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Research Article

Model Drug as Pore Former for Controlled Release of Water-Soluble Metoprolol Succinate from Ethylcellulose-Coated Pellets Without Lag Phase: Opportunities and Challenges

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Abstract. The objective of the present study was to evaluate the feasibility of using model drug metoprolol succinate (MS) as a pore former to modify the initial lag phase (*i.e.*, a slow or non-release phase in the first 1–2 h) associated with the drug release from coated pellets. MS-layered cores with high drug-layering efficiency (97% *w*/*w*) were first prepared by spraying a highly concentrated drug aqueous solution (60% *w*/*w*, 70°C) on non-pareils without using other binders. The presence of MS in ethylcellulose (EC) coating solution significantly improved the coating process by reducing pellets sticking, which often occurs during organic coating. There may be a maximum physical compatibility of MS with EC, and the physical state of the drug in the functional coating layer of EC/MS (80:20) was simultaneously crystalline and non-crystalline (amorphous or solid molecule solution). The lag phase associated with hydroxypropylcellulose (HPC) as a pore former was not observed when MS was used as a pore former. The drug release from EC/MS-coated pellets was pH independent, inversely proportional to the coating levels, and directly related to the pore former levels. The functional coating layer with MS as a pore former was not completely stabilized without curing. Curing at 60°C for 1 day could substantially improve the stability of EC/MS-coated pellets. The physical state of the drug in the free film of EC/MS (85:15) changed partially from amorphous to crystal when cured at 60°C for 1 day, which should be attributed to the incompatibility of the drug with EC.

KEY WORDS: coated pellets; curing treatment; lag phase; metoprolol succinate; pore former.

INTRODUCTION

Ideal ethylcellulose (EC)-coated pellets should release the drug upon entering the target environment and allow large drug loading to minimize the dosage size with a minimum number of ingredients (1,2). However, a slow/non-drug-release phase (lag phase) prior to the constant release phase and declining rate phase was often observed from ethylcellulose-coated pellets (3–5). It is known that the initial drug release from coated pellets is through diffusion of the dissolved drug from the core through the polymeric coating (6). After coated pellets are introduced into a release medium, the medium penetrates through the polymeric coating, accumulates inside the formulation to solubilize the drug or excipients, and builds up a hydrostatic pressure gradually which drives the drug release. Therefore, an initial lag phase is inevitable before the formation of sufficient hydrostatic pressure (7). The lag phase leads to a slow drug onset, especially when the drug has a short biological half-life (8). For this kind of drug, the drug concentration in the blood will decline rapidly over time unless a means is found to provide continued absorption of the drug at a rate that is fast enough to overcome the clearance rate at a therapeutic blood level (9).

Several formulation techniques have been evaluated to reduce the lag phase, but each has its own drawback. One technique involves adding partial immediate-release drug doses in the formulation, but additional processing steps are required that lead to two different release rates, which may be undesirable for mass production (9,10). Thin coatings around the dosage form is an alternative approach to provide high-permeability and fast initial release (11,12). However, the thin coating lacks strength and often bursts in use or provides insufficient protection to the dosage form which becomes vulnerable to damage during handling (2). Adding water-soluble particles/material as a pore former in the polymeric coating layer is the most popular and widely used approach to increasing the coating permeability (13,14). After administration of the dosage form, the pore former dissolves and forms pores or channels in the coating, or leaves the polymer coating micro-porous so that the drug-release rate is increased (15). The hydrophilicity and levels of the pore formers and the

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coating levels mainly govern the lag phase and the release rate (16).

To date, different pore formers in the release-controlling membranes have been evaluated (17), such as inorganic agents including dibasic calcium phosphate (15), or water-soluble organic agents including D-mannitol (18), lactose (19), dextran (20), polyethylene glycol (PEG) (21), glycerin (22), and dibutyl phthalate (23), or water-soluble polymers such as hydroxypropyl methylcellulose (HPMC) (13), polyvinylpyrrolidone (PVP) (24), poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG) (14), and hydroxypropylcellulose (HPC) (5,25). Among those pore formers, water-soluble polymers are also soluble in the organic coating solution and compatible with the polymeric coat materials and therefore are most commonly used (26,27). However, those water-soluble polymers could not completely leach out from the polymeric coatings and do not create well-defined porous structures (16,28). In addition, the coating process is often not smooth due to the electrostatic charge effect in the presence of the hydrophilic polymer in the coating solution (29). Hence, searching for alternative pore formers for polymeric film coating is valuable.

In the present study, the model drug was used as a pore former in order to modify the lag phase and increase overall drug loading. Metoprolol succinate (MS), a β-blocker clinically used to treat hypertension, angina pectoris, and arrhythmia, was chosen as the model drug because of its good solubility in water (15.7% at 25°C, pH 5.5) (30) and short half-life (3–4 h) (31). MS-layered cores were first prepared by layering a highly concentrated drug solution without any binder to eliminate the possible effects of excipients in the drug layer on the drug release of EC-coated pellets. To understand how model drug MS in the coating layer improves the initial drug release, the drug-layered cores were also coated with EC using HPC as a pore former for comparison. The physical state of the drug in the functional coating layer and the effects of such formulation factors as the pore former levels and coating levels on drug release were studied. The curing effects of EC/MS-coated pellets and EC/MS free film were further investigated.

MATERIALS AND METHODS

Materials

Metoprolol succinate (99.5% purity, Beijing Jiashi Lianbo Medical Development, Co. Ltd., Beijing, China), non-pareils (sugar sphere, 212–355 and 600–710 μm, Hangzhou Gaocheng Biotech&Health, Co. Ltd., Hangzhou, China), ethylcellulose (EC, Ethocel standard 10 premium, Dow Chemical, Wilmington, USA), hydroxypropyl cellulose (HPC, grade LF, Hercules Incorporated Co., Wilmintong, USA), and ethanol (95%, Beijing Zhenyu Minsheng Pharmaceutical, Co. Ltd., Beijing, China) were used as received. Other chemicals and reagents were of analytical grades.

Preparation and Characterization of Drug-Layered Cores

Preparation of Drug-Layered Cores

Drug layering was performed in a fluidized bed coater (GPCG-1, Glatt GmbH, Binzen, Germany) using a bottom spray technique. The highly concentrated solutions of metoprolol succinate (25, 45, or 60%, *w*/*v*) were prepared in hot water (30, 50, or 70°C, respectively) and sprayed on non-pareils (212–355 μm, 400 g) until a drug loading of 80% (*w*/*w*) was achieved. The process parameters were as follows: inlet temperature 70°C, product temperature 46–52°C, outlet temperature 43–48°C, air flow rate 40–60 m^3/h, nozzle diameter 0.8 mm, spray pressure 1.5 bar, and spray rate 20 ml/min. The drug was first dissolved in water at 70°C within 40 min before layering onto 400 g of non-pareils, without using a binder. During the drug-layering process, the concentrated drug solution was maintained at 30, 50, or 70°C, respectively, to prevent drug recrystallizating in the passageway. After layering, the drug-layered cores were further dried at 70°C for 15 min in the coating chamber and subsequently transferred out of the fluid-bed mesh screening (mesh 30/40).

Drug-Layering Efficiency

Drug-layering efficiency (%) was calculated by comparing the actual drug content with the theoretical drug content. The actual drug content in drug-layered cores was determined by solubilizing drug-layered cores in water and measuring UV spectrophotometrically (λ=274 nm; UV-1750, Shimadzu, Japan). The theoretical drug content was equivalent to the amount of drug in the drug solution.

Moisture Content

Moisture content of the drug-layered cores was determined as a percentage of constant weight loss upon drying at 105°C for 2 h. Three parallel determinations were performed in each case.

Surface Morphology and Particle Size

The surface morphology, particle size, and drug layer thickness of the drug-layered cores were characterized using an S-4800 Analytical Electron Microscope (Hitachi, Japan). The samples were loaded onto the copper sample holder, sputter coated with carbon followed by gold in a vacuum using a sputter coater (E-1010, Hitachi, Tokyo, Japan), and then observed under an excitation voltage of 15 kV.

Preparation and Characterization of Coated Pellets

Preparation of Coated Pellets

Firstly, drug-layered cores were coated with EC/HPC (80:20) solution in 95% *w*/*w* ethanol in a GPCG-1 fluidized bed coater using bottom spray. The EC/HPC solution was prepared by dissolving 8.9% (*w*/*v*) EC and 2.2% (*w*/*v*) HPC LF in 95% *w*/*w* ethanol and sprayed onto drug-layered cores (400 g) until the weight gains of 25, 37.5, and 50% *w*/*w* of the drug-layered cores were achieved. The coating conditions were as follows: inlet temperature 45°C, product temperature 38–39°C, outlet temperature 36–37°C, air flow rate 50–60 m^3/h, nozzle diameter 0.8 mm, spray pressure 1.5 bar, and spray rate 14 ml/min.

Secondly, model drug MS replaced HPC in the EC solution as a pore former. The EC/MS (90:10, 85:15, or 80:20)

solutions were prepared by dissolving 8.9% (*w*/*v*) EC and predefined amounts of MS in 95% *w*/*w* ethanol and sprayed onto the drug-layered cores (400 g) until the predetermined weight gains were achieved. The coating conditions were similar to the aforementioned EC/HPC coating, but at a faster spray rate of 18 ml/min.

Finally, EC/MS (80:20) with a weight gain of 50% (*w*/*w*) was also coated on large non-pareils (600–710 μm) without a drug layer in order to evaluate the physical state of the drug in the EC/MS coating layer.

After coating, the pellets were further fluidized at 45°C for 15 min in the chamber to reduce the residual solvents prior to collection in a tray.

Coating Efficiency

The coating efficiency (%) was calculated by dividing the actual weight gain of the coated pellets by the theoretical weight gain and multiplying it by 100.

Surface Morphology and Particle Size

The surface morphology, particle size, and coating layer thickness of coated pellets were characterized by the abovementioned SEM.

Physical State of Drug in Coating Layer

To evaluate the physical state of the drug in the EC/MS coating layer, drug MS, non-pareils, EC, physical mixture (PM) of EC, MS, and non-pareils (80:20:200), and 50% EC/MS (80:20)-coated pellets without a drug layer were analyzed by differential scanning calorimetry (DSC) (Q2000 instrument, TA, New Castle, Germany). The samples were milled into a fine powder and analyzed over a temperature range of 40–200°C at a rate of 10°C/min under a nitrogen atmosphere in the DSC instrument.

In Vitro Drug Release

In vitro drug release from the coated pellets was studied in 500 ml of water using the USP 35 paddle method (37°C, 50 rpm, $n=3$; SR8PLUS dissolution tester, Hanson, California, United States). At predetermined time intervals, 5-ml samples were withdrawn, filtered through a 0.45-μm filter, and analyzed UV spectrophotometrically ($\lambda=274$ nm; UV-1750, Shimadzu, Japan).

In order to study the effects of *in vitro* release conditions on drug release, *in vitro* drug release of 30% EC/MS (85:15)-coated pellets was also carried out in different release media (water, 0.1 M HCl pH 1.2, and 0.2 M phosphate buffer solution (PBS) pH 6.8) at different paddle rotation speeds (50, 100, and 150 rpm).

Curing Effect and Stability

To completely stabilize the functional coating film, 50% EC/MS or EC/HPC (80:20)-coated pellets were subjected to curing at 60°C for 0, 1, 2, and 5 days in a petri dish in a cabinet. The cured samples were evaluated for appearance and *in vitro* drug release.

EC/MS (80:20)-coated pellets of 50% with or without curing were packed into 0.04-mm-thick strips of aluminum foil laminated with PVC and stored at 40°C and 75% relative humidity (RH). After 6 months of storage, the samples were evaluated for appearance and *in vitro* drug release.

Preparation and Characterization of Free Film of EC/MS

To explain the curing effect of EC/MS-coated pellets, the free film of EC/MS (85:15 or 80:20) was prepared and characterized. First, the EC/MS solution was prepared by dissolving 8.9% (*w*/*v*) EC and 1.6 or 2.2% (*w*/*v*) MS in 95% *w*/*w* ethanol and stirred for at least 4 h to ensure that all substances were in the solution. The resulting solution was cast on Teflon plates (14×14 cm^2) and dried in an oven at 40°C until constant weight was achieved. The obtained free film of EC/MS (85:15) was further subjected to curing at 60°C for 1 day in a petri dish in a cabinet to simulate the curing mechanism of EC/MS coating film.

The photo of the free film of EC/MS with or without curing was taken with an optical light microscope (magnification ×400) (ECLIPSE E100, Nikon, JAPAN) linked to a digital camera (D5100, Nikon, Japan).

The physical state of the drug in the free film of EC/MS with or without curing was analyzed by X-ray powder diffraction (XRD) (D8-advance, Bruker, Germany). Nickel-filtered Cu-Kα radiation operated at 40 kV and 20 mA was used as the radiation source, and the free film, crushed to a fine powder before analysis, was scanned at a speed of $d°/2\theta$/min.

Statistical Analysis

All experiments were performed in triplicate. Statistical analysis conducted was with SPSS v 13.0 software.

RESULTS AND DISCUSSION

Drug Layering

The drug-layering process is identified as a critical step in the manufacturing process, as this step directly impacts not only the smooth surface and loading efficiency of drug-loaded cores but also the coating efficiency and uniformity of outer polymeric coating and the reproducibility of drug release from obtained pellets (32,33). Therefore, irrespective of the physical–chemical properties of drugs, a binder is often used during

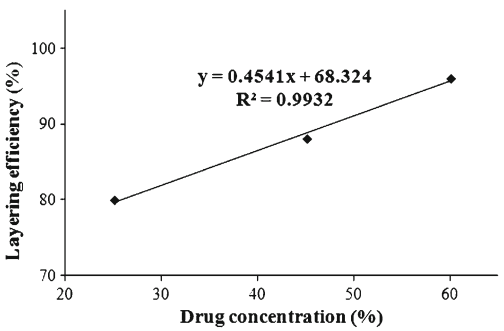

Fig. 1. The layering efficiency of the binder-free drug-layering process as a function of drug concentration

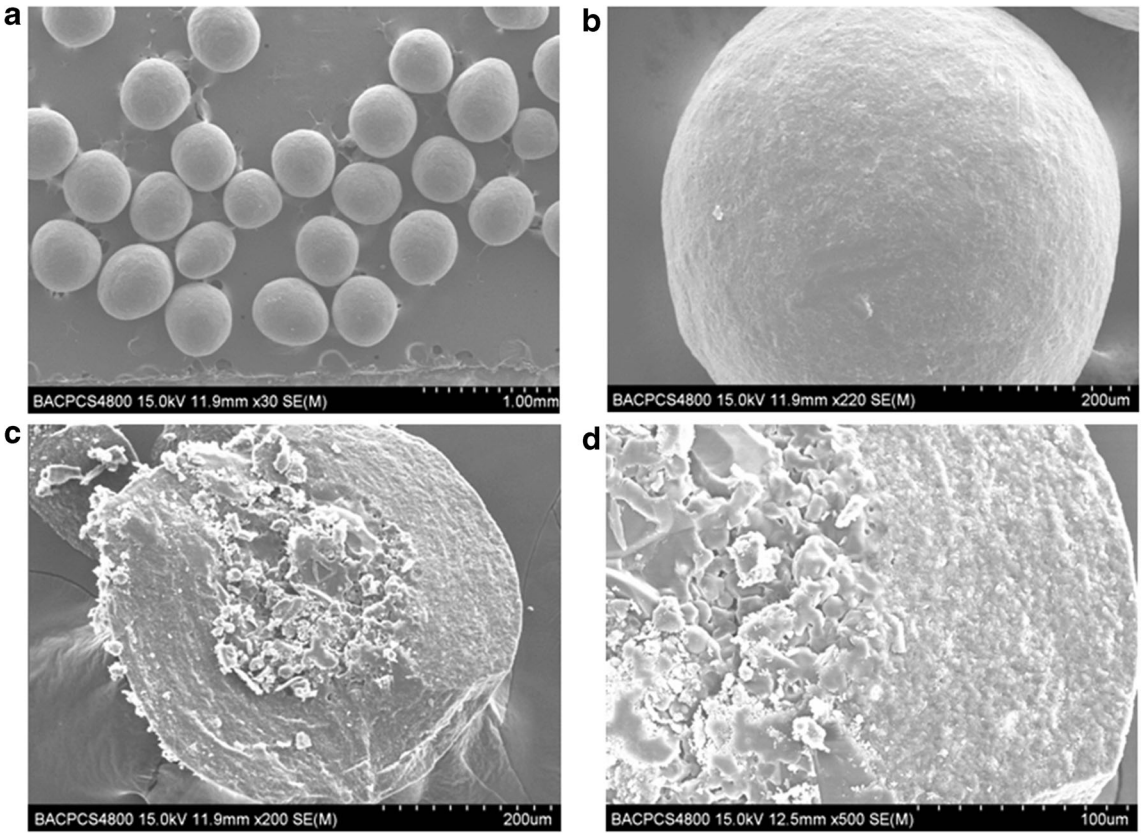

Fig. 2. Morphology of (**a** ×30; **b** ×220) the surface and (**c** ×200; **d** ×500) the cross-section of binder-free MS-layered cores under a scanning electron microscope

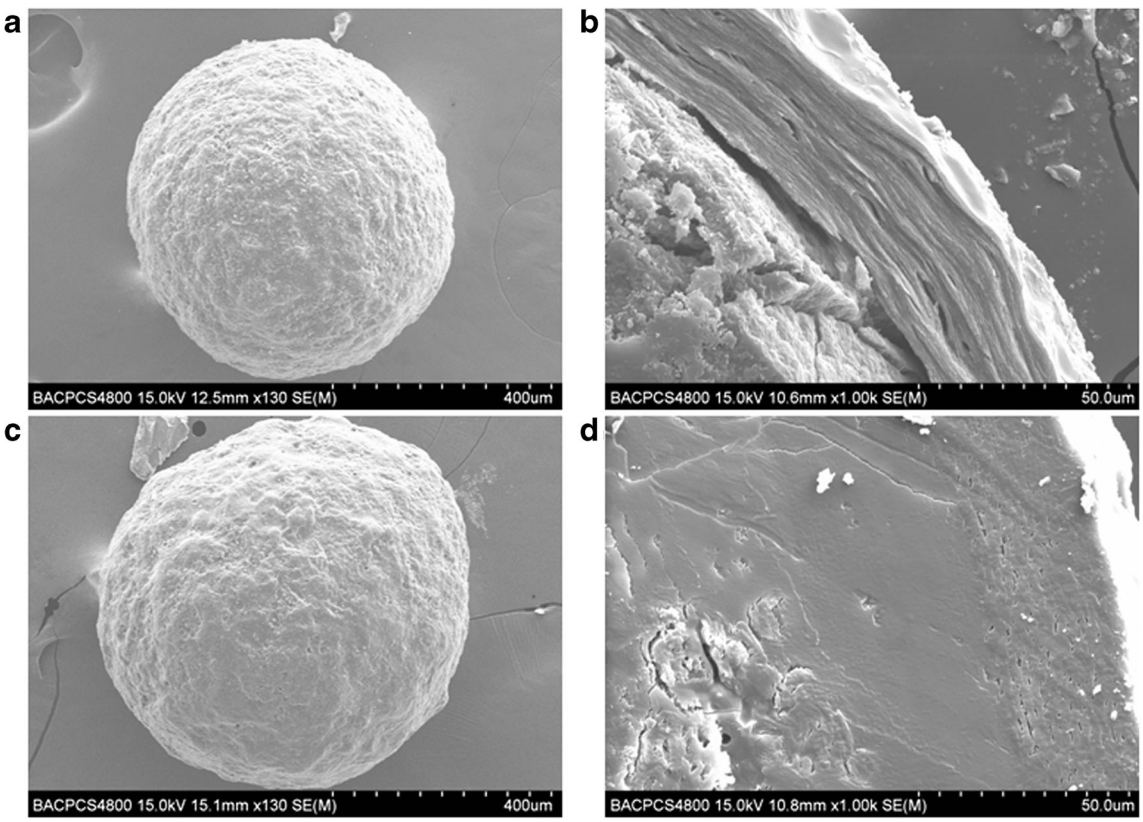

Fig. 3. Morphology of (**a** or **c** ×130) the surface and (**b** or **d** ×1,000) the cross-section of 50% EC/MS- or EC/HPC (80:20)-coated pellets under a scanning electron microscope

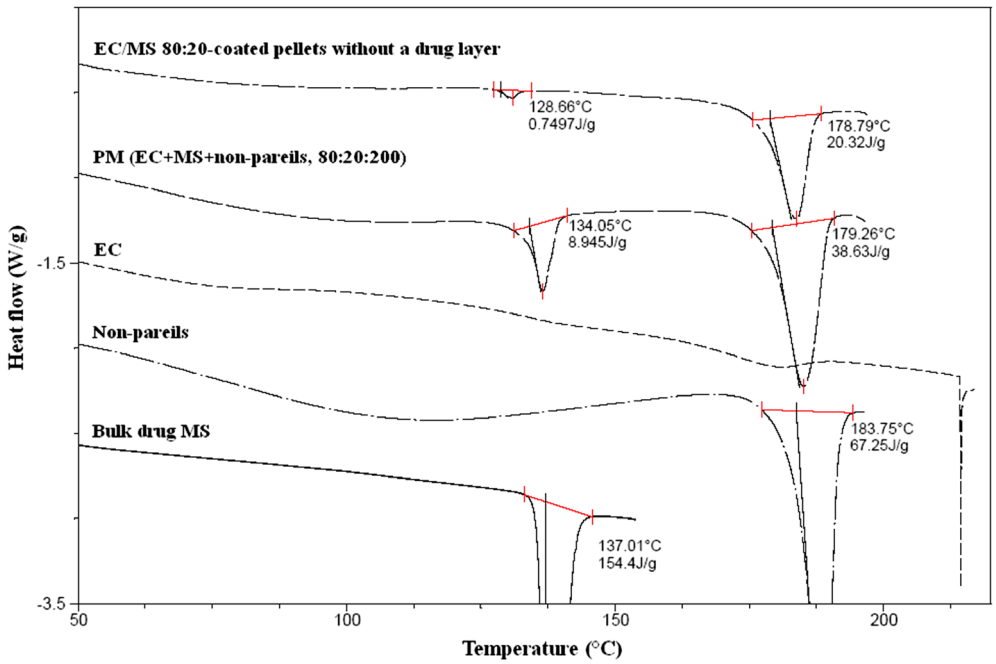

Fig. 4. DSC thermograms of 50% EC/MS (80:20)-coated pellets without a drug layer, the physical mixture (PM) of EC, MS, and non-pareils (80:20:200), EC, non-pareils, and bulk drug MS

drug layering to improve the drug-layering efficiency and the surface smoothness of drug-layered cores. The disadvantages of incorporating a binder in the drug layer are the slow-layering process due to the electrostatic charge effect, relatively low drug load, and influence on *in vitro* drug release (29).

Interestingly, the present binder-free drug-layering approach, employing a highly concentrated drug solution of 60% *w*/*v* at 70°C without using other binders, enabled a high drug-layering efficiency (97%), and the layering efficiency was proportional to the drug concentration (Fig. 1). The loss of 3% product might be due to the loss of layering solution to exhaust. The moisture content of the drug-layered cores was below 1%, which would not contribute to the product loss. Lowering the drug concentration (45% at 50°C and 25% at 30°C) led to lower drug-layering efficiency (88 and 80%) and longer process time and more fines were generated. It is likely that the drug functioned as a binder at a high concentration. A similar investigation was also reported recently that layering diltiazem hydrochloride at a high concentration on sugar cores with low binder content and the binder levels did not impact the drug-loading efficiency (34).

More importantly, the binder-free drug-layered cores had a spherical form and a smooth surface, and the drug layer was dense, homogenous, and uniform (Fig. 2). The particle sizes of drug-layered cores ranged from 470 to 540 μm while the drug layer ranged from 123 to 130 μm because of the high drug loading (80% *w*/*w*). The smooth surface of drug-layered cores is essential to the uniformity of outer EC coating and the reproducibility of drug release from the obtained pellets (35,36).

Therefore, the current drug-layering approach has the following advantages: (1) simple formulation without other excipients, (2) high-layering efficiency (97%), (3) good morphology, and (4) short process time.

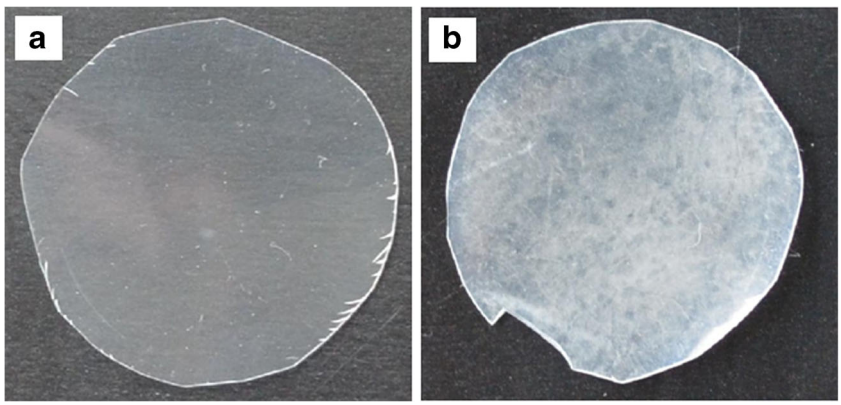

Fig. 5. Appearance photo of the free film of **a** EC/MS (85:15) and **b** EC/MS (80:20)

Effect of Pore Former Types on Coating Process (HPC *vs.* MS)

During the coating process, sticking of the coated substrates often occurs due to the tackiness and viscosity of polymer coating solutions (15). This tackiness causes a tremendous handling problem as the coated substrates stick to each other or on the coating chamber. Sometimes, irreversible agglomeration of pellets or loss of the complete batch can occur, especially at high product temperature and/or using high plasticizer content in the coating formulation. Therefore, anti-tacking agents, such as simethicone, talc, and magnesium stearate, are usually added in polymer solutions in order to prevent agglomeration (37,38). However, the additives might modify drug release from the coated pellets in terms of the swelling behavior of the coated pellets in water and the potential additive-polymer interactions (39,40).

It was a surprise to find that in the present study, model drug MS as a pore former greatly reduced pellet sticking and the entire coating process went smoothly even at a faster spray rate (18 ml/min), regardless of pore former levels ranging from 10 to 20% in the coating layer. However, sticking during the coating process was indeed observed when HPC was used as a pore former regardless of inlet air dew point (5–15°C). Part of the coated substrates adhered to the bottom of the partition column, especially when the spray rate was above 14 ml/min.

In general, the tackiness of polymer coating solution results from the interaction between polymer chains (41). The anti-tack effect of model drug MS as a pore former in EC coating solution should be attributed to its ability to interact with the EC chains. Due to the small molecule nature, MS is easy to be interspersed between the EC polymer chains, which results in a net reduction of the interaction strength between the EC polymers. So, MS serves as an anti-tacking agent during the coating process.

Additionally, using model drug MS as a pore former had no significant effect on the coating efficiency and morphology of coated pellets (Fig. 3). The coating efficiency of 50% EC/MS (90:10, 85:15, or 80:20)-coated pellets (93, 94, or 94%, respectively) was comparable with that of 50% EC/HPC (80:20)-coated pellets (93%). Particle size distributions (580~640 μm) and coating layer thickness (28~30 μm) were similar at the 50% *w*/*w* weight gain and 20% pore former level. The surface of coated pellets, whether model drug MS or HPC was used as a pore former, appeared slightly rougher than that of the drug-layered cores (Fig. 2), which may be attributed to higher EC concentrations (8.9% *w*/*w*) in the coating solution. Generally, phase separation between EC and the pore former (HPC or MS) occurs during film drying process, and subsequently, EC- and HPC- or drug-rich domains are formed (42). The higher the EC concentration, the longer time it takes to lock the film structure and the rougher the surface of the obtained pellets eventually is.

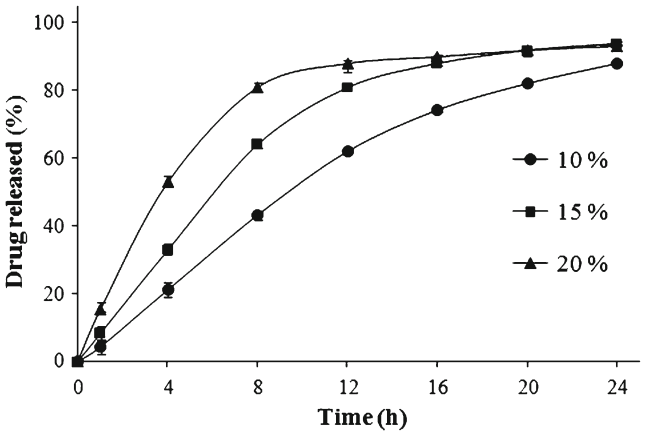

Fig. 7. Effect of pore former MS level of on MS release in water from 30% EC/MS-coated pellets without curing

Drug physical states in the coating layer were evaluated using thermal analysis in the present study. EC/MS-coated pellets without a drug layer were prepared by spraying EC/MS coating solution directly onto non-pareils to eliminate the impact of the drug layer. Figure 4 showed the DSC thermograms of 50% EC/MS (80:20)-coated pellets without a drug layer, the physical mixtures (PM) (MS/EC/non-pareils, 80:20:200), non-pareils, EC, and bulk drug MS. Bulk drug MS produced a large endothermic peak with an intensity of 154.4 J/g at 137°C in consistent with its melting point of 136–137°C, showing that the drug is crystalline in nature. As expected, EC or non-pareils did not display any thermal event around this temperature. When compared to that of the PM (8.9 J/g), the intensity of the characteristic peak of MS acting as a pore former in the coating layer became low greatly (0.75 J/g), suggesting that the physical state of the drug in the EC coating layer was simultaneously crystalline and non-crystalline (amorphous or solid molecular solution). There may be a maximum physical compatibility of MS with EC demonstrated further by the appearance of EC/MS free film (Fig. 5). When the drug content was below 15% in EC/MS free film, the drug was compatible with EC and in a non-crystalline state (amorphous or solid molecular solution) (Fig. 5a). Further increasing the drug content to 20% in EC/MS

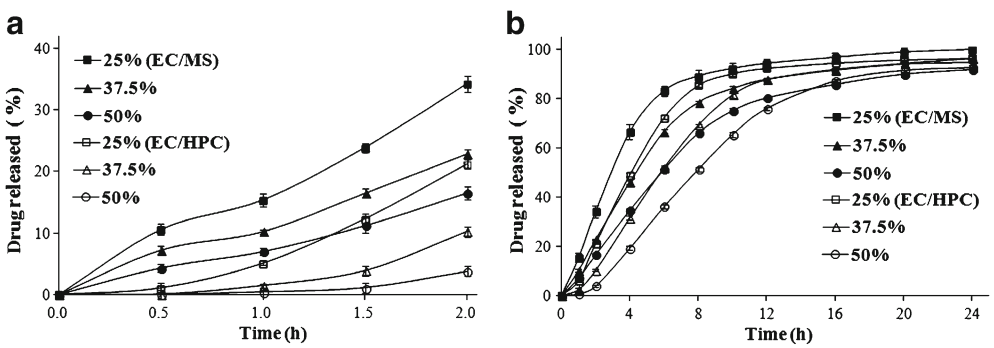

Fig. 6. Effect of pore former type on MS release in water from EC/MS or EC/HPC (80:20)-coated pellets **a** within 2 h or **b** within 24 h

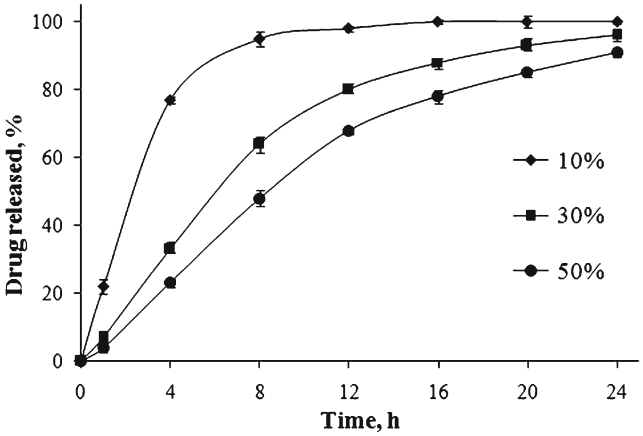

Fig. 8. Effect of coating level of on MS release in water from EC/MS (85:15)-coated pellets without curing

free film caused a phase separation of drug and EC (Fig. 5b). The drug above this amount was crystallized.

Effect of Pore Former Types on Drug Release (HPC *vs.* MS)

The overall release profiles of the drug from EC/HPC- or EC/MS-coated pellets with different coating levels were compared except for a marked difference in the initial release phase of 1–2 h (Fig. 6). The lag phase with EC/HPC coating disappeared when drug MS was used as a pore former (20% level). More than 10, 7, or 4% of the drug was released in the initial 0.5 h from 25, 37.5, or 50% EC/MS (80:20)-coated pellets, respectively (Fig. 6a). Contrarily, a low or no drug release happened in the initial 0.5 h from the coated pellets with HPC as a pore former regardless of the coating level. The lag phase was more than 1 h at the 37.5~50% coating levels. The films were initially not permeable to the drug investigated, indicating that the lag phase was determined by the time of pore forming in the film due to HPC leaching and that the drug was released mainly through the water-filled pores (43).

In comparison to HPC, model drug MS was easily leached out from the film because of its small molecular weight and good water solubility, creating pores quickly and abolishing the lag time. Hence, the rate at which the water-soluble material was leached out of the film (leaching rate)

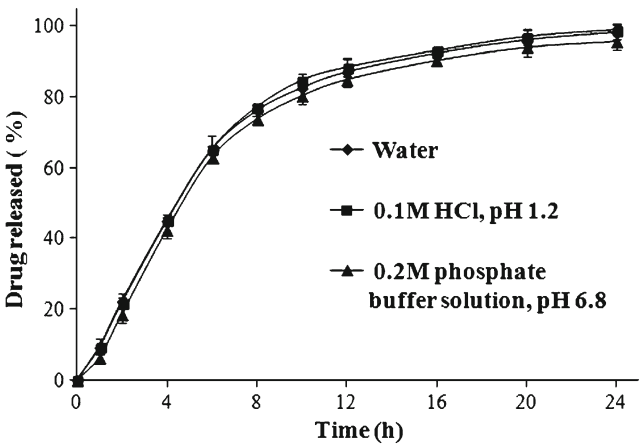

Fig. 9. Effect of type and pH of the release media on MS release from 30% EC/MS (85:15)-coated pellets without curing

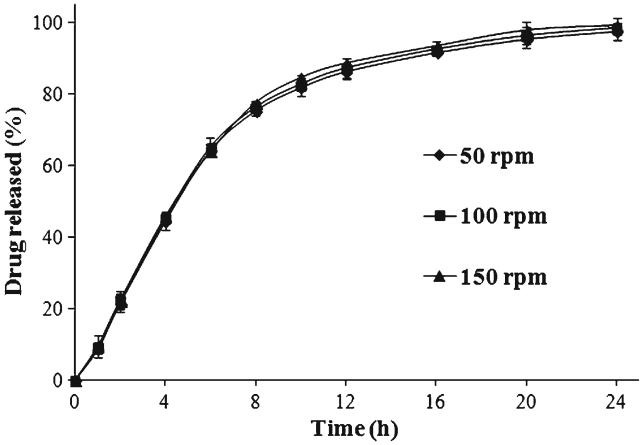

Fig. 10. Effect of paddle rotation speed on MS release in water from 30% EC/MS (85:15)-coated pellets without curing

was not only influenced by the film thickness (5) but also closely related to the property of the pore former in the film (15). Overall, the drug release from EC/MS-coated pellets was faster compared to EC/HPC-coated pellets.

Effect of Pore Former MS Levels on Drug Release

The effect of the pore former level in the coating layer was evaluated by varying the ratio of EC/MS from 90:10, 85:15, to 80:20 at a fixed coating level of 30% *w*/*w*. Drug release increased with the level of the pore former (MS) (Fig. 7). Of the drug, 80% was released after 8, 12, and 20 h with 20, 15, and 10% MS present in the coating layer. As the level of the pore former increased, the membrane became more porous after coming into contact with the aqueous environment, resulting in faster drug release from both the coating layer and the drug layer (11). In a word, 10 to 20% (*w*/*w*) of MS as a pore former created sufficient pores for drug release and resulted in an approximately zero-order release pattern up to 8, 12, and 16 h, respectively.

It was reported that the burst strength was inversely related to the initial level of the pore former in the membrane (12). By increasing the pore former level, the membrane became more porous after exposure to water, leading to decreased strength. Therefore, the effect of MS (as a pore former) levels on EC film strength should be further evaluated,

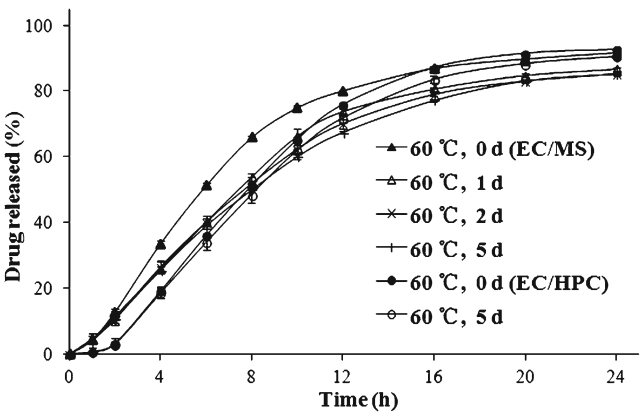

Fig. 11. Effect of curing conditions on MS release in water from 50% EC/MS or EC/HPC (80:20)-coated pellets

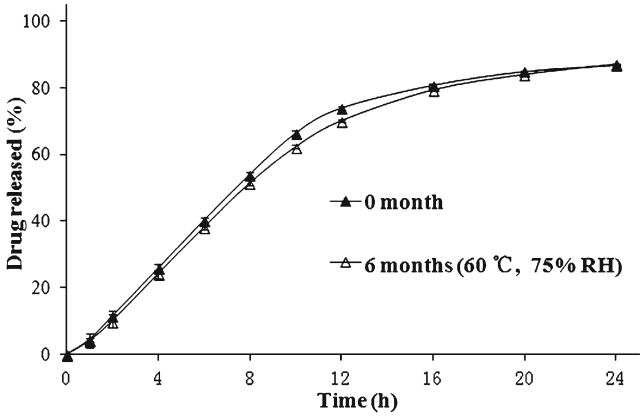

Fig. 12. The release profiles in water of MS from 50% EC/MS (80:20)-coated pellets without or with curing after 0 or 6 months of storage at 40°C and 75% RH

though no bursting of the systems was observed during the dissolution test in any of the formulations.

Effect of Coating Level on Drug Release

The effect of coating levels on drug release was evaluated at 10, 30, and 50% with the pore former MS level at 15% *w*/*w* of the coats. Release of MS from coated pellets as a function of coating levels is shown in Fig. 8. Drug release decreased with an increase in coating levels and appeared more sensitive to the coating levels ranging from 10 to 30%. No lag phase was observed even at 50% coating levels. Especially, an approximately zero-order release pattern was obtained up to 8 h at 30% and up to 12 h at 50% coating level, respectively. Hence, coating levels and pore former levels are the most important determinants of drug release from the coated pellets.

Effect of Release Conditions (pH and rpm) on Drug Release

Ideal-controlled release dosage forms should release the drug independent of the release conditions, *e.g.*, buffer pH and mechanical shear force. This will minimize the variability and bioavailability *in vivo* (44). In this study, drug release from 30% EC/MS (85:15)-coated pellets without curing was conducted in three different dissolution media (water, 0.1 M HCl pH 1.2, and 0.2 M PBS pH 6.8) at 100 rpm and at three different paddle rotation speeds (50, 100, and 150 rpm) in water and the drug-release profiles are shown in Figs. 9 and 10. The results showed that MS release from coated pellets was pH independent in the range of pH 1.2 to pH 6.8 (Fig. 9). In addition, MS release was also immune to the paddle rotation speed in the range of 50–150 rpm (Fig. 10).

Curing Effect of EC/MS-Coated Pellets

For organic coating systems, the formation of the functional coating film does not usually involve further coalescence of the polymer particles associated with the aqueous colloidal polymer dispersions, and thus, no post coating enhancement of the film formation is necessary (45). Figure 11 showed the release profiles of MS from 50% EC/HPC or EC/MS (80:20)-coated pellets prepared from the organic coating system under different curing conditions.

As expected, drug release from EC/HPC-coated pellets was almost independent of curing, and curing at 60°C for 5 days did not change the drug release compared to the uncured pellets. However, when model drug MS was used as a pore former, drug release substantially decreased after 1 day curing at 60°C and then slightly decreased by further curing for 2 and 5 days. The results indicated that the coating film with MS as a pore former was not completely stabilized without curing. One-day curing at 60°C was sufficient to stabilize the coating layer, which was validated by the results of accelerated stability tests (Fig. 12). The pellets cured at 60°C for 1 day exhibited pretty much

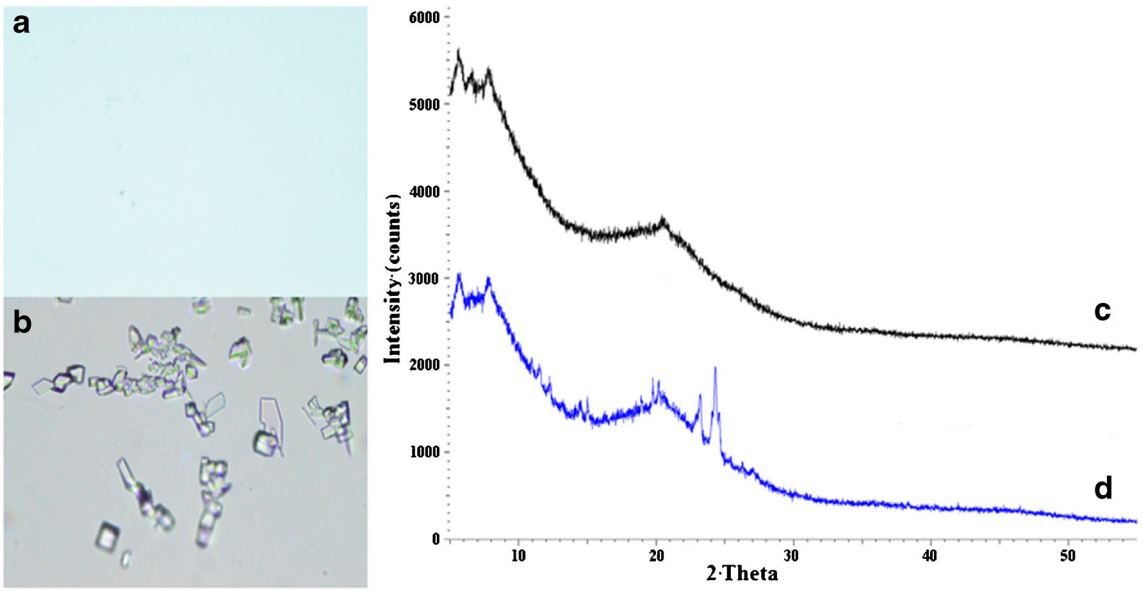

Fig. 13. **a** or **b** The appearance photo and **c** or **d** X-ray powder diffraction (XRD) of the free film of EC/MS (85:15) without or with curing

the same drug-release profiles as $T=0$ after 6-month storage at 40°C and 75% RH.

Given the fact that curing causes a reduction of the drug-release rates for EC/MS-coated pellets prepared from the organic coating system, it is likely that the precise mechanism responsible for the formation of EC/MS coating film from organic polymer solution cannot be fully clarified by the evaporation of the organic solvent. The physical state of pore former MS in the functional film might play a role. Figure 13 showed the appearance and X-ray powder diffraction (XRD) of the free film of EC/MS (85:15) without or with curing.

It was evident that the curing (60°C, 1 day) indeed affected the physical state of the drug in the film. The appearance (Fig. 13a) and the XRD (Fig. 13c) of the free film demonstrated that the drug was in an amorphous form or a state of solid molecular solution in the free film without curing. However, when the free film was cured at 60°C for 1 day, crystalline substances appeared markedly on the free film (Fig. 13b) and several characteristic peaks could also be observed in the XRD (Fig. 13d), which suggested that the phase separation between EC and the pore former MS happened, and MS-rich domains were formed. Accordingly, the physical state of the drug was altered partially from amorphous or molecular to crystal. With the crystal drug increasing, the network density of water-filled capillaries in the functional EC film decreases, which is associated with the pores formed by MS leaching. Therefore, there is a declining trend of drug-release rates from the EC/MS-coated pellets with the pore density decreasing.

CONCLUSIONS

A binder-free drug-layering approach that involved layering a highly concentrated metoprolol succinate solution on non-pareils was developed successfully. Using the drug as a pore former significantly reduced the pellet stickiness during the polymeric coating process, thus enhancing the process smoothness and shortening the process duration. These findings are of great value for mass production. Meanwhile, the strategy of using the drug as a pore former contributed to mitigating the initial lag phase associated with the drug release from EC-coated pellets. However, such formulation needed to be stabilized by curing at 60°C for 1 day.

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REFERENCES

1. Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm. 1997;43:1–8.
2. Appel LE, Beyerinck RA, Chidlaw MB, Curatolo WJ, Friesen DT, Smith KL, Thombre AG. Hydrogel-driven drug dosage form. In: US Patent 2011/0182947 A1; 2011.
3. Lindstedt B, Ragnarsson G, Hjärtstam J. Osmotic pumping as a release mechanism for membrane-coated drug formulations. Int J Pharm. 1989;56:261–8.
4. Ragnarsson G, Sandberg A, Johansson MO, Lindstedt B, Sjögren J. *In vitro* release characteristics of a membrane-coated pellet formulation—influence of drug solubility and particle size. Int J Pharm. 1992;79:223–32.
5. Marucci M, Ragnarsson G, von Corswant C, Welinder A, Jarke A, Iselau F, *et al*. Polymer leaching from film coating: effects on the coating transport properties. Int J Pharm. 2011;411:43–8.
6. Haddish-Berhane N, Jeong SH, Haghighi K, Park K. Modeling film-coat non-uniformity in polymer coated pellets: a stochastic approach. Int J Pharm. 2006;323:64–71.
7. Ensslin S, Moll KP, Paulus K, Mader K. New insight into modified release pellets-Internal structure and drug release mechanism. J Control Release. 2008;128:149–56.
8. Kaunisto E, Marucci M, Borgguist P, Axelsson A. Mechanistic modeling of drug release from polymer-coated and swelling and dissolving polymer matrix systems. Int J Pharm. 2011;418:54–77.
9. Appel LE, Friesen DT, Herbig SM, Thombre AG. Controlled release dosage forms combining immediate release and sustained release of low-solubility drug. In: US Patent 2008/0299188 A1; 2008.
10. Avramoff A, Domb AJ. *In-vitro* and *in-vivo* characteristics of a modified-release double-pulse formulation for a water soluble drug. Int J Clin Pharmacol Ther. 2010;48:250–8.
11. Verma RK, Garg S. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. Eur J Pharm Biopharm. 2004;57:513–25.
12. Kumaravelrajan R, Narayanan N, Suba V. Development and evaluation of controlled porosity osmotic pump for nifedipine and metoprolol combination. Lipids Health Dis. 2011;10:51–64.
13. Gunder W, Lippold BH, Lippold BC. Release of drugs from ethyl cellulose microcapsules (diffusion pellets) with pore formers and pore fusion. Eur J Pharm Sci. 1995;3:203–14.
14. Siepmann F, Hoffmann A, Leclercq B, Carlin B, Siepmann J. How to adjust desired drug release patterns from ethylcellulose-coated dosage forms. J Control Release. 2007;119:182–9.
15. Bodmeier R, Paeratakul O. Constant potassium chloride release from microporous membrane-coated tablets prepared with aqueous colloidal polymer dispersions. Pharm Res. 1991;8:355–9.
16. Lin WJ, Shiue GR. Elucidation of two water leachable polymers impact on microporous membrane performance and drug permeation. J Memb Sci. 2011;373:189–95.
17. Tuntikulwattana S, Mitrevej A, Kerdcharoen T, Williams DB, Sinchaipanid N. Development and optimization of micro/nanoporous osmotic pump tablets. AAPS PharmSciTech. 2010;11:924–35.
18. Kim JE, Kim SR, Lee SH, Lee CH, Kim DD. The effect of pore formers on the controlled release of cefadroxil from a polyurethane matrix. Int J Pharm. 2000;201:29–36.
19. Heckötter UM, Larsson A, Sriamornsak P, Kumpugdee-Vollrath M. Effect of annealing time and addition of lactose on release of a model substance from Eudragit® RS coated pellets produced by a fluidized bed coater. Chem Eng Res Des. 2011;89:697–705.
20. Mishra M, Mishra B. Design and evaluation of microporous membrane coated matrix tablets for a highly water soluble drug. Chem Pharm Bull (Tokyo). 2010;58:995–1000.
21. Zhang X, Wang Y, Wang J, Wang Y, Li S. Effect of pore former on the properties of casted film prepared from blends of Eudragit NE 30 D and Eudragit L 30 D-55. Chem Pharm Bull (Tokyo). 2007;55:1261–3.
22. Garg A, Gupta M, Bhargava HN. Effect of formulation parameters on the release characteristics of propranolol from asymmetric membrane coated tablets. Eur J Pharm Biopharm. 2007;67:725–31.
23. Wakode R, Bhanushali R, Bajaj A. Development and evaluation of push-pull based osmotic delivery system for pramipexole. PDA J Pharm Sci Technol. 2008;62:22–31.
24. Verma RK, Kaushal AM, Garg S. Development and evaluation of extended release formulations of isosorbide mononitrate based on osmotic technology. Int J Pharm. 2003;263:9–24.
25. Marucci M, Ragnarsson G, Nilsson B, Axelsson A. Osmotic pumping release from ethyl–hydroxypropyl–cellulose-coated pellets: a new mechanistic model. J Control Release. 2010;142:53–60.
26. Andersson H, Hjärtstam J, Stading M, von Corswant C, Larsson A. Effects of molecular weight on permeability and microstructure of mixed ethyl-hydroxypropyl-cellulose films. Eur J Pharm Sci. 2013;48:240–8.

27. Lecomte F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. pH-sensitive polymer blends used as coating materials to control drug release from spherical beads: elucidation of the underlying mass transport mechanisms. Pharm Res. 2005;22:1129–41.
28. Siepmann F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. Polymer blends for controlled release coatings. J Control Release. 2008;125:1–15.
29. Yang MY, Xie S, Li Q, Wang YL, Chang XY, Shan L, *et al*. Effects of polyvinylpyrrolidone both as a binder and pore-former on the release of sparingly water-soluble topiramate from ethylcellulose coated pellets. Int J Pharm. 2014;465:187–96.
30. Hema R, Preeti P, Ashwini S, Ulrich PH, Rosario L, Jayanthi IC. Modulated release metoprolol succinate formulation based on ionic interactions: *in vivo* proof of concept. J Control Release. 2006;111:65–72.
31. Kendall MJ, Maxwell SR, Sandberg A, Westergren G. Controlled release metoprolol, clinical pharmacokinetic and therapeutic implications. Clin Pharamcokinet. 1991;5:319–30.
32. Sinchaipanid N, Chitropas P, Mitrevej A. Influences of layering process on theophylline pellet characteristics. Pharm Dev Technol. 2004;9:163–70.
33. Baki G, Bajdik J, Djuric D, Knop K, Kleinebudde P, Pintye-Hódi K. Role of surface free energy and spreading coefficient in the formulation of active agent-layered pellets. Eur J Pharm Biopharm. 2010;74:324–31.
34. Ahmad H, Khalifeh I, Alkhalidi B, Aiedeh K, AlKhatib HS. Application of active layering and coating techniques in the development of a multiparticulate, controlled release dosage form of a high-dose, highly soluble drug. Pharm Dev Technol. 2014;19:556–64.
35. Lee MJ, Seo DY, Lee HE, Wang IC, Kim WS, Jeong MY, *et al*. In line NIR quantification of film thickness on pharmaceutical pellets during a fluid bed coating process. Int J Pharm. 2011;403:66–72.
36. Ho L, Cuppok Y, Muschert S, Gordon KC, Pepper M, Shen YC, *et al*. Effects of film coating thickness and drug layer uniformity on vitro drug release from sustained-release coated pellets: a case study using terahertz pulsed imaging. Int J Pharm. 2009;382:151–9.
37. Erdmann H, Gebert S, Kolter K, Schepky G. Studies on modifying the tackiness and drug release of Kollicoat EMM 30 D coatings. Drug Dev Ind Pharm. 2003;29:429–40.
38. Nimkulrat S, Suchiva K, Phinyocheep P, Puttipipatkhachorn S. Influence of selected surfactants on the tackiness of acrylic polymer films. Int J Pharm. 2004;287:27–37.
39. Wan LSC, Lai WF. The influence of antitack additives on drug release from film-coated granules. Int J Pharm. 1993;94:39–47.
40. Felton LA, McGinity JW. Influence of insoluble excipients on film coating systems. Drug Dev Ind Pharm. 2002;28:225–43.
41. Chan LW, Wong TW, Chua PC, York P, Heng PWS. Anti-tack action of polyvinylpyrrolidone on hydroxypropylmethylcellulose solution. Chem Pharm Bull. 2003;51:107–12.
42. Marucci M, Arnehed J, Jarke A, Matic H, Nicholas M, Boissier C, *et al*. Effect of the manufacturing conditions on the structure and permeability of polymer films intended for coating undergoing phase separation. Eur J Pharm Biopharm. 2013;83:301–6.
43. Marucci M, Hjartstam J, Ragnarsson G, Iselau F, Axelsson A. Coated formulation: new insight into the release mechanism and changes in the film properties with a novel release cell. J Control Release. 2009;139:206–12.
44. Dashevskya A, Kolterb K, Bodmeier R. pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat® SR 30 D and the enteric polymer dispersion Kollicoat® MAE 30 DP. Eur J Pharm Biopharm. 2004;58:45–9.
45. Wesseling M, Bodmeier R. Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution. Eur J Pharm Biopharm. 1999;47:33–8.