tag{2}$$

with Q_∞ the total amount of drug in the matrix and k_1 the first-order constant.

The drug release mechanism was studied descriptively using the semi-empirical Korsmeyer–Peppas model, also known as the power law[14]. As the release mechanism from swellable matrices is complex, this model is descriptively used when the exact mechanism is unknown or when more than one release mechanisms are involved in drug release:

$$\frac{Q_t}{Q_\infty} = kt^n \tag{3}$$

with Q_t/Q_∞ the fraction of drug released at time t, k a constant depending on the structural and geometric characteristics of the tablet, and n the release exponent.

In this study, the values of n for cylindrical systems as determined by Ritger–Peppas were used as an approximation, with $n = 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (anomalous transport), and $n = 0.89$ (case II transport)[14]. When determining the n exponent, only the portion of the release curve where $Q_t/Q_\infty \leq 0.6$ was used.

Liquid uptake, swelling, and erosion

Tablets (n = 3) were introduced into the dissolution medium and subjected to a dissolution test under the same conditions as described above. At predetermined time intervals, the tablets were withdrawn from the medium and weighed after excessive water was removed from the surface. The liquid uptake, expressed as percentage weight gain of the total polymer content, was calculated from the original weight, taking the amount of drug released at that particular time into account.

$$\%\,\text{liquid uptake} = \frac{(W_w - DR_t) - (W_i - DR_0)}{(W_i - DR_0)} \times 100 \tag{4}$$

with W_w the weight of the matrix tablet at time t, W_i the initial weight of the tablet before immersion (time 0), DR_0 the amount of drug in the tablet at time 0, and DR_t the amount of drug in the tablet at time t.

The radial and axial swelling of the matrices during dissolution was determined by measuring the individual diameter and height of the tablets using an electric digital caliper (Bodson, Luik, Belgium). In addition, the degree of erosion (expressed as percentage loss of polymer content) was determined based on the weight difference between dried matrices and the initial weight of the tablet, taking the amount of drug released at each time point into account.

$$\%\,\text{erosion} = \frac{(W_i - DR_0) - (W_d - DR_t)}{(W_i - DR_0)} \times 100, \tag{5}$$

with W_d the dry weight of the matrix tablet at time t, W_i the initial weight of the tablet before immersion (time 0), DR_0 the amount of drug in the tablet at time 0, and DR_t the amount of drug in the tablet at time t.

Images of tablets prior to and after dissolution were made with a digital camera (C3030 Olympus) attached to an image analysis system (analySIS®, Soft Imaging system, Münster, Germany).

Differential scanning calorimetry

The thermal behavior of the different individual components, physical mixtures, and tablets was evaluated using a differential scanning calorimeter (2920 standard DSC, TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. The flow rate of dry nitrogen gas was 150 mL/min. Samples (5–10 mg) were run in hermetically sealed aluminum pans supplied by TA Instruments. Temperature and enthalpic calibration was done using indium as a standard. Samples were cooled to −40°C, held isothermal for 5 minutes, and heated to 200°C at a linear heating rate of 10°C/min. To study the thermal history as well as the glass transition temperature, samples were subjected to a second heating cycle to 200°C, following cooling to −40°C and a 5 minutes isothermal phase. The result was analyzed using the TA Instruments Universal Software.

X-ray diffraction

To analyze crystallinity, X-ray diffraction (D-500, Siemens, Germany) with CuK_λ radiation (0.154 nm) was performed on the different individual components (EC with 20% w/p DBS, PEO, and MPT) as well as on physical mixture and tablets (processed at 120°C and 140°C) containing EC and PEO in a 35:35 (w/w) ratio. The angular range (2θ) varied from 10° to 60° with steps of 0.02° and the measuring time was 1 second/step.

Tablet characteristics

The tablet hardness was measured using the Pharma Test PTB 311 tablet tester (Hainberg, Germany). At least three tablets were evaluated per formulation. The tablet porosity was calculated based on the difference between the bulk and skeletal volume of the tablets. The skeletal volume of the tablets was measured by means of a He pycnometer (AccuPyc 1330, Micromeretics, Norcross, GA, USA) and the bulk volume was determined from the dimensions of the mold because extra material was added during the after-filling stage to prevent shrinkage of the tablet during cooling. The tablet porosity (ε) was calculated using the following Equation (6):

$$\varepsilon = \frac{\text{bulk volume} - \text{skeletal volume}}{\text{bulk volume}} \times 100. \qquad (6)$$

Scanning electron microscopy was used to visualize the morphology of the tablet surface. 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).

X-ray tomography

The internal three-dimensional structure of the tablets was studied by using the nano-CT scanner of the UGCT facility (www.ugct.ugent.be). This scanner uses a transmission X-ray tube (Feinfocus) with a focal spot size of 900 nm and a Radeye1 detector as X-ray detector (Rad-icon Imaging Corporation, Santa Clara, CA, USA). The tube was operated at 60 kV tube voltage in microfocus mode at 2.8 W, which results in a 3 μm spot size. During the scans, the sample was rotated over 360° in 0.45° steps where four shadow images were recorded in every step. The reconstruction software Octopus (www.xraylab. com) was used for the conversion of the raw images into the reconstructed cross-sectional images. To process the images, two selections were made: one with the tablet material and another one with the pores. This was achieved by segmentation based on the gray-scale, and some subsequent filtering to remove the noise (these results should be skeptically analyzed as limiting factors such as noise and resolution make the obtaining of these results slightly operator dependent). The voids were subsequently separated and classified for equivalent diameters. Separating the pores makes it possible to have a better analysis of the porosity but it removes the pore interconnectivity; however, the pores are mostly connected through ducts with a diameter of about 1 μm and to analyze this, the resolution of the scan is not sufficient. The set of 600 cross-sections that were statistically analyzed was subsequently loaded in a 3D rendering software (VGstudio). In this way, it is made possible to represent the porosity and the size distribution of the pores via the formation of 3D images.

Raman spectroscopic conditions

The distribution of MPT was evaluated by Raman spectroscopic imaging. A 1900 × 1400 μm area of the surface from an injection-molded tablet was scanned by a 10× long working distance objective lens (spot size laser = 50 μm) in point-by-point mapping mode with a step size of 100 μm in both the x and y directions (=266 points per mapping). The resulting image provides information about the distribution of MPT on the tablet surface.

The image system was a RamanRxn 1 Microprobe (Kaiser Optical Systems, Ann Arbor, MI, USA), equipped with an air-cooled CCD detector (back-illuminated deep depletion design). The laser wavelength during the experiments was 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 30 seconds per collected spectrum. Before data analysis, spectra were baseline corrected. Data collection and data analysis were done using the

HoloGRAMS™ (Kaiser Optical Systems, Ann Arbor, MI, USA) data collection software package, the HoloMAP™ (Kaiser Optical Systems, Ann Arbor, MI, USA) data analysis software package, and the Matlab® software package (version 6.5) (The Mathworks Inc., Natick, MA, USA).

Chemical and physical stability of injection-molded tablets

The drug content ($n = 3$) of the injection-molded tablets following production at 120°C and 140°C was determined by crushing the tablets. An accurately weighed amount of the mixture was transferred to a volumetric flask containing 100 mL ethanol to completely dissolve the polymeric material. This mixture was placed for at least 12 hours on a magnetic stirrer until the material was completely dissolved. After dissolution and filtration, the samples were spectrophotometrically analyzed to determine the drug content. A thermogravimetric analyzer (Hi-res TGA 2950, TA Instruments) was employed to investigate the thermal stability of PEO. Samples (±15 mg) were equilibrated at 50°C and heated to 500°C at a heating rate of 10°C/min while the percentage weight loss was recorded.

Statistical analysis

The influence of matrix composition, process temperature, and molecular weight of EC on tensile strength and tablet porosity was statistically evaluated with a one-way ANOVA at a significance level of 0.05. The normality of the data was checked by means of a Kolmogorov–Smirnov test and the homogeneity of variances by a Levene test. A multi-comparison among pairs of means was performed using a Scheffé test with $P < 0.05$ as significance level. All analyses were performed with SPSS 15.0 for Windows (SPSS, Chicago, IL, USA).

Results and discussion

Processability via extrusion and injection molding

EC is an inert, hydrophobic ethylether of cellulose used for numerous pharmaceutical applications. Moreover, EC has excellent thermoplastic properties which make it extremely feasible for HME and IM. However, these processes involve the comprehensive generation of shear and heat, whereby polymers are subjected to mechanical, thermal, and oxidative degradation. In previous work, the stability of EC was investigated whereby EC was proven to be stable under the extrusion conditions used in this study[11]. The inherent thermoplasticity of PEO makes it an ideal choice as hydrophilic filler in HME. The chemical stability of PEO depended on the processing temperature, screw speed, and molecular weight of the polymer whereby the onset of degradation was reported at approximately 200°C[15]. TGA measurements of Polyox WSR N10 (Mw: 1×10^5), N12K (Mw: 1×10^6), and WSR 303 (Mw: 1×10^7) showed an onset decomposition temperature around 182°C, 194°C, and 198°C, respectively. Therefore, degradation of PEO and EC can be regarded as negligible under these processing parameters. Metoprolol was stable as less than 1% of the drug was degraded for tablets processed at 140°C. It was possible to easily extrude and process mixtures composed of different concentrations of EC plasticized by 20% (w/p) DBS and PEO in a temperature range between 120°C and 140°C. The melt viscosity was either too high below 120°C or too low above 140°C to allow proper tablet manufacture via HME and IM. All formed extrudates and tablets were opaque, white colored, and had a smooth surface.

Dissolution properties of injection-molded matrix tablets

Influence of matrix composition and process temperature

One of the major problems associated with hydrophobic matrix tablets is in the reduction in terminal release rate because of the quick release of drug at the surface, followed by a progressive decrease of the drug release rate as the diffusion path length increases over time. It was the aim of this study to evaluate the potential of PEO as drug-release-modifying agent when added to EC-based formulations. The dissolution profiles of different formulations composed of various amounts of EC and PEO and described in this section are presented in Figure 1. The drug release from EC matrices containing 30% (w/w) metoprolol was too slow (formulation 1), less that 50% of the drug was released after 24 hours of dissolution. This could be attributed to the integrity of the tablet as it remained intact during dissolution and to the hydrophobic and non-swellable nature of EC. Addition of PEO increased the hydrophilicity of the tablet, and because of its swelling properties, forming a hydrogel after being wetted by water, it was able to open the lipophilic EC matrix structure and promote drug release. Consequently, this hydrogel layer regulates further penetration of the dissolution medium into the matrix and diffusion of the

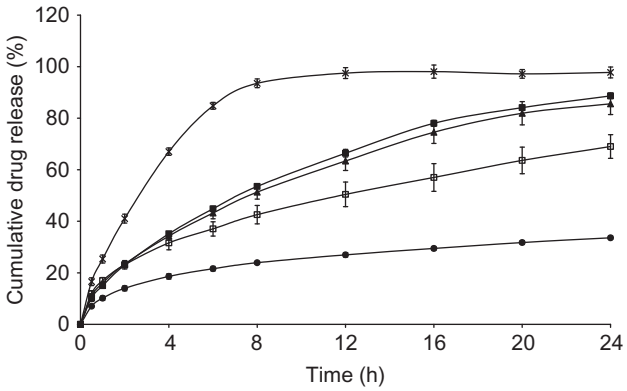

Figure 1. Influence of concentration PEO (Mw: 7×10^6) on drug release from injection-molded matrices. Mean dissolution profiles (±SD) of matrices (produced at 120°C) containing 30% MPT and variable PEO and EC4 concentrations. PEO concentration: (●) 0%, (□) 10%, (▲) 20%, (■) 35%, (×) 70%.

Table 2. Data from regression fitting between dissolution profiles (obtained from different matrix tablets processed at different temperatures) and several kinetic models (zero-order and first-order) and the Ritger–Peppas model (release mechanism).

Formulation	Process temperature (°C)	Zero-order model (R^2)	First-order model (R^2)	Ritger–Peppas (R^2)	Ritger–Peppas n
1	120	0.9197	0.9564	0.9958	0.4478
2	120	0.8919	0.9756	0.9988	0.4534
3	120	0.9493	0.9970	0.9998	0.5548
4	120	0.9913	0.9987	0.9998	0.6014
5	120	0.9490	0.8429	0.9992	0.6671
1	140	0.9070	0.9200	0.9906	0.3391
2	140	0.8306	0.9184	0.9978	0.3777
3	140	0.9084	0.9900	0.9990	0.4478
4	140	0.9894	0.9755	0.9997	0.6322
5	140	0.9405	0.9648	0.9990	0.6424
6	120	0.9564	0.9977	0.9993	0.6005
7	120	0.9396	0.9980	0.9980	0.5807
8	120	0.9189	0.9987	0.9998	0.6151
9	120	0.9070	0.9960	0.9991	0.6056
10	120	0.9084	0.9928	0.9992	0.5740
11	120	0.8812	0.9771	0.9992	0.5723
4	DC	0.7861	0.9431	0.9950	0.3442
8	DC	0.8343	0.9184	0.9964	0.4876
9	DC	0.7019	0.8766	0.9973	0.6705
10	DC	0.7592	0.9223	0.9995	0.6633
11	DC	0.7439	0.9190	0.9982	0.6658

The fitting of the different models and the dissolution profiles is expressed via the correlation coefficient R^2. The release mechanism is identified via n values: $n = 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (anomalous transport), and $n = 0.89$ (case II transport). DC, directly compressed tablets.

drug molecules from the dosage form. Introducing 10% PEO (formulation 2) in the formulation resulted in a considerable increase of drug release whereby 70% of the drug was released after 24 hours. Regarding the release kinetics, the best fit was obtained with the first-order model indicating time-dependent drug release (Table 2). The Ritger–Peppas model was used in a descriptive way to study the drug release mechanism: drug release occurred via drug diffusion as the release exponent n was about 0.45. The MPT release did not differ when 20% and 35% PEO (w/w) (formulations 3 and 4) was added to the formulation: similar release profiles were obtained whereby ± 90% of the drug was released after 24 hours dissolution and best fitted with the first-order model. When the release mechanism was studied, the release exponent n denoted anomalous transport which is a combination of diffusion and swelling/erosion controlled drug release. As PEO has excellent thermoplastic properties, it was possible to produce tablets composed of purely PEO (formulation 5). However, drug release was too fast as most of the drug was released after 8 hours of dissolution. For this formulation, the release kinetics was best described by the zero-order model, anomalous transport being the main release mechanism for these matrix tablets ($n = 0.67$). Faster drug release rates were also observed when higher concentrations of PEO with Mw of 1×10^5 and 1×10^6 were included in the formulation (results not shown). When the influence of process temperature on drug release was investigated, a considerable decrease in drug release was observed for tablets processed at 140°C when low PEO concentrations were included in the formulation (10% and 20%, w/w, PEO for all PEO viscosity grades); no difference in drug release in function of process temperature was observed for tablets containing 35% and 70% PEO (results not shown). It has been reported that increasing the process temperature during melt extrusion resulted in a lower free-volume, a small pore radius, and a more tortuous pore network of the extrudates, thus reducing the drug release rates[9,16]. It can be assumed that higher PEO concentrations were more effective in opening the matrix structure thereby promoting drug release and impairing the influence of production temperature. Varying the amount of PEO in the formulation resulted in similar tensile strengths ($n = 5$; $P < 0.05$): for formulations containing 0%, 10%, 20%, and 35% (w/w) PEO and processed at 120°C, 1.67 ± 0.17, 1.68 ± 0.20, 1.46 ± 0.12, and 1.22 ± 0.10 MPa, respectively. In contrast, formulations containing 70% PEO yielded significantly harder tablets: 2.60 ± 0.24 MPa ($n = 5$; $P < 0.05$) (graph not shown). Manufacturing tablet at 140°C resulted in slightly harder tablets. All formulations had a low porosity (<5%) independent of the composition of the matrix formulation. This low porosity is because of the extensive densification of the molten material during extrusion and IM. Polymer swelling, drug dissolution, and matrix erosion

are the phenomena that determine drug release from swellable matrices[17]. Therefore, these phenomena were studied in detail: increasing the PEO amount in the formulation resulted in a higher water uptake and radial swelling but a similar erosion level: formulations composed of 20/50/30% (w/w) PEO/EC/MPT had a water uptake, radial swelling, and erosion of 450%, 183%, and 26%, respectively, after 24 hours dissolution compared to 770%, 209%, and 22% for matrices containing 35% (w/w) PEO (graph not shown). These results state that the drug was not only released via drug diffusion but that polymer swelling and erosion also contributed to the overall drug release mechanism, and confirm anomalous transport to be the main drug release mechanism as determined with the Ritger–Peppas model. From these results, it was concluded that incorporating PEO in the formulation was effective to promote and regulate drug release by making the matrix structure more accessible to the dissolution medium.

Influence of PEO molecular weight

PEO resins are nonionic, water-soluble polymers available in different viscosity grades, whereby the molecular weight considerably influences the swelling properties and hence drug release[18]. The influence of the molecular weight of PEO on drug release was investigated and presented in Figure 2. Complete drug release after 12 hours (following zero-order kinetics for the initial 6 hours of dissolution) was observed for formulations composed of 35% (w/w) PEO 1×10^5 (formulation 7) (Table 2). In contrast, drug release was slower for formulations based on PEO 1×10^6 and 7×10^6, releasing ±90% of the drug after 24 hours (formulations 6 and 4). These formulations containing PEO 1×10^6 and 7×10^6 were best described via the first-order model with anomalous transport as the drug release mechanism. Upon hydration, the PEO polymers start to swell forming a gel layer and creating pores in the lipophilic EC matrix. In this gel layer, polymer chains start to unfold and become solvated until the point where the polymer chains at the outside disentangle and dissolve as single molecules or aggregates. This gel formation and polymer dissolution was reported to be highly dependent on PEO molecular weight: a higher molecular weight resulted in a stronger gel formation because of a higher polymer entanglement resulting in a gel network that is more resistant to erosion/polymer dissolution[19,20]. Therefore, the water uptake, tablet swelling, and polymer erosion of tablets containing different PEO viscosity grades were determined to investigate their impact on drug dissolution (Figure 3). Tablets containing PEO 7×10^6 showed the highest water uptake

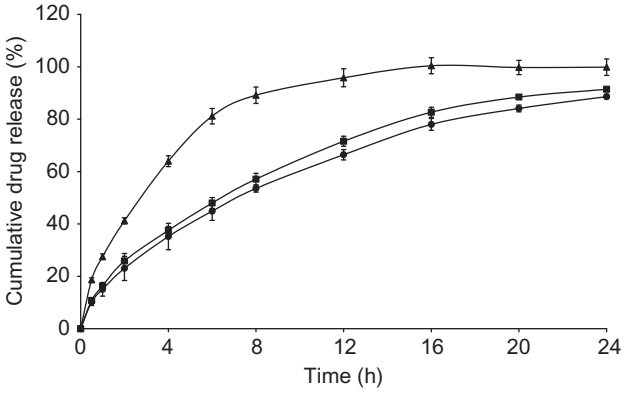

Figure 2. Influence of PEO viscosity grade on drug release from injection-molded matrices. Mean dissolution profiles (±SD) of matrices containing MPT, EC, and PEO (ratio 30:35:35) processed at 120°C. PEO molecular weight: (●) 7×10^6, (■) 1×10^6, (▲) 1×10^5.

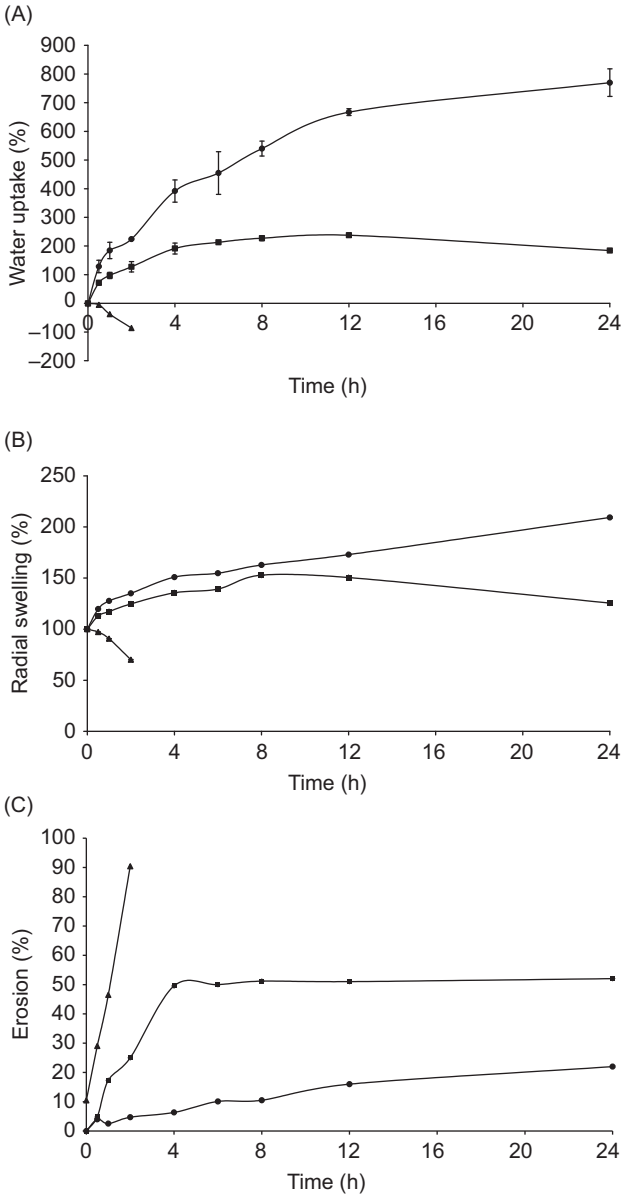

Figure 3. Influence of PEO viscosity grade on (A) water uptake, (B) radial swelling, and (C) erosion (means ± SD, $n = 3$) of matrices composed of 35/35/30% (w/w) EC/PEO/MPT, processed at 120°C. PEO molecular weight: (●) 7×10^6, (■) 1×10^6, (▲) 1×10^5.

and tablet swelling but the lowest erosion level: 770%, 209%, and 22% after 24 hours dissolution, respectively. When PEO 1×10^6 was incorporated in the formulation, only during the first 8 hours of dissolution an increase in water uptake (227%) and radial swelling (153%) was observed and tablet erosion (up to 50%) occurred during the initial 4 hours. In contrast, tablets containing PEO 1×10^5 already lost their integrity after 1 hour of dissolution with EC agglomerates being captured in a viscous PEO gel network that completely dissolved after 4 hours of dissolution. For the higher-molecular-weight PEO, a stronger hydrogel was formed because of more polymer entanglements, which was therefore less susceptible to erosion, restricted water penetration, and probably reduced drug diffusion resulting in slower drug release rates. In contrast, drug release from PEO 1×10^5 based matrices was more related to polymer dissolution or erosion. Similar results were observed for formulations containing 20% (w/w) PEO (results not shown). The tablet hardness and porosity of matrix tablets containing 20% or 35% PEO 1×10^5, PEO 1×10^6, and 7×10^6 were similar and hence did not account for changes in drug release ($n = 5$, $P < 0.05$).

Influence of molecular weight of EC and processing technique

The dissolution profiles of injection-molded tablets containing different EC viscosity grades are shown in Figure 4A. In contrast to previous reported results based on matrices composed of EC and L-HPC, the release profiles of tablets containing 35% PEO 7×10^6 and 35% EC of different molecular weights were similar[12]. All formulations released more than 80% of the drug and a good fit was obtained by the first-order model, burst release was limited and the drug release mechanism was via anomalous transport (Table 2). An influence of the EC molecular weight on the IM process was observed, as the melt viscosity of higher EC viscosity grades was higher because of higher interchain entanglements in the case of longer polymer chains restricting the polymer flow during processing. Matrices (containing EC4 and PEO 7×10^6, ratio 35:35, formulation 4) prepared via direct compression had a faster drug release rate compared to the other different EC molecular weight grades (Figure 4B). All directly compressed matrix tablets demonstrated a considerable burst release and faster drug release rates compared to injection-molded tablets following first-order drug release (formulation 8–11). Because the polymeric carrier is molten and pressurized inside the extruder, the injection-molded tablet is anticipated to possess a lower porosity and higher tortuosity forming a denser network than tablets prepared by direct compression methods consequently resulting in slower drug release[9]. This was confirmed by tablet hardness and porosity measurements: for all EC viscosity grades, the tensile strength of compressed tablets was significantly lower and the porosity significantly higher

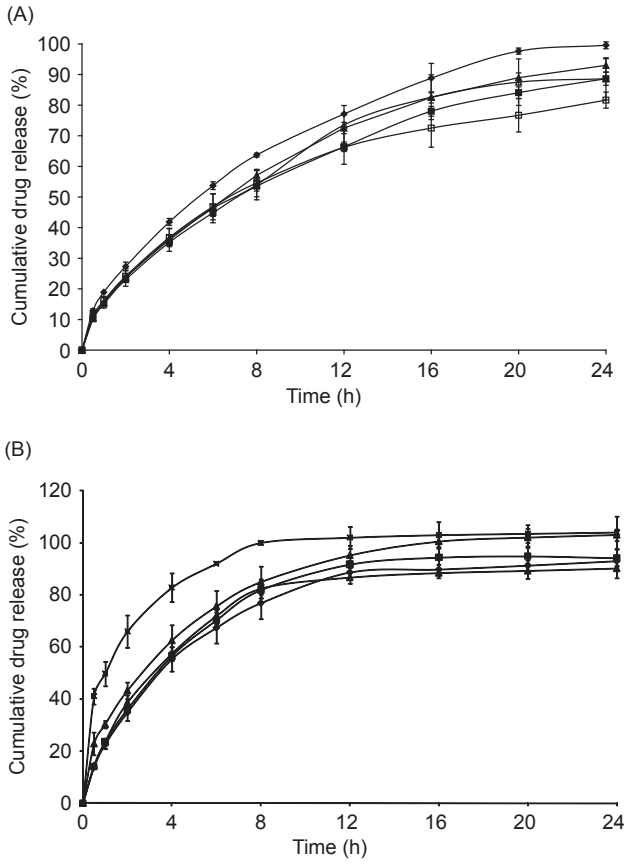

Figure 4. (A) Influence of EC viscosity grade on drug release from injection-molded matrix tablets. Mean dissolution profiles (±SD) of formulations composed of MPT, EC, and PEO 7×10^6 (ratio 30:35:35), processed at 120°C. EC viscosity grade (mPa·s): (■) EC4; (▲) EC10; (△) EC20; (◆) EC45; and (□) EC100. (B) Influence of EC viscosity grade on drug release from matrix tablets made by direct compression. Mean dissolution profiles (±SD) of formulations composed of MPT, EC, and PEO 7×10^6 (ratio 30:35:35). EC viscosity grade (mPa·s): (■) EC4; (▲) EC10; (△) EC20; (◆) EC45; and (□) EC100.

compared to injection-molded tablets, possibly accounting for faster drug release rates ($n = 5$, $P < 0.05$) (Figure 5). Moreover, injection-molded tablets composed of EC4 showed a significant lower tensile strength and porosity compared to the other EC molecular weights. In contrast, lower EC viscosity grades were better compressible than higher viscosity grades, allowing production of stronger tablets. This allowed for injection-molded tablets to retain their structural integrity much longer compared to direct compressed tablets during dissolution, resulting in slower release rates.

Physicochemical characterization of injection-molded tablets

The DSC thermogram of MPT showed a melting endotherm at 125.8°C, indicating its crystalline nature (Figure 6). EC plasticized by 20% (w/p) DBS had a glass transition temperature at 51.7°C. PEO is a semi-crystalline polymer having a T_g around −67°C and a

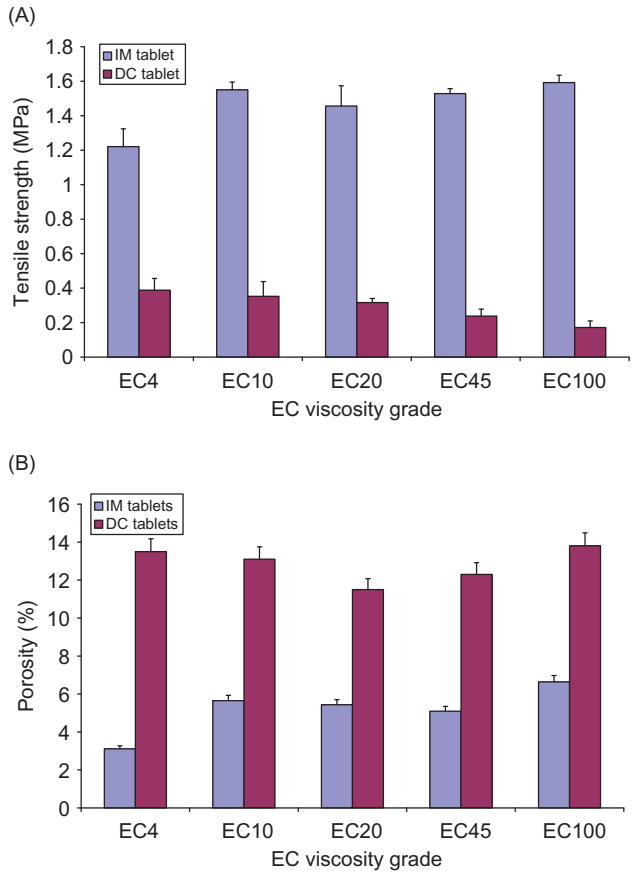

Figure 5. Influence of EC viscosity grade and tablet processing technique on (A) tensile strength and (B) porosity. Formulations composed of 35% EC, 35% PEO 7×10^6, and 30% MPT, processed at 120°C for IM tablets.

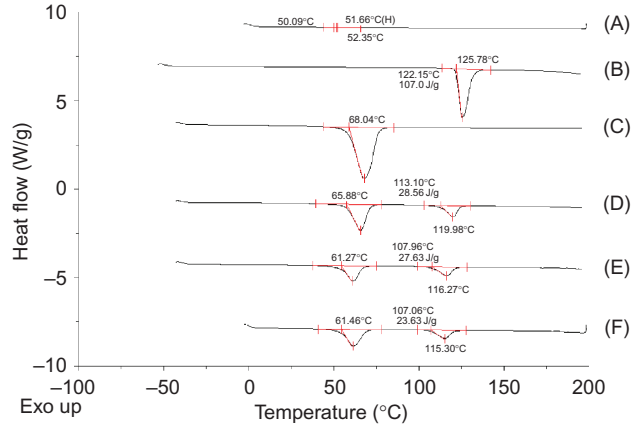

Figure 6. Differential scanning calorimetry profiles of ethylcellulose with 20% DBS w/p (A), metoprolol tartrate (B), polyethylene oxide 7×10^6 (C), physical mixture of 35/35/30% EC/PEO/MPT (D), injection-molded tablet composed of 35/35/30% EC/PEO/MPT processed at 120°C (E), and 140°C (F).

melting temperature around 68–72°C[21]. This melting point depended on the PEO molecular weight: for PEO 1×10^5, 1×10^6, and 7×10^6, a melting endotherm was observed at 68.0°C, 71.9°C, and 72.0°C, respectively. For the physical mixture as well as tablets produced at 120°C and 140°C, the melting points of PEO and MPT were broadened and lowered suggesting partial miscibility of drug and excipients. In addition, the melting enthalpy (ΔH) of MPT in IM tablets decreased at higher processing temperatures because of a higher degree of solubilization of MPT in molten EC/PEO, which acted as a solvent during processing causing partial loss of crystallinity: 27.6 and 23.6 J/g for tablets produced at 120°C and 140°C, respectively, compared to 28.6 J/g for the physical mixture[22]. The presence of melting peaks in the thermogram of IM tablets confirmed that metoprolol was slightly solubilized in molten EC/PEO melt during processing and suggested that a two-phase solid dispersion was formed upon cooling in which metoprolol was present in both amorphous and crystalline form. These results were confirmed by hot-stage microscopy. These results were confirmed by X-ray diffraction measurements: the X-ray diffractograms (Figure 7) identified no peaks for EC confirming its amorphous state. Metoprolol

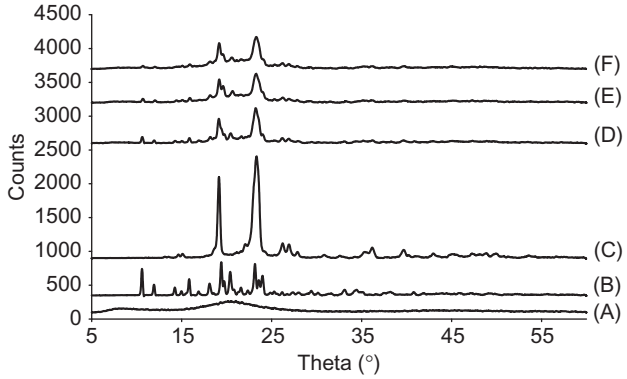

Figure 7. Wide-angle diffraction profiles of ethylcellulose with 20% DBS w/p (A), metoprolol tartrate (B), polyethylene oxide 7×10^6 (C), physical mixture of 35/35/30% EC/PEO/MPT (D), injection-molded tablet composed of 35/35/30% EC/PEO/MPT processed at 120°C (E), and 140°C (F).

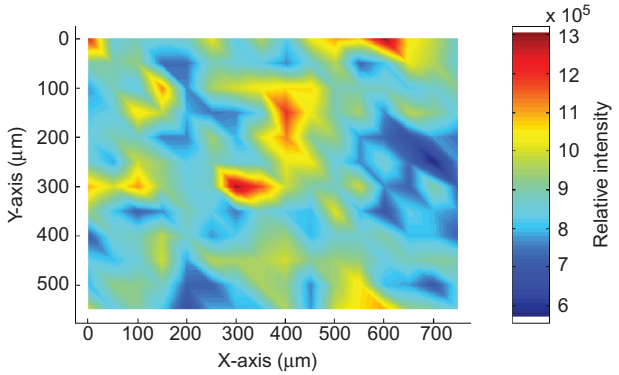

Figure 8. Distribution mapping of metoprolol tartrate in an injection-molded tablet composed of 35/35/30% EC/PEO (7×10^6)/MPT manufactured at 120°C. Blue corresponds to a low MPT concentration, red to a high MPT concentration.

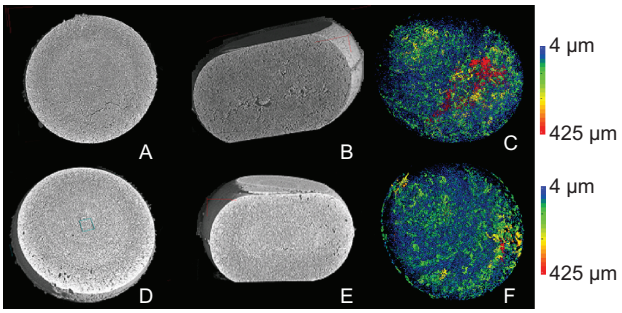

Figure 9. Reconstructed CT scans of an injection-molded tablet composed of 30/35/35% MPT/EC/PEO 7×10^6 processed at 120°C (A–C) and 140°C (D–F) with A and C being longitudinal trans-sections and B and D transversal cross-sections. C and F represent the equivalent diameter distribution of the pores.

had distinct crystalline peaks at 2θ of 10.64, 19.44, and 23.20 and a series of smaller peaks at 11.98, 15.86, 20.40, and 24.04. The semi-crystalline polymer PEO showed two characteristic peaks at 2θ of 19.17 and 23.37. The physical mixture as well as tablet formulations processed at 120°C and 140°C exhibited peaks corresponding to PEO and MPT; however, their intensity was reduced indicating loss of crystallinity of MPT and PEO. This was even more pronounced in the case of tablets manufactured at 140°C, confirming that a higher proportion of drug was dissolved in the EC/PEO melt during processing. Raman spectroscopy was applied to determine the drug distribution in the matrix tablet. The spectrum of MPT showed intense Raman bands at 622–653 and 785–871 cm^{-1} and these peaks were monitored to map the distribution of MPT in the matrix because there were no spectral interferences from the other excipients in this region. Figure 8 shows the distribution of MPT in the tablet by distributing the peak area of the selected Raman bands over the entire scanned area, red color corresponds to a high MPT concentration, whereas blue color signifies a lower MPT concentration at the spot. In this way, MPT was proven to be distributed in the entire matrix; however, some local drug concentrations in the tablet were detected. This could be caused by incomplete melting of MPT clusters or insufficient mixing with the excipients during tablet production. In addition, Raman spectroscopy confirmed the existence of crystalline MPT in the matrix.

X-ray tomography was performed to further elucidate the influence of process temperature on matrix characteristics (Figure 9). From these figures, it is clear that the tablets processed at 120°C and 140°C both possessed a very dense structure with pores distributed throughout the whole tablet. For tablets processed at 120°C, larger voids were observed in the middle of the tablet, possibly because of a poor coalescence of different melt fronts injected into the mold during processing. In contrast, in tablets manufactured at 140°C, larger pores opposite to the injection point were visible in the outer layers of the matrix tablet, but no voids in its internal structure, probably because of a better fusion of the molten material in the mold at higher manufacturing temperatures. This finding was confirmed by determining the equivalent

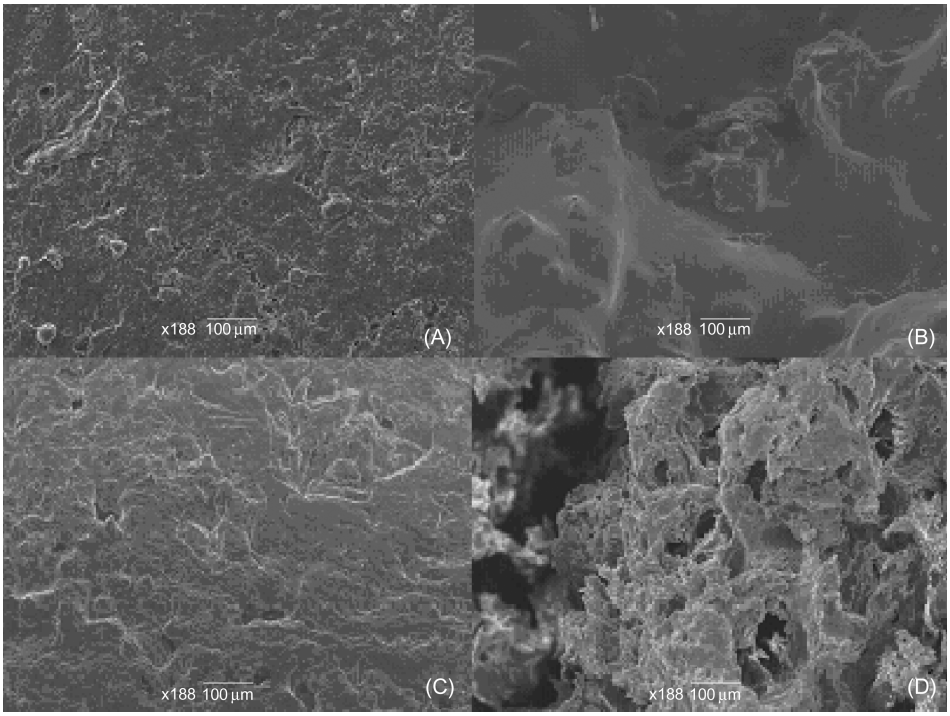

Figure 10. Surface morphology of injection-molded tablet composed of 30/35/35% MPT/EC/PEO 7×10^6 prior to and after dissolution testing (magnification 100×). Injection-molded tablet processed at 120°C before (A) and after 24 hours (B) dissolution testing. Injection-molded tablet processed at 140°C before (C) and after 24 hours (D) dissolution testing.

diameter of the pores: tablets processed at 120°C possessed slightly bigger pores compared to tablets processed at 140°C (Figure 9C and F). The surface morphology of these tablets prior to and after dissolution is presented in Figure 10. On the surface of tablets processed at 120°C as well as 140°C, small pores can be observed in an otherwise smooth surface, with more pores present in tablets produced at 120°C. After 24 hours of dissolution, tablets produced at 120°C demonstrated a smooth surface; however, the surface of tablets manufactured at 140°C showed numerous cracks and pores caused by both the swelling capacity of PEO and by the capillary diffusion of MPT.

Conclusion

IM of thermoplastic formulations based on EC and PEO seems to be a promising technique to prepare sustained-release matrix tablets. All components were stable during processing. Increasing the PEO concentration in the formulation resulted in faster drug release rates because of a higher level of water uptake, swelling, and erosion. Decreasing the PEO molecular weight resulted in faster drug release rates because these matrices eroded much faster compared to the other PEO viscosity grades, which demonstrated a higher level of water uptake and swelling. For all formulations, the drug release mechanism is based upon a combination of drug diffusion and swelling/erosion. The lowest EC molecular weight showed slightly faster release rates. Injection-molded matrix tablets were able to sustain drug release longer compared to direct compressed tablets because of an extensive densification of the matrix. DSC and XRD demonstrated the formation of a solid dispersion, whereby part of the drug was dissolved after processing. The drug was distributed over the entire surface; however, some small drug clusters were observed. X-ray tomography revealed a small change in pore localization and seize in function of processing temperature.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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