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Research paper

Correlation between the permeability of metoprolol tartrate through plasticized isolated ethylcellulose/hydroxypropyl methylcellulose films and drug release from reservoir pellets

Zhi-wei Ye [a], Patrick Rombout [a], Jean Paul Remon [b], Chris Vervaet [b], Guy Van den Mooter [a,*]

[a] *Laboratorium voor Farmacotechnologie en Biofarmacie, Katholieke Universiteit Leuven, Leuven, Belgium*
[b] *Laboratorium voor Farmaceutische Technologie, Universiteit Gent, Gent, Belgium*

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Abstract

The present study investigates if drug diffusion through plasticized isolated ethylcellulose (EC)/hydroxypropyl methylcellulose (HPMC) films prepared by solvent casting can be used as a tool to develop spray-coated dosage forms. In particular, the importance of the level and type of plasticizers was investigated. The permeability of the model drug metoprolol tartrate through plasticized isolated films could be adjusted by selecting the type and amount of plasticizer in the films due to the different hydrophilicity of the plasticizers. The release of metoprolol tartrate from coated pellets is consistent with the drug diffusion through the films made up of the same polymer blends. This indicated that it is useful to test isolated films for early predictions and for formulation optimization.

Keywords: Ethylcellulose; Hydroxypropyl methylcellulose; Metoprolol tartrate; Diffusion; Release; Plasticizer

1. Introduction

Developing oral controlled release systems for highly water-soluble drugs has always been a challenge to the pharmaceutical technologist. Most of these highly water-soluble drugs, if not formulated properly, are released at a high rate and are likely to produce toxic concentrations, when administered orally. Polymeric film coatings have often been used for achieving controlled release of an active substance from a pharmaceutical preparation because a coated dosage form enables prolonged and precise release of drugs with good reproducibility [1,2]. Some formulations of a drug–polymer mixed coat for highly water-soluble drug pellets had a dissolution profile that matched the commercial product [3].

Several commercially available polymers are suitable for the coating of pharmaceutical dosage forms [4], one of them being ethylcellulose (EC). In many ways EC is an ideal polymer for modified release coatings. It is odorless, tasteless and it exhibits a high degree of stability not only under physiological conditions but also under normal storage conditions [5]. The polymer is usually not used on its own but in combination with secondary polymers such as hydroxypropyl methylcellulose (HPMC) which gives a more hydrophilic nature to the film and alters its structure by virtue of pores and channels through which the drug substance can diffuse more easily.

Because the properties of a membrane on the surface of a coated pellet are not easily characterized, isolated films have been reported as an alternative to predict membrane

* Corresponding author. Laboratorium voor Farmacotechnologie en Biofarmacie, Katholieke Universiteit Leuven, Leuven, Belgium. Tel.: +32 16 330300; fax: +32 16 330305.
E-mail address: Guy.Vandenmooter@pharm.kuleuven.be (G. Van den Mooter).

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properties on the surface of a dosage form, and hence a good way to screen the properties of formulations intended for coating [6].

However, EC films are brittle and the addition of a plasticizer is essential to enhance film-forming characteristics, workability and serviceability of the coatings [7]. In polymeric solutions, plasticizers increase the free volume between the polymer chains by reducing the number of active centers available for rigid polymer–polymer contacts [8,9]. Pliable films are generally produced from EC by using long chain esters as plasticizers; e.g., dimethyl-, diethyl- and dibutyl phthalates, triethyl- and tributyl citrates, dibutyl sebacate, triacetin, and also butyl and glycol esters of fatty acids [10]. The type and amount of plasticizer affects the drug diffusion rate through the film via structural changes [11]. Hamed et al. found that the curing time can affect the film formation process especially at low level of plasticizer [12].

The film forming process for isolated solvent casted films is expected to be different at least from a kinetic point of view from that of a film formed during a spraying process since the rate of solvent evaporation differs at least a few orders of magnitude in both processes.

The purpose of the present study was to investigate how the permeability of the model drug metoprolol tartrate through plasticized isolated polymer films is related to its release from a reservoir system made up of pellet coated with the same plasticized polymer combination. The polymer films in the present study are ternary in nature, made up of an essentially hydrophobic polymer (EC), a hydrophilic polymer (HPMC) and a hydrophobic or hydrophilic plasticizer. Hence, the value of permeability tests with isolated plasticized polymer films as a prediction tool for optimization of coated dosage forms will be assessed.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: ethylcellulose (EC) (ethoxyl content 48–49.5%; viscosity 9–11 mPa s (5% solution in toluene–ethanol 80/20) Fluka, Switzerland); hydroxypropyl methylcellulose (HPMC) (Pharmacoat 606 and 615, Shin-etsu, Japan); trietyl *O*-acetylcitrate (ATEC), glyceryl triacetate (Triacetin), dibutyl sebacate (DBS) (all Fluka, Switzerland); dibutyl phthalate (DBP) (Acros, USA), diethyl phthalate (DEP) (PRL, Belgium); sodium dihydrogen phosphate (BDH, UK), dipotassium hydrogen phosphate (BDH, UK); sodium phosphate tribasic dodecahydrate (Acros, USA), hydrochloric acid 37% (Chem-Lab, Belgium); metoprolol tartrate (Roig Pharma, Spain), microcrystalline cellulose (Avicel PH101, FMC Biopolymer, USA). The water used in the diffusion test was purified with an ELGA MAXIMA UF system (ELGA, UK). All other reagents were of analytical or HPLC grade.

2.2. Methods

2.2.1. Preparation of isolated films

Polymers were dissolved in ethanol/dichloromethane (1/1, v/v) for EC/HPMC films. The composition of the polymer blends is listed in Table 1. Polymer solutions (5% w/w) were cast on a Teflon-coated glass plate. To slow down solvent evaporation, the glass plate was covered with a funnel. After complete evaporation of the solvent at room temperature, the film was removed from the Teflon-coated glass plate, dried to constant weight, and stored in a desiccator until use. The plasticizers were mixed together with the polymer solutions before casting. The films prepared in this way were completely transparent. The thickness of the film was measured with a micrometer (Lorentzen and Wetters, Van der Heyden, Brussels, Belgium).

2.2.2. Diffusion of metoprolol tartrate

The drug permeation through a film was determined using an in-house manufactured diffusion cell (Fig. 1). The film was clamped between the donor and acceptor compartments which both contained 100 ml of 0.02 M phosphate buffer pH 5.5. The initial concentration of metoprolol tartrate in the donor compartment was 1.0 mg/ml. The permeability coefficient, P of metoprolol tartrate through the film was calculated using the following equation [13]:

$$\frac{2PS}{V}t = -\ln\left(\frac{C_0 - 2C_a}{C_0}\right)$$

where S denotes the surface through which diffusion take place, V denotes the volumes of the two compartments, C_0 and C_a denote the respective solute concentration in the donor compartment at the initial time and acceptor compartment at finite time. P can be calculated from a plot of $-\ln[(C_0 - 2C_a)/C_0]$ vs time.

Table 1
Composition (% w/w) of plasticized isolated films

Film			
A1	56% EC	24% Pharmacoat 615	20% DBS
A2	48% EC	32% Pharmacoat 615	20% DBS
A4	40% EC	40% Pharmacoat 615	20% DBS
A5	63% EC	27% Pharmacoat 615	10% DBS
A6	61.2% EC	26.3% Pharmacoat 615	12.5% DBS
A7	59.5% EC	25.5% Pharmacoat 615	15% DBS
A8	52.5% EC	22.5% Pharmacoat 615	25% DBS
A9	50.8% EC	21.7% Pharmacoat 615	27.5% DBS
A10	49% EC	21% Pharmacoat 615	30% DBS
A11	56% EC	24% Pharmacoat 615	20% DBP
A12	56% EC	24% Pharmacoat 615	20% DEP
A13	56% EC	24% Pharmacoat 615	20% ATEC
A14	56% EC	24% Pharmacoat 615	20% Triacetin
B1	56% EC	24% Pharmacoat 606	20% DBS
B2	56% EC	24% Pharmacoat 606	20% DBP
B3	56% EC	24% Pharmacoat 606	20% DEP
B4	56% EC	24% Pharmacoat 606	20% ATEC
B5	56% EC	24% Pharmacoat 606	20% Triacetin

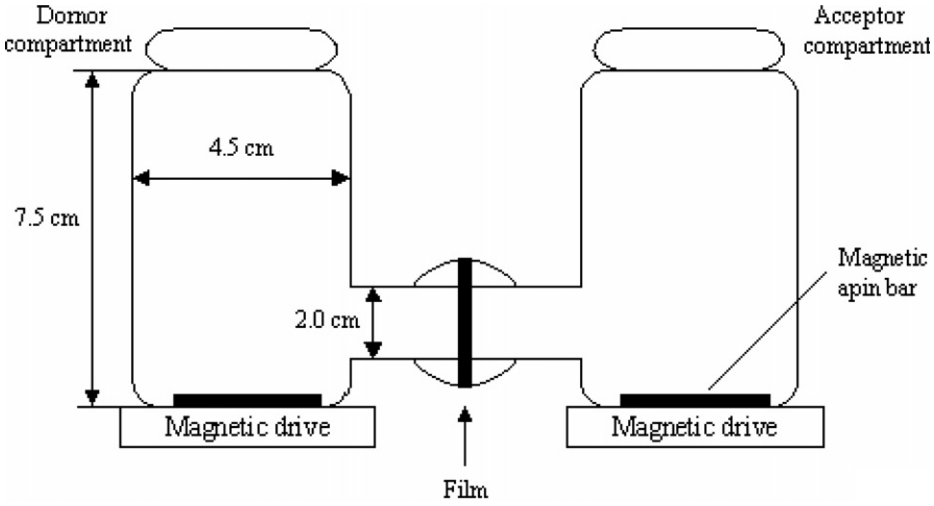

Fig. 1. Drug permeability measurement apparatus.

2.2.3. HPLC analysis

The amount of metoprolol tartrate diffusing from the donor compartment through the polymer film into the acceptor compartment was determined with HPLC using a Merck Hitachi pump L 7100, a Merck Hitachi autosampler L 7200 and a Merck Hitachi UV-detector L 7400 (Merck, Darmstadt, Germany). A LiChrospher® 100 RP-8 (5 μm, 4.0 × 250 mm) column (Merck, Darmstadt, Germany) was used. All measurements were performed at room temperature. 0.02 M phosphate buffer pH 5.5/acetonitrile (60/40, v/v) was used as mobile phase at a flow rate of 1 ml/min; the injection volume was 10 μl and the detection wavelength was set at 274 nm.

2.2.4. Preparation of metoprolol tartrate pellets

A physical mixture (batch size 400 g) of 20% (w/w) metoprolol tartrate and 80% (w/w) microcrystalline cellulose was prepared in a planetary mixer (Kenwood Chef, UK) equipped with a K-shaped mixing arm (mixing time 10 min; mixing speed 60 rpm). Subsequently, the powder mixture was wetted with demineralized water (60% of the dry powder mass) and granulated for 10 min at 60 rpm. Next the wet mass was extruded at an extrusion rate of 50 rpm by means of a single screw extruder (Dome extruder lab model DG-L1, Fuji Paudal, Japan) equipped with a screen having 1 mm cylindrical perforations. The extrudates were spheronized in a spheronizer (Caleva Model 15, UK) using a friction plate with crosshatched geometry. The spheronization time and speed were 200 s and 750 rpm, respectively. The pellets were tray dried in a hot air oven at 40 °C until constant weight and the 800–1250 μm fraction was separated by sieving.

2.2.5. Pellet coating

The pellets (fraction 800–1250 μm) were coated in a fluidized bed equipped with a Wurster insert (Uniglatt, Glatt Lufttechnische Apparate, Binzen, Germany). The nozzle had a diameter of 0.8 mm. The coating solution was prepared by mixing suitable amounts of EC, HPMC and plasticizer in ethanol/dichloromethane (1/1, v/v). The composition of the coating solutions was the same as those of the casting process.

In each run, known weights of pellets (300 g) were preheated (32 °C) in the Wurster coater for 10 min. The coating solutions (300 ml, 10% w/w) were then sprayed (bottom spray) at a flow rate of 1.5 ml/min with an air pressure of 1.2 bar, the temperature of the incoming air was set at 60–65 °C. After coating, the pellets were further fluidized during 15 min and subsequently dried at 40 °C overnight.

2.2.6. Release of metoprolol tartrate

Release of metoprolol tartrate from the pellets was conducted using the USP XXIV Apparatus 2 (paddle method) in 750 ml of 0.1 M HCl at 100 rpm and 37 ± 0.5 °C for the first 2 h. Then, 250 ml of 0.2 M tribasic sodium phosphate that had been equilibrated to 37 ± 0.5 °C was added. The pH was adjusted to 6.8. The test was continued for another 4 h. Five microliter samples were taken and immediately replaced with fresh dissolution medium at 5, 10, 20, 30, 45, 60, 120, 135, 150, 180, 210, 240, 300, and 600 min, and filtered with a cellulose acetate membrane filter of 0.45 μm. After discarding the first 2 ml, the filtrates were analyzed using the above mentioned HPLC method. All tests were done in triplicate. The percent drug released during dissolution from the pellets was calculated from the actual drug content of each pellet batch.

3. Results and discussion

3.1. Diffusion of metoprolol tartrate through isolated plasticized EC/HPMC films

A representative diffusion profile through the isolated films (film A1) is shown in Fig. 2. The data points were fitted using linear regression analysis. Correlation was in both cases >0.99. Similar results were obtained with all

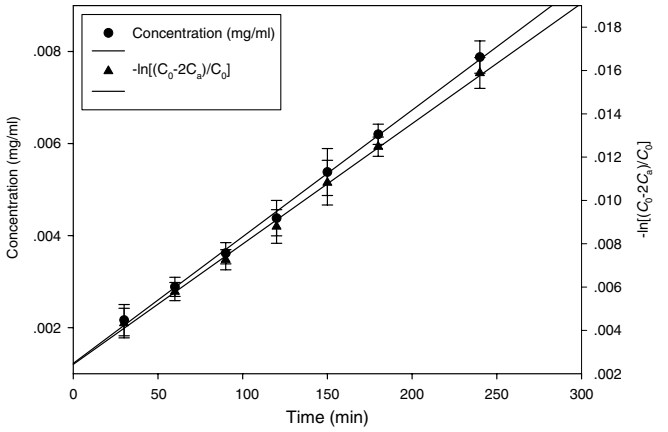

Fig. 2. Diffusion of metoprolol tartrate through isolated EC/HPMC films (containing 24% HPMC and 20% DBS): Plot of the drug concentration in the acceptor compartment and $-\ln[(C_0 - 2C_a)/C_0]$ vs time.

investigated polymer films and P was calculated from these plots.

Fig. 3a illustrates influence of the type of plasticizer on the permeability coefficient of metoprolol tartrate through the isolated EC/HPMC film (containing 24% HPMC and 20% plasticizer (w/w)). The permeability coefficient, P using different types of plasticizer ranged from 1.47 ± 0.02 to 2.09 ± 0.03 (10^{-5} cm/s). This shows that the type of plasticizer has a pronounced effect on the diffusion properties of the drug.

The influence of plasticizers on film permeability very much depends on their chemical nature and polarity as well as on the properties of the polymeric film former and the diffusing species. Further complication exists in that permeation through a film can occur by three mechanisms: diffusion through the polymer matrix itself; diffusion through a network of capillaries caused by the leaching out of an added ingredient to the polymer matrix and diffusion through cracks and imperfections within the film [14].

Hence, it is difficult to predict accurately the effect of plasticizers unless the mechanism of permeation is known. When coated pellets are exposed to the dissolution media, the release of metoprolol tartrate from pellets is affected by factors, such as solubility of plasticizer, temperature, water, pH and so on. Frohoff et al. [15] already found that the relatively water-soluble plasticizer DEP migrates almost completely from the pellet coatings within 0.5–5 h in 0.1 M HCl solution at 37 °C. In the same period of time approximately 70% of DBP was leached. Lecomte et al. also observed the lipophilic DBS was shown to remain within the polymeric films upon exposure to the release media, assuring mechanically resistant coatings during drug release. In contrast, the hydrophilic triethyl citrate leached out of the films, resulting in decreased mechanical resistance and, thus, facilitated pore formation and drug release [16]. The solubility of the plasticizer in water and the polymer–plasticizer interaction may account for such deviation.

An effective tool to modify the drug diffusion kinetics through isolated films is to vary the relative amount of

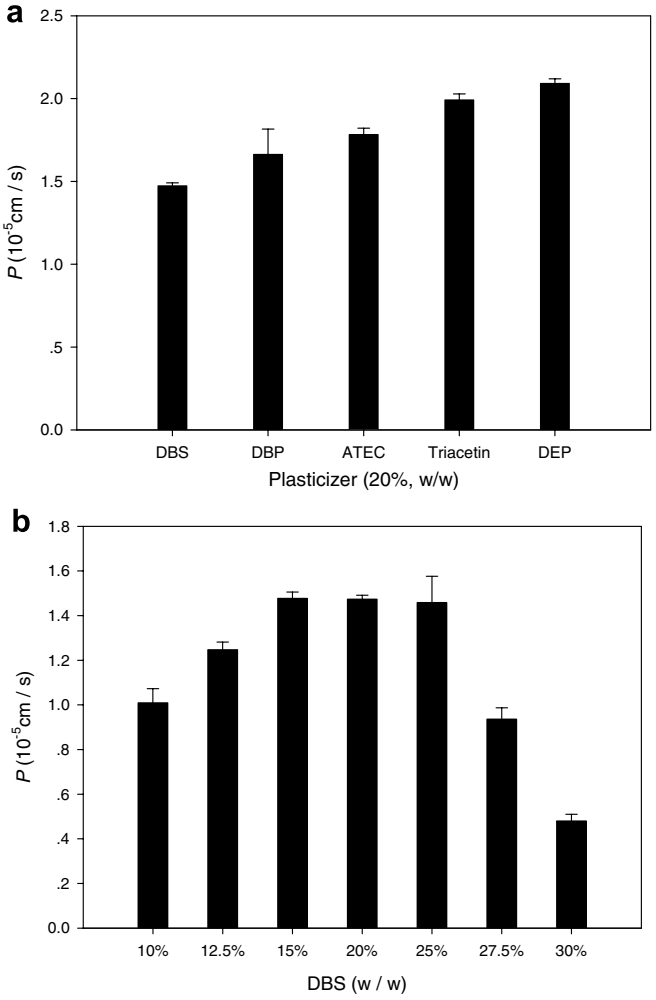

Fig. 3. Influence of plasticizers on the permeability coefficient of metoprolol tartrate through plasticized isolated EC/HPMC films. (a) Films containing 24% HPMC plasticized with different plasticizers (all at 20%, w/w concentration). (b) Films containing 24% HPMC plasticized with DBS (10–30%, w/w).

plasticizer. Fig. 3b shows a significant influence of the level of DBS on the permeability coefficient of metoprolol tartrate through the isolated EC/HPMC films (containing 24% (w/w) HPMC). It was interesting to observe that the permeability coefficient increased with increasing amount of DBS, but when the level of DBS reached 25%, the diffusion of metoprolol tartrate decreased gradually. These observations can be explained by the free volume theory of diffusion [17]. With increasing concentration of plasticizer, the intermolecular attractive forces between the polymer chains are reduced, due to the higher number of plasticizer molecules located between the macromolecules. Thus, the mobility of the polymer chains is increased, resulting in more opportunities for drug diffusion. When the plasticizer in the film increased to a certain amount, the mobility of the polymer chains remained stable, and at the highest concentration, drug diffusion decreased gradually because of the hydrophobic nature of DBS.

EC is a water-insoluble polymer and its degree of swelling is relatively small. However, the swelling of EC films containing HPMC as hydrophilic polymer increased as the amount of HPMC in the EC film increased [18]. Fig. 4 shows the effect of the HPMC level on the diffusion profile of metoprolol tartrate through the isolated EC/HPMC films plasticized with DBS (20%, w/w). The permeability increased at higher HPMC concentrations as upon hydration of the film water channels within the film become the major pathway for drug release [19]. Adding a hydrophilic polymer into an EC film coating may increase the degree of swelling of the film so that the drug permeation rate can be modified. The enhanced permeability can thus be explained by increased hydrophilicity of the films.

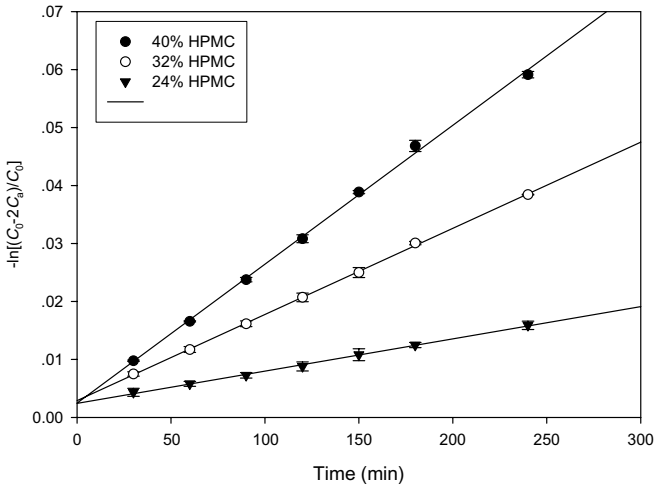

Fig. 4. Influence of HPMC concentration (24–40%, w/w) on the diffusion profile of metoprolol tartrate through the isolated EC/HPMC films plasticized with 20% DBS.

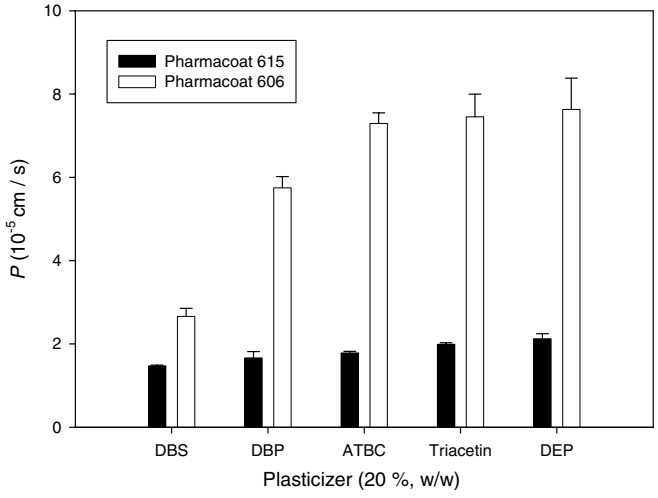

Fig. 5. Influence of type of HPMC on the diffusion profile of metoprolol tartrate through the isolated EC/HPMC films (containing Pharmacoat 615 or Pharmacoat 606 and 20% w/w plasticizer).

The effect of the chain length of HPMC was further investigated. Different viscosity grades of HPMC (Pharmacoat 615 and Pharmacoat 606) were studied. Fig. 5

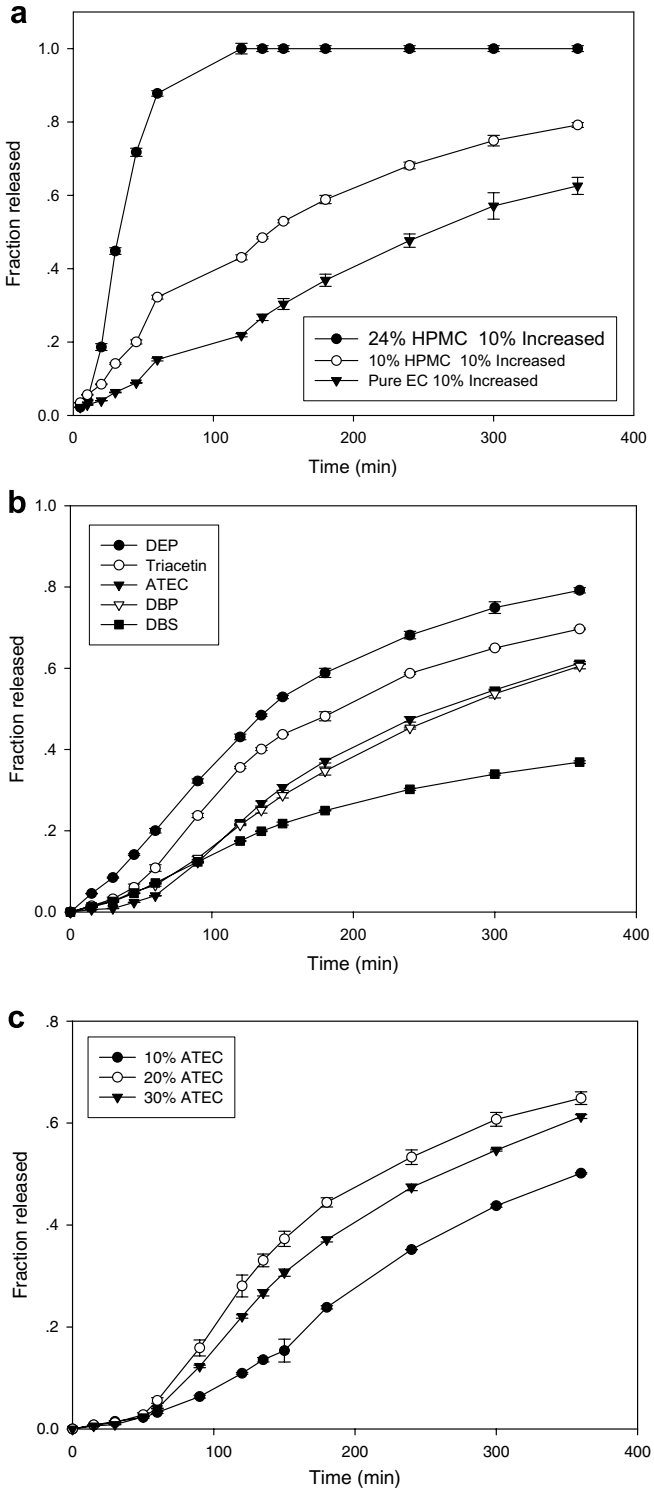

Fig. 6. Dissolution profiles (fraction released) of metoprolol tartrate from EC/HPMC coated pellets in 0.1 M HCl (first 2 h) followed by phosphate buffer pH 6.8 (during the next 4 h). (a) coatings containing HPMC from 0% to 24% and DEP 20% (w/w); (b) coatings containing 10% HPMC and 20% plasticizer; (c) coatings containing 10% HPMC and 10–30% ATEC.

shows that the permeability decreased with increasing viscosity grade of HPMC irrespective of the plasticizer used. With increasing viscosity grade the average molecular weight of the polymer increased, resulting in an increased entanglement of the macromolecules. Thus, the mobility of the polymer chains decreased, reducing the free volume available for diffusion. Hence, the probability for a drug molecule to jump from one cavity to another is decreased, leading to a decreased mass transfer rate.

3.2. Metoprolol tartrate release from coated pellets

In Fig. 6a the release profiles are presented for EC/HPMC coated pellets plasticized with DEP (20%, w/w). Increasing the amount of HPMC in the EC films leads to higher drug release and concurred with the permeability in previous experiments with isolated films.

The influence of plasticizer on the release of metoprolol tartrate from pellets coated with EC/HPMC was studied using different plasticizers (Fig. 6b). The increase of the release rate of metoprolol tartrate from EC/HPMC coated pellets plasticized with the different plasticizers investigated was consistent with the trend of diffusion of Metoprolol tartrate through the EC/HPMC films. This indicated a correlation between properties of casted and sprayed films.

We found that the permeability of metoporolol tartrate through the isolated EC/HPMC films increased with increasing amount of DBS, however, when the level of DBS reached 25%, the permeability of metoprolol tartrate again decreased gradually most likely due to decreased hydrophilicity of the films.

The release of metoprolol tartrate from pellets coated with EC/HPMC and plasticized with ATEC (from 10% to 30%, w/w) showed the same trend (Fig. 6c). When the level of ATEC in the coating reached 20%, the highest release rate was observed. Hence, these results are consistent with those of the diffusion test.

4. Conclusion

The results of the present investigation indicate that drug diffusion through isolated plasticized polymer films can be predictive for the release of film coated dosage forms, despite the fact that the film forming process is different.

References

[1] J.J. Sousa, A. Sousa, M.J. Moura, J.M. Newton, The influence of core materials and film coating on the drug release from coated pellets, Int. J. Pharm. 233 (2002) 111–122.
[2] S. Vaithiyalingam, M.A. Khan, Optimization and characterization of controlled release multi-particulate beads formulated with a customized cellulose acetate butyrate dispersion, Int. J. Pharm. 234 (2002) 179–193.
[3] N. Rahman, K.H. Yuen, N.A. Khan, J.W. Wong, Drug-polymer mixed coating: a new approach for controlling drug release rates in pellets, Pharm. Dev. Technol. 11 (2006) 71–77.
[4] J.W. McGinity, Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, second ed., Marcel Dekker, New York, 1997.
[5] G. Cole, J. Hogan, A. Michael, Mechanical properties of film coats: tests for the assessment of film mechanical properties, in: Pharmaceutical Coating Technology, Taylor & Francis, London, 1995.
[6] S.C. Porter, The effect of additives on the properties of an aqueous film coating, Pharm. Technnol. 4 (1980) 67–75.
[7] G.S. Rekhi, S.S. Jambhekar, Ethylcellulose-a polymer review, Drug Dev. Ind. Pharm. 21 (1995) 61–77.
[8] M.E. Aulton, M.H. Abdul-Razzak, J.E. Hogan, The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems. Part 1: the influence of plasticizers, Drug Dev. Ind. Pharm. 7 (1981) 649–668.
[9] F.W. Billmeyer, Polymer processing, plastic technology, in: Textbook of Polymer Science, third ed., Wiley-Interscience, New York, 1984.
[10] A.H. Kibbe, Handbook of Pharmaceutical Excipients, third ed., American Pharmaceutical Association and Pharmaceutical Press, Washington DC, 2003.
[11] J.H. Guo, An investigation into the formation of plasticizer channels in plasticized polymer films, Drug Dev. Ind. Pharm. 20 (1994) 1883–1893.
[12] E. Hamed, A. Sakr, Effect of curing conditions and plasticizer level on the release of highly lipophilic drug from coated multiparticulate drug delivery system, Pharm. Dev. Technol. 8 (2003) 397–407.
[13] G. Van den Mooter, C. Samyn, R. Kinget, Characterization of colon-specific azo polymers: a study of the swelling properties and the permeability of isolated polymer films, Int. J. Pharm. 111 (1994) 127–136.
[14] A.T. Florence, Plasticizers used in film coating, in: Materials Used in Pharmaceutical Formulation, Belgrave Square, London, 1984.
[15] M.A. Frohoff-Hülsmann, B.C. Lippold, J.W. McGinity, Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films, Eur. J. Pharm. Biopharm. 48 (1999) 67–75.
[16] F. Lecomte, J. Siepmann, M. Walther, Polymer blends used for the aqueous coating of solid dosage forms: importance of the type of plasticizer, J. Control. Release 99 (2004) 1–13.
[17] L.T. Fan, S.K. Singh, Controlled Release: A Quantitative Treatment, Springer-Verlag, Berlin, 1989.
[18] J. Hjartstam, T. Hjertberg, Swelling of pellets coated with a composite film containing ethyl cellulose and hydroxypropyl methylcellulose, Int. J. Pharm. 161 (1998) 23–28.
[19] Y.M. Sun, C.C. Chang, W.F. Huang, H.C. Liang, Fluidized-bed spray coated porous hydrogel beads for sustained release of diclofenac sodium, J. Control. Release 47 (1997) 247–260.