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Research paper

Evaluation of injection moulding as a pharmaceutical technology to produce matrix tablets

Thomas Quinten [a], Thomas De Beer [b], Chris Vervaet [a,*], Jean Paul Remon [a]

[a] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium
[b] Department of Pharmaceutical Analysis, Ghent University, Ghent, Belgium

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ABSTRACT

The aim of this study was to develop sustained-release matrix tablets by means of injection moulding and to evaluate the influence of process temperature, matrix composition (EC and HPMC concentration) and viscosity grade of ethylcellulose (EC) and hydroxypropylmethylcellulose (HPMC) on processability and drug release. The drug release data were analyzed to get insight in the release kinetics and mechanism. Formulations containing metoprolol tartrate (30%, model drug), EC with dibutyl sebacate (matrix former and plasticizer) and hydrophilic polymer HPMC were extruded and subsequently injection moulded into tablets (375 mg, 10 mm diameter, convex-shaped) at temperatures ranging from 110 to 140 °C. Tablets containing 30% metoprolol and 70% ethylcellulose (EC 4 mPa s) showed an incomplete drug release within 24 h (<50%). Increasing production temperatures resulted in a lower drug release rate. Substituting part of the EC fraction by HPMC (HPMC/EC-ratio: 20/50 and 35/35) resulted in faster and constant drug release rates. Formulations containing 50% HPMC had a complete and first-order drug release profile with drug release controlled via the combination of diffusion and swelling/erosion. Faster drug release rates were observed for higher viscosity grades of EC (Mw > 20 mPa s) and HPMC (4000 and 10,000 mPa s). Tablet porosity was low (<4%). Differential scanning calorimetry (DSC) and X-ray powder diffraction studies (X-RD) showed that solid dispersions were formed during processing. Using thermogravimetrical analysis (TGA) and gel-permeation chromatography no degradation of drug and matrix polymer was observed. The surface morphology was investigated with the aid of scanning electron microscopy (SEM) showing an influence of the process temperature. Raman spectroscopy demonstrated that the drug is distributed in the entire matrix, however, some drug clusters were identified.

1. Introduction

Hot-melt extrusion (HME) and injection moulding (IM) are widely applied in the plastic processing industry, but are relatively new techniques to the pharmaceutical industry. Injection moulding is a well-known versatile technique in preparing complex articles from thermoplastic materials with the aid of heat and pressure. It is a repetitive process in which molten polymer is injected into a closed and shape-specific mould cavity, basically duplicating the cavity of the mould. After solidification, the article is recovered by opening the mould to release the product. 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]. Extrusion can be combined with injection moulding to manufacture solid dosage forms in an efficient and semi-continuous way [2]. For pharmaceutical applications, these techniques can be applied to prepare solid dispersions or solutions in order to increase the bioavailability of poorly soluble drugs or to produce controlled-release preparations via the homogeneous embedding of drug particles in release-controlling polymers [3]. Several research groups have demonstrated that hot-melt extrusion is a viable, continuous technique to prepare different pharmaceutical dosage forms: granules [4], sustained-release mini-tablets [5], pellets [6], matrix tablets [7], matrix-in-cylinder systems [8], implants [9], films [10] and transdermal or transmucosal drug delivery systems [11]. Although injection moulding was already introduced by Speiser in 1964 as a pharmaceutical technology to produce sustained-release dosage forms [12], its use within the pharmaceutical industry has been limited to a few specific applications: the development of polyethylene [13] and polyethylene glycol matrices [14], the use of soy protein in a injection [2] and co-injection moulded [15] matrices. Eith et al. evaluated the development of an injection-moulded starch capsule [16]. Egalet, a novel drug delivery system prepared by IM consisted of an impermeable shell of cetostearyl alcohol and ethylcellulose enclosing a matrix plug

* Corresponding author. Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium. Tel.: +32 9 264 80 69; fax: +32 9 222 82 36.
E-mail address: Chris.Vervaet@UGent.be (C. Vervaet).

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composed of polyethylene glycol monostearate and polyethylene oxide, controlling the drug release by modulating the erosion of the matrix [17]. Finally, this technique has been used for the production of several implants, biodegradable and bio-inert bone-analogue composites and hard tissue replacements. The aim of this work was to further explore the potential of hot-melt extrusion in combination with injection moulding as an innovative pharmaceutical process technology to produce sustained-release matrix tablets. To achieve this objective, ethylcellulose (EC) was used as release-controlling polymer and hydroxypropylmethylcellulose (HPMC) was added to the formulation as a hydrophilic drug release modifier in order to tailor the drug release profiles. The influence of process temperature, EC and HPMC viscosity grade and HPMC concentration on processability, physicochemical characteristics and drug release kinetics of the matrix tablets was assessed.

2. Materials and methods

2.1. Materials

Metoprolol tartrate (MPT) (EQ Esteve, Barcelona, Spain) was selected as model drug. Different viscosity grades of ethylcellulose (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, 80:20% toluene:ethanol, measured at 25 °C). Hydroxypropylmethylcellulose of different viscosity grades (HPMC 50, 4000 and 10,000 mPa s) (Metolose 60-SH, substitution type 2910, Shin-Etsu Seppic, Paris, France) was added to the formulation. The hydrophobic plasticizer dibutyl sebacate (DBS) was purchased from Sigma (St. Louis, USA).

2.2. Composition of the matrices

The metoprolol tartrate content in all the formulations was 30% w/w. EC was plasticized by 20% w/p (weight/polymer) dibutyl sebacate. The influence of the viscosity grade of EC and HPMC, as well as of the matrix composition and processing temperature on processability and drug release was investigated (Table 1).

2.3. Production of injection-moulded tablets

Dibutyl sebacate was added to ethylcellulose and mixed with mortar and pestle. This mixture was stored overnight to allow the plasticizer to migrate into the polymer. HPMC and metoprolol tartrate were added in the proper amount to the plasticized ethylcellulose blend, followed by mixing for 15 min in a tumbling mixer (batch size 100 g) prior to melt processing. The physical mixtures were extruded at different processing temperatures (110, 120, 130 and 140 °C) using a co-rotating twin-screw mini-extruder at a screw speed of 90 rpm (HAAKE MiniLab II Micro Compounder, Thermo Electron Corporation, Karlsruhe, Germany). This machine was equipped with a pneumatic feeder, two Archimedic screws and a cylindrical die of 2 mm. The hot extrudates were collected and moulded into tablets using a lab-scale injection moulder operating at the same temperature as the extruder (HAAKE MiniJet System, Thermo Electron Corporation, Karlsruhe, Germany). An injection pressure of 400 bar during 10 s was used to mould tablets in combination with an after pressure of 200 bar for 5 s in order to prevent the shrinkage of the tablet during cooling. The temperature of the mould was set at 20 °C. After cooling, biconvex tablets (diameter: 10 mm/height: 5 mm) with a mass of ±375 mg were obtained.

2.4. Chemical and physical stability of injection-moulded tablets

The drug content ($n = 3$) of the injection-moulded tablets following production at 110 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 h on a magnetic stirrer until the material was completely dissolved. After dissolution and filtration, the samples were spectrophotometrically analyzed to determine the drug content.

The weight average (Mw) and number average (Mn) molecular weight of ethylcellulose before and after injection moulding was determined by gel-permeation chromatography using Waters equipment (Brussels, Belgium). Polymer solutions in chloroform (10 mg/mL) were injected into a PL gel 5 μm 10^3 Å column (Polymer Laboratories, Heerlen, The Netherlands) and analyzed by a MELZ LCD-212 refractive index detector. The flow was maintained at 1 mL/min. Polystyrene standards of known molecular weight were used as a reference material.

The melt flow index (MFI) was determined by means of a capillary Davenport Melt flow indexer MFI-10 (Lloyd Instruments, Fareham, United Kingdom) according to the ISO 1133 standard. A die with a diameter of 2.095 mm and a constant load of 2.16 kg was applied. After manual compression of the material to remove air, the powder mixture was preheated for 360 s and the measurements were performed at different temperatures.

Table 1
Composition of the formulations and injection moulding temperatures

Formulation	Drug load (%)	EC visc. grade (mPa s)	EC content (%)	HPMC content (%)	HPMC visc. grade (mPa s)	Injection moulding temperature (°C)
Influence of production temperature and EC viscosity grade						
1	30	4	70	–	–	110–120–130–140
2	30	7	70	–	–	110
3	30	10	70	–	–	110
4	30	20	70	–	–	110
5	30	45	70	–	–	110
6	30	100	70	–	–	110
Influence of HPMC concentration						
1	30	4	70	–	–	110
7	30	4	50	20	50	110
8	30	4	35	35	50	110
9	30	4	30	40	50	110
10	30	4	20	50	50	110
Influence of HPMC viscosity grade						
8	30	4	35	35	50	110–140
11	30	4	35	35	4000	110–140
12	30	4	35	35	10,000	110–140

A thermogravimetric analyser (Hi-res TGA 2950, TA instruments, Leatherhead, UK) was employed to investigate the thermal stability of EC, EC plasticized by 20% w/w DBS, HPMC 50 mPa s, metoprolol tartrate, the physical mixture and tablets processed at 110 and 140 °C. Samples (±15 mg) were equilibrated at 50 °C and then heated to 500 °C at a heating rate of 10 °C/min and the percentage weight loss was recorded.

2.5. 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 Industries, NJ, 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, while 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 h without media replacement) and spectrophotometrically assessed for metoprolol tartrate concentration at a wavelength of 222 nm by means of a double beam spectrophotometer (UV-1650PC, Shinmadzu Benelux, Antwerpen, Belgium). The metoprolol tartrate 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.

In order to investigate the drug release kinetics, several mathematical models were applied describing the kinetic behaviour of drug release from matrix tablets. The drug release kinetics were determined by finding the best fit between the experimental data (amount drug released vs. time) and several kinetic models: zero-order (Eq. (1)), Higuchi (Eq. (2)) and first-order (Eq. (3)) release model.

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

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

$$Q_t = k_h \sqrt{t} \tag{2}$$

with k_h representing the Higuchi rate constant.

$$Q_t = Q_\infty \left(1 - e^{-klt}\right) \tag{3}$$

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

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

$$Q_t/Q_\infty = kt^n \tag{4}$$

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 were used (Table 2) as an approximation, with $n = 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (anomalous transport) and $n = 0.89$ (case-II transport). When determining the n exponent, only the portions of the release curve where $Q_t/Q_\infty \leqslant 0.6$ was used.

2.6. 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 gained of the polymer content, was calculated from the original weight, taken the amount of drug released at that particular time into account.

$$\%\ \text{liquid uptake} = \left(\frac{(W_w - DR_t) - (W_i - DR_0)}{(W_i - DR_0)}\right) \times 100 \tag{5}$$

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 the height of the tablets using an electric digital caliper (Bodson, Luik, Belgium). In addition, the degree of erosion (expressed as percent-

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

Formulation	Process temp. (°C)	Zero-order model (R^2)	Higuchi equation (R^2)	First-order model (R^2)	Ritger–Peppas	
					(R^2)	n
1	110	0.920	0.993	0.956	0.996	0.448
1	120	0.883	0.978	0.911	0.996	0.450
1	130	0.890	0.981	0.907	0.997	0.468
1	140	0.907	0.984	0.920	0.984	0.373
2	110	0.935	0.996	0.966	0.997	0.445
3	110	0.939	0.998	0.972	0.999	0.452
4	110	0.938	0.998	0.966	0.999	0.432
5	110	0.896	0.985	0.973	0.996	0.410
6	110	0.908	0.989	0.990	0.996	0.441
7	110	0.967	0.999	0.992	0.997	0.487
8	110	0.958	0.999	0.992	0.999	0.532
9	110	0.941	0.998	0.996	0.999	0.515
10	110	0.931	0.996	0.941	0.999	0.542
8	140	0.994	0.995	0.998	0.999	0.833
11	110	0.954	0.996	0.999	0.999	0.458
11	140	0.991	0.997	0.997	0.999	0.564
12	110	0.953	0.995	0.997	0.998	0.336
12	140	0.988	0.998	0.998	0.990	0.268

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).

age loss of polymer content) was determined based on the weight difference between dried matrices and the initial weight of the tablet, taken the amount of drug released at each time point into account.

$$\%\ \text{erosion} = \left(\frac{(W_i - DR_0) - (W_d - DR_t)}{(W_i - DR_0)}\right) \times 100 \quad (6)$$

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).

2.7. Differential scanning calorimetry

The thermal behaviour of the different individual components, physical mixtures and tablets was evaluated using a differential scanning calorimeter (2920 standard DSC, TA instrument, 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 hermetical sealed aluminum pans supplied by TA Instruments (Leatherhead, UK). Temperature and enthalpic calibration were done using indium as a standard. The samples were cooled to −40 °C, held isothermal for 5 min and heated to 200 °C at a linear heating rate of 10 °C/min. In order 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-min isothermal phase. The results were analyzed using the TA Instruments Universal Software.

2.8. Tablet hardness

The tablet hardness was measured using the Pharma Test PTB 311 tablet tester (Hainberg, Germany). At least three tablets were evaluated per formulation.

2.9. Tablet porosity

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, USA) and the bulk volume was determined from the dimensions of the mould since an after pressure was used to counteract shrinkage of the tablet during cooling. The tablet porosity (ε) was calculated using the following equation:

$$\varepsilon = (\text{bulk volume} - \text{skeletal volume})/\text{bulk volume} \times 100 \quad (7)$$

2.10. 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, HPMC and metoprolol tartrate) as well as on a physical mixture and tablets (processed at 110 and 140 °C) containing EC and HPMC 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 s/step.

2.11. Raman spectroscopic conditions

The distribution of metoprolol tartrate in the tablets was evaluated by Raman spectroscopic imaging. Each tablet was radially broken into two parts and a 1900 μm × 1400 μm area of the fracture plane 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 metoprolol tartrate in the tablet.

The image system 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 30 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 package and the Matlab® software package (version 6.5).

2.12. Scanning electron microscopy

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).

2.13. Statistical analysis

The influence of process temperature and molecular weight of EC on tensile strength and tablet porosity were 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.

3. Results and discussion

3.1. Processability via extrusion and injection moulding

Ethylcellulose is an inert, non-ionic water-insoluble cellulose derivative that has been used successfully for many years as the rate-controlling polymer in controlled release formulations. EC is available in various molecular weights, has a T_g of 129–133 °C and is a good candidate for extrusion because it exhibits thermoplastic behaviour at temperatures above its glass transition temperature and below the temperature at which it shows degradation. Formulations composed of unplasticized ethylcellulose could only be processed via extrusion and injection moulding at temperatures above the T_g of EC (133 °C) and the resulting tablets were transparent and very brittle. Adding 20% w/w DBS facilitated the production of the matrix tablets by lowering the T_g of EC (52.8 °C) and melt viscosity of EC, allowing a lower processing temperature and enhancing melt flow. The melt index of EC plasticized by 20% w/w DBS was 0.15 g/10 min measured at 110 °C, while the melt flow index increased at higher temperatures: 0.74, 4.85 and 12.90 g/10 min for 120, 130 and 140 °C, respectively. In contrast, the melt index of unplasticized EC could not be determined below 160 °C, at this temperature the MFI was 0.46 g/10 min. In addition, lowering the polymer T_g with plasticizers also reduced the risk of thermal decomposition of the API since lower process temperatures can be applied during manufacturing. When metoprolol tartrate and HPMC were added, homogeneous tablets could be processed over a broad temperature range. However, at IM temper-

ature below 110 or above 140 °C, the melt viscosity was too high or too low, respectively, resulting in an inadequate flow from the extruder, thus compromising the manufacturing of tablets via injection moulding. At higher production temperatures increased the overall cycle time of the injection moulding process due to a longer cooling phase. Although the mould was bi-convex shaped, a silicon-based anti-sticking spray was necessary to enhance the release of the solidified tablets from the mould, irrespective of the processing temperature. The runners, along which the melt flows as it is injected towards the mould cavity, were constricted to a narrow gate at the entrance of the cavity, allowing the tablet to be easily sheared off after demoulding. The deviation of the individual tablet weight from the average mass was less than 1%, confirming the uniformity of mass of these sustained-release preparations: 98.6 ± 0.7% and 98.5 ± 0.9% of the drug were recovered for tablets processed at 110 and 140 °C, respectively. In spite of manufacturing tablets well above the melting point of metoprolol tartrate at the highest production temperature (140 °C) and despite the slightly yellow discolouration of the tablets at this temperature, no significant degradation of the drug was observed. The thermal stability of metoprolol tartrate could be attributed to the short residence time of the drug in the equipment during the extrusion and injection moulding process (<5 min). The weight average molecular weight (Mw) of unprocessed ethylcellulose and ethylcellulose processed at 110 and 140 °C was 40.558, 40.893 and 44.269, respectively, with polydispersity indices (Mw/Mn) of 3.133, 2.906 and 2.992 as determined by GPC, indicating that ethylcellulose was also stable during the extrusion and injection moulding process. The stability of the individual components, the physical mixture as well as the tablets manufactured at 110 and 140 °C was determined by thermogravimetric analysis under a nitrogen atmosphere. Ethylcellulose and HPMC showed only a significant mass loss at high temperature, with an extrapolated onset temperature of decomposition around 232 and 253 °C, respectively. DBS started to degrade at a temperature of 155 °C, while metoprolol tartrate was stable below 160 °C. No difference in the onset temperature of decomposition of the pure drug, the physical mixture and the tablets manufactured at 110 and 140 °C was observed, indicating that the physical stability of metoprolol tartrate was not compromised at the temperatures used during extrusion and injection moulding. Follonier et al. and Debrabander et al. also reported about the stability of EC/HPMC-based systems processed by melt-extrusion, the degradation of these polymers was only observed at higher temperatures, with an onset decomposition temperature above 185 and 190 °C for HPMC and EC, respectively [18,19]. In conclusion, despite the fact that extrusion and injection moulding involves the comprehensive generation of heat, shear and pressure, no significant degradation of metoprolol tartrate and the release controlling polymer were observed during processing.

3.2. In vitro drug release

3.2.1. The influence of process temperature on drug release

Drug release profiles from injection-moulded tablets composed of 70/30% w/w EC/MPT, processed at different temperatures are presented in Fig. 1. Drug release was incomplete after 24 h, as less than 50% of the drug was released from tablets processed at 110 °C. When the processing temperature increased, a significant decrease in the drug release rate was observed: only 20% of the drug was released after 24 h from tablets processed at 140 °C. No burst release was observed and the dissolution profile showed fairly constant release rates. Similar results were obtained for matrices consisting of higher viscosities of EC (results not shown). At the end of the dissolution test (24 h), the tablets were slightly swollen due to the polymer relaxation after water uptake and no erosion had occurred since the tablets remained intact during dissolution.

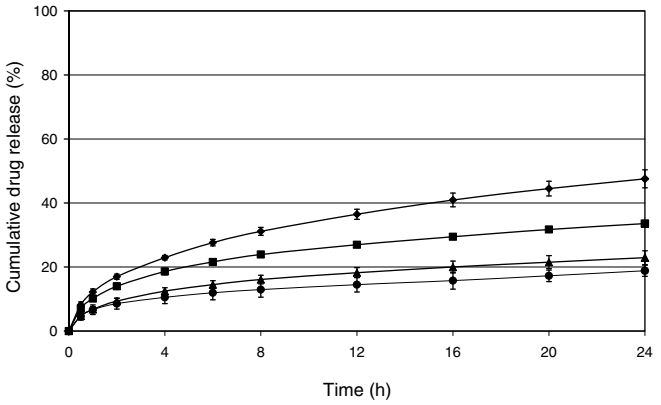

Fig. 1. Influence of process temperature on drug release. Mean dissolution profiles (±SD) of injection-moulded tablets containing 70% EC4 and 30% MPT (Formulation 1) processed at different temperatures (♦) 110 °C, (■) 120 °C, (▲) 130 °C, and (●) 140 °C.

The best fit was obtained with the Power law equation ($R^2 > 0.99$) and the low values of n indicated that drug diffusion was the predominant release mechanism (Table 2). This could be expected as EC is an inert polymer and metoprolol tartrate is a very good water-soluble drug (>1000 mg/mL). The release kinetics adequately followed a square root of time according to the Higuchi model since Fickian diffusion occurred via the porous network formed when metoprolol tartrate dissolved from the inert matrix. As drug release continues, further dissolving of interconnecting drug clusters created additional pores, resulting in a decrease of matrix tortuosity. As the drug load was possibly below the percolation threshold, drug release was incomplete due to the limited accessibility of drug particles which are encapsulated by water-insoluble polymers. No significant difference in tablet hardness was observed in function of production temperature, tablets manufactured at 110, 120, 130 and 140 °C had a tensile strength of 1.66 ± 0.10, 1.67 ± 0.17, 1.76 ± 0.08 and 1.75 ± 0.17 mPa, respectively. In addition, all tablets had a very low porosity: 2.8 ± 0.2%; 3.6 ± 0.4%; 3.2 ± 0.2% and 2.7 ± 0.1% for process temperatures of 110, 120, 130 and 140 °C, respectively. Zhang et al. [20] demonstrated that thermal treatment of wax matrix tablets resulted in the formation of a more tortuous and less porous product, although the retarding effect on drug release was mainly attributed to the increase in tortuosity. Crowley et al. [21] demonstrated that the median pore radius was smaller, the tablets were less porous and more tortuous when higher extrusion temperatures were applied for the production of extrudates composed of 30% ethylcellulose and 70% guaifenesin w/w, consequently reducing drug release rates. Thermal processing also resulted in a decrease of polymer-free volume accounting for slower drug release rates, since higher production temperatures resulted in an increase of polymer-free volume and polymer chain motion, allowing drug molecules to enter voids between polymer strains during processing. After cooling, the polymer chain motions diminished reducing the free volume and dispersing the drug particles in a matrix of entangled polymers, resulting in a higher degree of packing. In this way, the matrix becomes less permeable causing slower drug release rates as the matrix network inhibits drug diffusion [22]. Another factor contributing to the lower dissolution rates at higher processing temperatures could be due to a better coalescence of the molten polymer fronts in the mould, promoting curing of the matrix.

3.2.2. The influence of HPMC concentration on drug release

One of the major problems associated with hydrophobic matrix tablets is the reduction of the terminal release rate, due to the quick release of the drug at the surface followed by a progressive decrease of the drug release rate as the diffusion path length increased over time. Drug release profiles can be tailored by the incorporation of a hydrophilic filler in the formulation, making the matrix more permeable to the dissolution medium or by controlling the erosion of the matrix using a disintegrant [23]. The influence of the amount of HPMC on drug release rate from injection-moulded HPMC/EC tablets is presented in Fig. 2. Substituting part of the ethylcellulose fraction by HPMC increased the drug release rate. However, for formulations containing less than 40% HPMC the increase in drug release rate was limited compared to formulations without HPMC as less than 60% of the drug was released after 24 h. In contrast, tablets containing 50% HPMC demonstrated complete drug release after 24 h dissolution. Tablets composed of 20 and 35% HPMC 50 mPa s had a respective hardness of 1.73 ± 0.16 and 1.78 ± 0.10 mPa respectively, with an initial porosity of 2.6 ± 0.1% and 3.4 ± 0.1% when produced at 110 °C. These findings suggest that the initial porosity and hardness is not affected by the composition of the tablets and therefore did not influence the drug release profiles. The release kinetics and mechanism of these formulations are presented in Table 2. For all formulations, a time-dependent drug release was observed and the best fit was obtained with the Higuchi square root model. A very good fit was obtained with the Ritger–Peppas model ($R^2 > 0.99$) and the values of the release exponent ($0.45 < n < 0.89$) denoted an anomalous transport, a combination of diffusion-controlled and swelling-controlled drug release. The water-insoluble EC polymer retained its structure during the dissolution. In contrast, HPMC was hydrated after immersion followed by a relaxation process and swelling of the matrix. Furthermore, the polymer chains started to disentangle and dissolved into the dissolution medium as matrices composed of 20 and 35% w/w HPMC 50 mPa s manufactured at 110 °C had an erosion of 9.4% and 18.6%, respectively, after 24 h. However, as this system is not a pure hydrophilic matrix, drug release also occurred via drug diffusion through the swollen HPMC regions and through a convoluted media-filled micro-porous and tortuous network formed by already dissolved metoprolol tartrate and HPMC clusters.

3.2.3. The influence of the EC viscosity grade on drug release

The dissolution profiles of tablets containing different EC viscosity grades are given in Fig. 3. A clear distinction in release profiles can be made between tablets containing EC of lower viscosities (EC4, EC7, EC10 and EC20) and tablets composed of higher EC viscosity grades (EC45 and EC100). For all viscosities, drug release followed Higuchi release kinetics, however, the lower viscosities yielded incomplete drug release as less than 50% of the dose is released after 24 h. In addition, a good fit was obtained with the first-order model for higher EC viscosities, releasing about 80% after 24 h dissolution (Table 2). Regarding the influence of the molecular weight of EC on tablet tensile strength, the highest values were observed for formulations consisting of EC 45 mPa s with (2.48 ± 0.03 mPa) and EC100 (2.16 ± 0.18 mPa). Tablets composed of EC4 and EC10 had a significant lower tensile strength of 1.66 ± 0.10 and 1.75 ± 0.28 mPa, respectively. No relevant differences on tablet porosity for the different viscosity grades EC could be observed as the porosity of the different formulations was low (<4%). An influence of the EC molecular weight on the IM process was observed, as a higher viscosity grade of EC resulted in a restricted melt flow due to the higher interchain friction and entanglement in case of longer polymer chains.

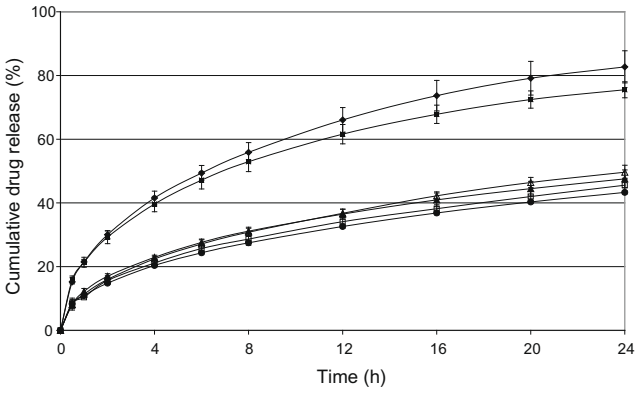

Fig. 3. Metoprolol tartrate release in function of the viscosity grade of ethylcellulose. Mean dissolution profiles (±SD) for formulations contained 70/30% w/w EC/MPT, processed at 110 °C (Formulations 1–6). EC grade (mPa s): (▲) EC4, (□) EC7, (Δ) EC10, (●) EC20, (■) EC45, and (♦) EC100.

3.2.4. The influence of the HPMC viscosity grade on drug release

Regarding the effect of HPMC viscosity grade on drug release, various HPMC types with the same degree of substitution were processed at 110 °C and subsequently tested for their dissolution properties. The release profiles of tablets consisting of different HPMC viscosity grades are given in Fig. 4.

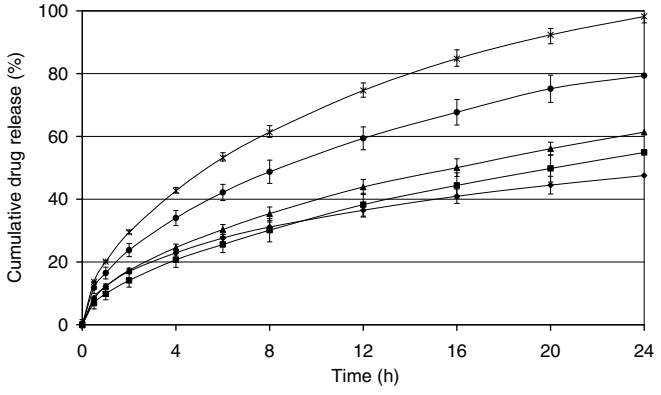

Fig. 2. Influence of HPMC concentration on drug release. Mean dissolution profiles (±SD) of injection-moulded tablets containing different proportions of HPMC and EC4, manufactured at 110 °C (Formulations 1 and 7–10). HPMC concentration: (♦) 0%, (■) 20%, (▲) 35%, (●) 40%, and (∗) 50%.

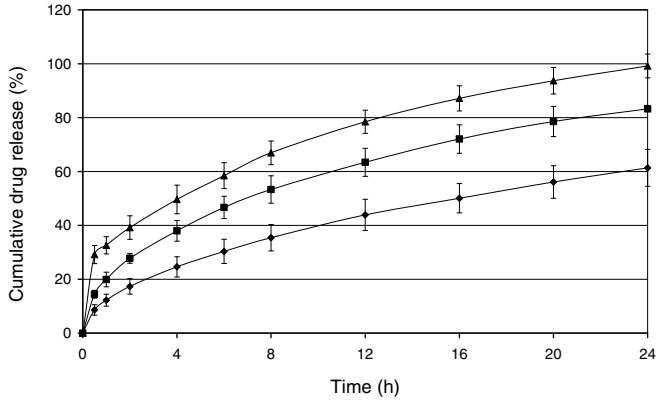

Fig. 4. Influence of HPMC viscosity grade on metoprolol tartrate release. Mean dissolution profiles (±SD) for matrices composed of 35/35% w/w EC/HPMC, processed at 110 °C (Formulations 8, 11, and 12). HPMC grade: (♦) 50 mPa s, (■) 4000 mPa s, and (▲) 10,000 mPa s.

The drug release depended on the viscosity grade of HMPC as shown in Fig. 4, increasing the molecular weight of HPMC enhanced the drug release rate. Since the rate of swelling and erosion determines the drug release mechanism and kinetics, matrix swelling, water uptake and polymer (EC and HPMC) erosion of the injection-moulded tablets were determined during dissolution (Fig. 5). A first-order drug release profile was observed for formulations containing 35% HPMC 10,000 mPa s showing complete drug release after 24 h of dissolution. This formulation had the highest water uptake (500%) and radial swelling (19 mm), but a very limited erosion rate (±7%). When 35% HPMC 4000 was incorporated into the formulation, 83% drug was released after 24 h following first-order kinetics with moderate water uptake (350%), radial swelling (19 mm) and erosion (16%). The best fit for the kinetics of the lowest HPMC viscosity grade was obtained with the Higuchi model, providing the slowest drug release (±60%) after 24 h (Table 2). Lower molecular weights of HPMC yielded the lowest degree of water uptake (260%) and swelling (15 mm), but demonstrated the highest degree of erosion (±18%). Similar trends were observed when different HPMC concentrations were incorporated in the formulation (results not shown). The water uptake, swelling and erosion rate clearly depended on the viscosity grade and concentration of HPMC. Although it has been reported in the literature [24] that the drug release from matrices containing high molecular weight HPMC was slower, drug release from the injection-moulded tablets was not hindered by the higher degree of swelling observed for high-viscosity HPMC grades. However, for a similar system (containing EC, HPMC and ibuprofen) processed by means of hot-melt extrusion into mini-tablets, similar results were described [19]. The higher swelling rate of higher viscosity HPMC grades opened the matrix structure matrix and made the tablet more accessible to the dissolution medium, resulting in higher drug release rates and increasing the initial burst in drug release observed for formulations containing HPMC 10,000 and 4000 mPa s. For all formulations, the presence of solid EC particles in the gel may reduce the swelling and the entanglement of polymers and therefore negatively affecting the resistance of the gel to erosion [25]. Higher rates of water uptake, swelling and erosion were observed for tablets manufactured at 110 compared to 140 °C as process temperature (results not shown).

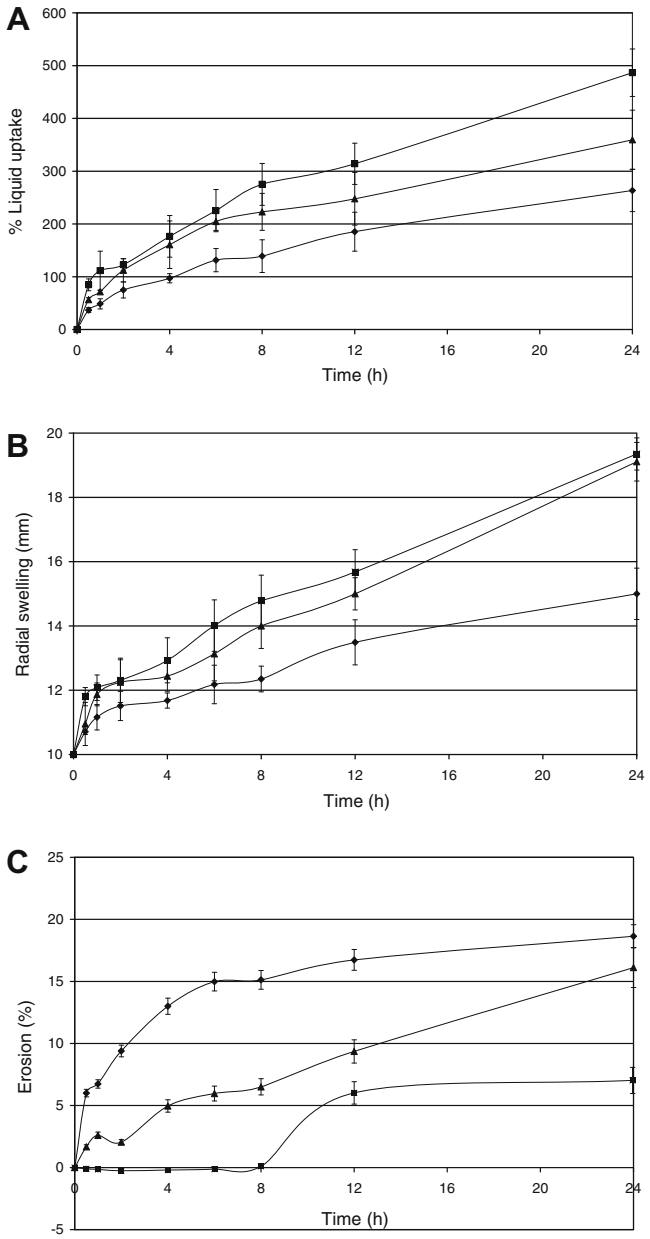

Fig. 5. Influence of HPMC viscosity grade on water uptake (a), radial swelling (b) and erosion (c) (means ± SD, $n = 3$) of matrices composed of 35/35/30% w/w EC/HPMC/MPT, processed at 110 °C. HPMC viscosity grade: (■) 10,000 mPa s, (▲) 4000 mPa s and (♦) 50 mPa s.

In order to fully investigate the mode of drug release from swellable matrices, the dissolution data were fitted to the semi-empirical equation proposed by Ritger and Peppas. The values for n are listed in Table 2. Low values of n were obtained for the highest viscosity grade indicating Fickian diffusion as the main drug release mechanism. However, the values of n increased for lower viscosity grades demonstrating that the drug release tended to anomalous transport. Depending on the properties of drug and polymers, three mechanisms are involved in drug release from hydrophilic matrices: Fickian diffusion, relaxation (i.e. swelling) and erosion of the polymer gel layer surrounding the matrix. HPMC swells and this gel becomes a viscous layer acting as a protective barrier controlling both the influx of water and efflux of drug in solution and as a consequence the viscosity of this gel layer determines the drug release mechanism [26,27]. In combination with the liquid uptake, swelling and erosion study, it can be concluded that for the higher molecular weights of HPMC drug diffusion is the predominant release mechanism with only a small contribution of erosion described by the Higuchi square root of time law kinetics ($n < 0.45$). The higher viscosity grades of HPMC have higher swelling capacities, making the tablet more accessible to the dissolution medium and as a consequence enhancing drug diffusion. In contrast, the release from low viscosity grades occurs by dissolution of the polymer following nearly zero-order kinetics and the drug release mechanism involved is based on both erosion of the matrix and diffusion of the API (anomalous transport). It should be mentioned that some values of the diffusional exponent n demonstrated a deviation from the theoretical values of n for a cylindrical swellable device proposed by Ritger and Peppas. This could originate from the tablets used in this study not being perfectly cylindrical and/or that for some formulations a swelling in excess of 25% of its original volume was observed [28].

3.3. Evaluation of the tablet characteristics

The DSC thermogram of metoprolol tartrate (Fig. 6) showed a clear melting endotherm at 125.8 °C, indicating its crystalline nature. EC plasticized by 20% w/p DBS and HPMC demonstrated a glass transition temperature at 52.8 and 164.6 °C respectively, denoting that both cellulose polymers are in the amorphous state. In the physical mixture, a single broad melting peak was observed

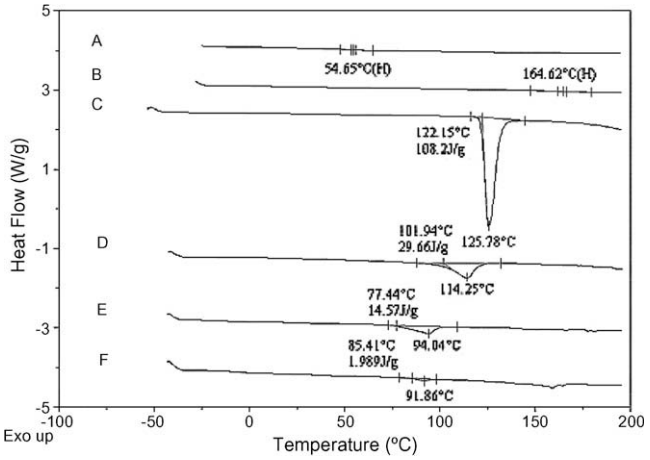

Fig. 6. Differential scanning calorimetry profiles of ethylcellulose with 20% DBS w/p (A), hydroxymethylpropylcellulose (B), metoprolol tartrate (C), a physical mixture of 35/35/30% EC/HPMC/MPT (D), injection-moulded tablet composed of 35/35/30% EC/HPMC/MPT (Formulation 8) processed at 110 °C (E) and 140 °C (F).

at 114.2 °C, whereas for tablets produced at 110 and 140 °C a broad endothermic melting peak could be observed at 94.0 and 91.0 °C, respectively. In all tablets, the melting point of MPT was depressed and broadened depending of the process conditions. In addition, a decrease of the melting enthalpy (ΔH) could be seen with increasing processing temperatures, due to the partially solubilization of MPT in the molten EC during processing. The decrease in the melting point after extrusion and injection moulding demonstrated molecular interactions between EC or HPMC with the crystal lattice of MPT during processing. Similar results have been reported for hot-melt extruded tablets containing chlorpheniramine maleate [29] or 5-aminosalicylic acid [30] as model drug. The presence of melting peaks in the thermogram of tablets indicated that metoprolol is only partially solubilised by the molten ethylcellulose during heating and suggested that a two-phase solid dispersion is formed upon cooling in which metoprolol was present in amorphous and crystalline form.

The X-ray diffractograms of EC and HPMC identified no peaks, confirming that these cellulosic polymers are amorphous (Fig. 7). Metoprolol tartrate had distinct crystalline peaks at 2θ of 19.4 and 23.1 (and a series of smaller peaks at 10.6, 15.8, 20.4 and 24.0). These primary peaks of MPT could also be identified in the physical mixture and in tablets processed at 110 and 140 °C. However, these peaks were less intensive compared to

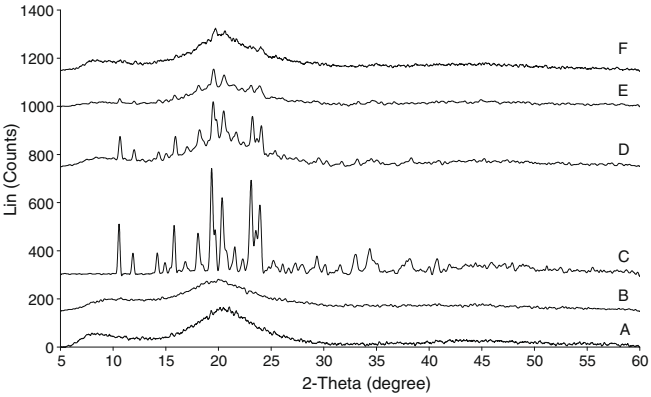

Fig. 7. Wide-angle diffraction profiles of ethylcellulose 4 mPa s (A); hydroxypropylmethylcellulose 50 mPa s (B); metoprolol tartrate (C); a physical mixture of 35/35/30% EC/HPMC/MPT (D), injection-moulded tablet composed of 35/35/30% EC/HPMC/MPT (Formulation 8) processed at 110 °C (E) and 140 °C (F).

the physical mixture, indicating loss of crystallinity. When the processing temperature was increased (110–140 °C), the peak intensity was also reduced, possibly due to a higher fraction of drug molecules dissolving in the ethylcellulose melt during processing. These measurements confirm the results obtained with DSC, indicating that a 2-phase solid dispersion of metoprolol tartrate was formed upon cooling within the polymer matrix.

The spectrum of metoprolol tartrate 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 since there were no spectral interferences from the other excipients in these regions.

Fig. 8A and B show the distribution of MPT in the tablet by plotting the peak area of the selected Raman bands over the entire scanned area, a red colour corresponds to a high MPT concentration, whereas a blue colour signifies a lower MPT concentration at the spot. Although small colour variations between the points can be caused by the changes in the distance between lens and tablet, due to the rough tablet surface, the large colour differences (red vs. blue) are caused by variations of the local metoprolol tartrate concentration. The spectra (Fig. 8C) show that API bands in the spectrum corresponding with a red area in the mapping have a higher intensity of the MPT-specific peaks than the spectrum at a blue spot. However, Raman bands of metoprolol tartrate were identified in the entire scanned area, indicating that the drug is distributed in the entire matrix. However, local differences of drug concentration in the tablet matrix were detected. Similar results were obtained for different formulations, (composed of 20% or 35% HPMC and processed at 110 or 140 °C). A possible reason for the local MPT clusters is that some metoprolol tartrate particles did not melt or sufficiently mix with the excipients during the tablet production.

The surface morphology of the injection-moulded tablets processed at 110 and 140 °C prior and after 24 h dissolution testing is presented in Fig. 9. For tablets produced at 110 °C, the surface was slightly rough, whereas the tablets processed at 140 °C provided a much smoother surface due to a better coalescence of the melt. After the dissolution the surface of tablets processed at 110 °C was very rough and showed numerous cracks and pores caused by the swelling capacities of HPMC and by capillary diffusion of metoprolol tartrate. In combination with the stronger swelling this resulted in faster drug release rates of tablets processed at lower temperatures, probably due to less coalescence of the matrix structure during processing. In contrast, a smooth surface was observed after dissolution of tablets produced at 140 °C as swelling was reduced and pores were only formed due to the capillary diffusion of HPMC and metoprolol tartrate.

4. Conclusions

Injection moulding of thermoplastic formulations seems to be a promising technique to prepare sustained-release matrix tablets using EC and HPMC as matrix forming polymers. No degradation of the drug (metoprolol tartrate) and the release controlling polymer (EC) was observed during processing. Increasing the process temperature during the injection moulding of the matrix tablets resulted in lower drug release rates. Since drug release of formulations composed of EC and MPT was incomplete, incorporation of HPMC as a hydrophilic filler was required to yield faster and constant drug release rates by promoting drug diffusion. Faster drug release rates were observed for the higher EC viscosity grades (EC45 and EC100) and for high molecular weight HPMC (4000 and 10,000 mPa s) due to increased water uptake and swelling. Tablet hardness and

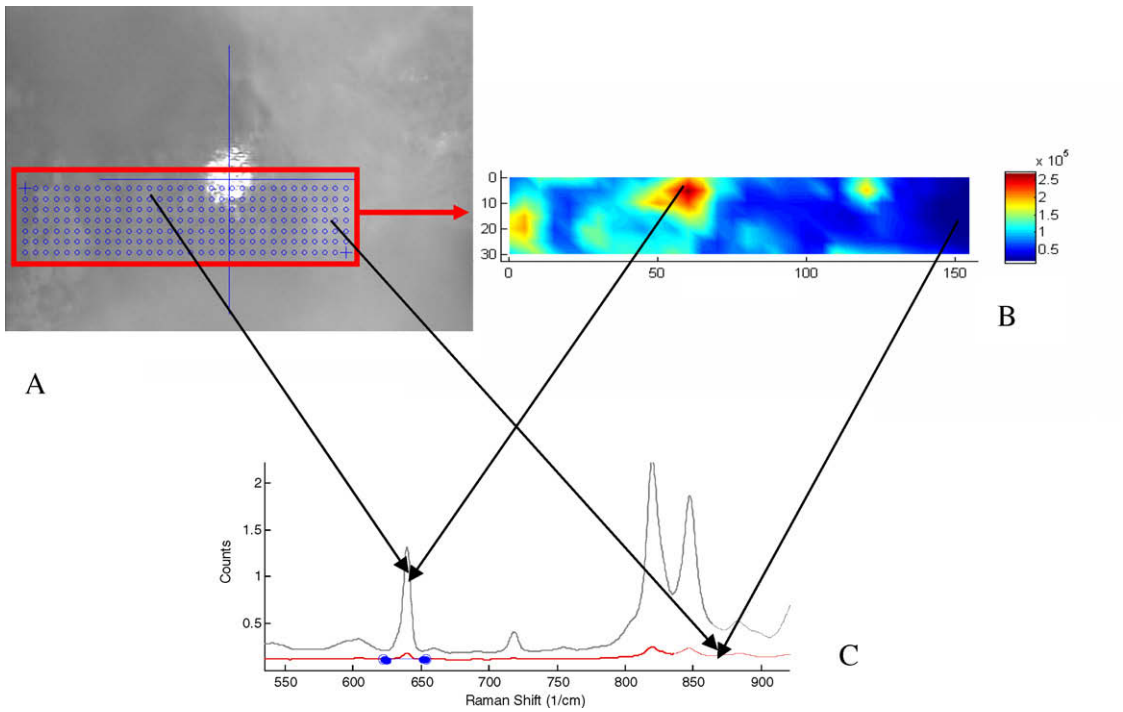

Fig. 8. Distribution mapping of metoprolol tartrate in a injection-moulded tablet composed of 35/35/30% EC/HPMC/MPT (process temperature: 110 °C). (A) Microscopic photo of scanned area, (B) MPT distribution in scanned area (blue corresponds to a low MPT concentration, red to a high MPT concentration, (C) Raman spectra recorded at selected spots for quantification of MPT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this paper.)

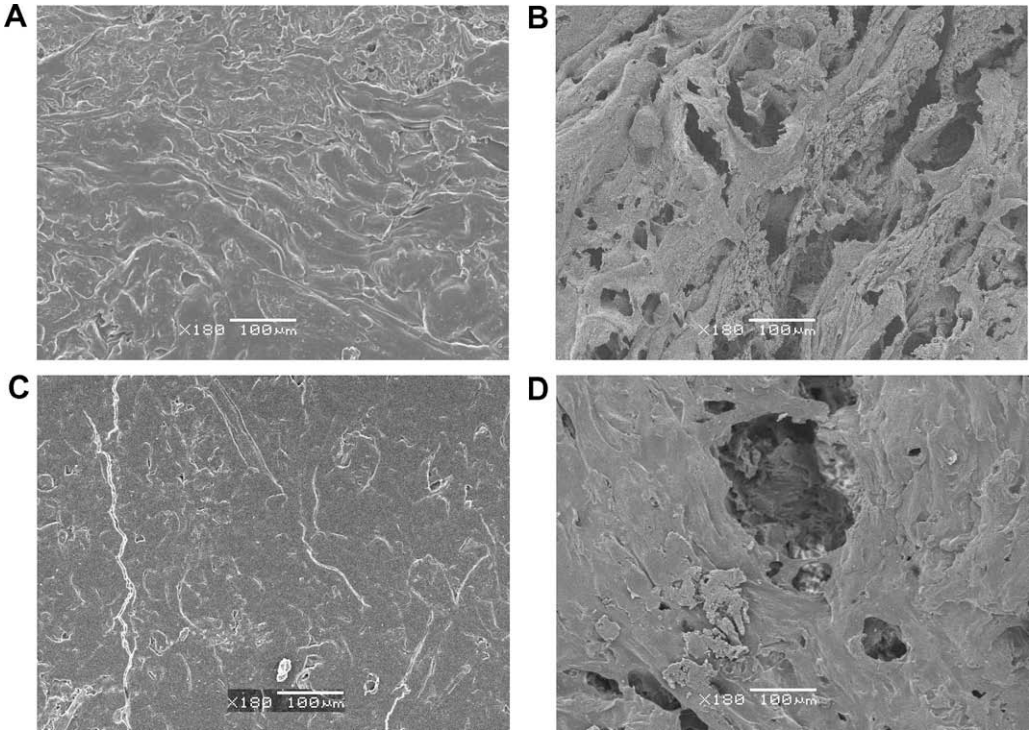

Fig. 9. Surface morphology of injection-moulded matrix tablets containing 35/35/30% w/w EC/HPMC 50 mPa s/MPT prior to and after dissolution testing (magnification 180×). Injection-moulded tablet processed at 110 °C before (A) and after 24 h (B) dissolution testing. Injection-moulded tablet processed at 140 °C before (C) and after 24 h (D) dissolution testing.

porosity had no significant influence on drug release. DSC and XRD analysis showed that a solid dispersion of MPT was formed after cooling of the injection-moulded tablets, whereby part of the drug was dissolved in the matrix carrier. Raman spectroscopy confirmed that the drug was distributed in the entire matrix; however, small drug clusters were identified.

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