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A novel powder coating process for attaining taste masking and moisture protective films applied to tablets

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Abstract

A novel powder coating process was developed for the application of taste masking and moisture protective films on tablets while avoiding the use of solvents or water. The coalescence of particles to form a polymeric film was investigated through studies of dry powder layering of micronized acrylic polymer (E PO) to produce free films. Theophylline containing tablets were coated with the same acrylic polymer in a laboratory scale spheronizer using a powder coating technique. The dry powder layer delayed the onset of drug release in pH 6.8 medium, depending on the coating level, while no delay was observed in pH 1.0 medium. The presence of hydrophilic polymers in the acrylic coating layer decreased the lag time for drug release in pH 6.8 medium, while only the presence of HPMC in the film slowed the drug release rate in acidic medium. The dry coating process was demonstrated to be a reliable alternative to solvent or aqueous film coating technologies for applying taste masking and moisture protective film coats onto compressed tablets. A controlled drug release profile was achieved in pH 6.8 media.

Keywords: Powder coating; Eudragit® E PO; Hydrophilic polymers; Taste masking; Moisture protective coatings; Free films

1. Introduction

Pharmaceutical coating technologies for solid oral dosage forms are generally based on the use of polymeric materials in solution or dispersed in aqueous or organic vehicles. The use of organic solvents is associated with toxicological, environmental and safety-related disadvantages, which also impact the manufacturing costs (Nagai et al., 1997; Cunningham and Fegely, 2001). These disadvantages have been circumvented by the introduction of aqueous-based coating systems. For aqueous film coating systems, the main problem during the coating process is the slow rate of drying and water removal due to its relatively high latent heat of vaporization (539.4 cal/g) (Lide, 2000). Compared to solvent-based coating systems, higher coating temperatures and slower spraying rates must be employed to prevent water from penetrating the surface of the substrate, and thus longer processing times are required (Cole, 1995). A reduction in the processing time for aqueous coatings can be obtained by increasing the solids content of

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the coating systems; however, in some cases, problems of solution viscosity and spray nozzle clogging can compromise the continuity of the coating process and the uniformity of the resulting film. Furthermore, the sensitivity of certain active compounds to water and the presence of residual moisture in the film can significantly affect the stability of the dosage form and the performance of the coating layer (Amighi and Moes, 1996). For these reasons, a process that avoids the use of water or organic solvents would be considered a significant advancement in film coating technology.

Recently, coating processes have been proposed in which the film forming polymer is layered onto the surface of the cores directly as powder while a mixture of liquid plasticizers or polymeric solution is simultaneously sprayed onto the substrate (Obara et al., 1999; Cerea et al., 2002; Pearnchob and Bodmeier, 2003). Film formation occurs during a subsequent curing phase at elevated temperatures. To improve the film formation of the layered polymer, water or a solution of HPMC can be sprayed onto the coated cores. This coating process limits the use of water, but often the presence of liquid plasticizers requires the application of a sub-coating layer to prevent the migration of liquid into the cores during the initial layering phase. This protective layer is applied using traditional water- or solvent-based systems. Furthermore, high concentrations of plasticizer could excessively lower the glass transition temperature (T_g) of the coating polymer, causing the final film to be sticky, and thus compromising the stability of the coated dosage form.

The aim of this study was to develop a novel powder coating process which avoided the use of water and organic solvents for attaining taste masking and moisture protective film coatings on tablets using Eudragit® E PO.

The use of pH dependent polymers offers a different approach to taste masking than the addition of artificial flavors or the use of rapidly disintegrating films. Eudragit® E is a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters and is soluble at a pH below 5.5 (Lehmann, 1968). This polymer can prevent the release of the delivered drug in saliva (pH 6.8–7.4) and readily dissolves in gastric fluids (pH 1.0–1.5) (Ishikawa et al., 1999). Furthermore, this polymer has been demonstrated to be an effective moisture protective film coating (Chowhan et al., 1982; Thoennes and McCurdy, 1989).

2. Materials and methods

2.1. Materials

Theophylline anhydrous, lactose monohydrate and magnesium stearate were purchased from Spectrum Chemical (Gardena, CA, USA); microcrystalline cellulose (Avicel® PH-101) was donated by FMC Corp. (Newark, DE, USA); polyvinylpyrrolidone K-30 and K-90 (PVP, Kollidon® 30 and 90 F) were provided by BASF (Ludwigshafen, Germany), amorphous fumed silica (Cab-O-Sil®, M-5P) by Cabot Corp. (Tuscala, IL, USA), talc (Altalc 500V) by Luzenac North America (Centennial, CO, USA). Glyceryl monostearate (GMS, Imwitor 491) was obtained from Condea Chemie (Antwerpen, Belgium), polyethylene glycol (Carbowax™ 3350) and hydroxypropyl methylcellulose (HPMC, Methocel K4M Premium) from the Dow Chemical Company (Midland, MI, USA). The polymer used for coatings, an acrylic copolymer based on dimethylaminoethyl methacrylate, methyl methacrylic and *n*-butyl methacrilate (Eudragit® E PO), was donated by Röhm America (Piscataway, NJ, USA).

2.2. Studies on dry powder coated free films

The free films were prepared according to The American Society for Testing and Materials (ASTM) standard practices for producing films of uniform thickness of paint, varnish and related products on test panels (Practice E: Hand-held blade film application) (ASTM, 2001a). The powder was spread onto flat Teflon® plates using a manual applicator with a blade that was 10 cm wide, 5 mm thick and a clearance of 0.63 mm. The plates were stored in a static oven (Model 107905, Boekel Scientific Inc., Feasterville, PA USA) at different temperatures (40, 60, 80, 100 °C) for 1, 2, 4, 8, 12, and 24 h. The films were produced in triplicate.

The thickness of the free films was measured in accordance with the ASTM standard test method for the measurement of dry film thickness of organic coatings using a micrometer (Digital thickness gage, Digimatic

Mod. 547-316, Kawasaki, Mitutoyo, Japan) ($n = 10$) (ASTM, 2001b).

2.3. Tablets preparation

Theophylline anhydrous (15.0%), microcrystalline cellulose (66.1%), lactose monohydrate (15.0%), PVP K-30 (3.0%), magnesium stearate (0.5%) and amorphous fumed silica (0.4%) were mixed in a V-shape blender (Model Yoke, Patterson-Kelley Co., East Stroudsburg, PA, USA,) for 30 min and the mixture was tableted using a rotary press (Model FJS-B2 Stokes, Bristol, PA, USA) equipped with shallow concave punches (diameter: 8 mm). Tablets were characterized by weight (178.4 ± 3.1 mg), height (3.63 ± 0.03 mm), diameter (7.99 ± 0.03 mm), friability (<1%), hardness (10 ± 2 kp) and disintegration time (<1 min).

2.4. Powder coating process

The powder coating process was performed in a laboratory scale spheronizer (Model 120, G.B. Caleva, Dorset, UK) with a smooth stainless steel disc (Fig. 1). A batch size of 50 g of tablets was coated in each process. An infrared lamp (250 W Infrared Red Heat Bulb, General Electric, USA) positioned 3 cm above the top of the spheronizing chamber was used as the heating source. The temperature of the coating bed was adjusted by regulating the lamp power with a variable transformer (Type PF1010, Staco Inc, Daiton, OH, USA). A digital thermoprobe (Model 600-1040, Barnant Company, Barrington, IL, USA) was used to constantly monitor the temperature of the coating process. The coating powders were mixed in a mortar and pestle for 5 min and then passed through a 100 mesh sieve. The compositions of the powder mixtures used for the coatings are reported in Table 1. During the coating process, the mixture was continuously spread onto the cores by way of a motorized single screw powder feeder, at a rate of 0.5 g/min.

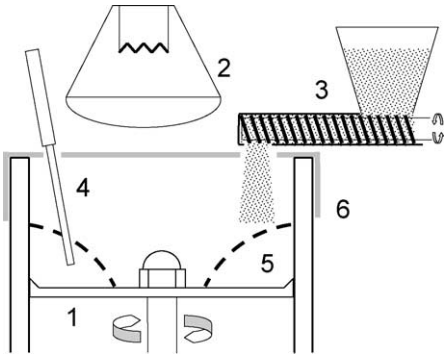

Fig. 1. Schematic representation of the laboratory scale spheronizer used for the powder coating process: (1) rotating disk; (2) infrared lamp; (3) powder feeder; (4) temperature probe; (5) coating cores; (6) glass cover.

Curing of powder coated tablets was carried out in a static oven (Model 107905, Boekel Scientific Inc.) on Teflon® plates at 80 °C for 12 h.

2.5. Thermal analysis of the polymer

The thermal properties of Eudragit® E PO were characterized using modulated differential scanning calorimetry (MDSC, Model 2920, TA Instruments, New Castle, DE, USA). Samples of approximately 10 mg were accurately weighed and hermetically sealed in aluminum pans. The samples were analyzed under a nitrogen atmosphere at a heating rate of 3 °C/min over the temperature range of −30 to 110 °C. Modulation was set at ±1 °C every 60 s. The samples were subjected to two heating cycles. The reported glass transition temperature (T_g) was the midpoint of the integrated second heating cycle transition. MDSC analysis of samples was performed in triplicate.

Table 1
Coating powders compositions

	Eudragit® E PO (%)	Talc (%)	GMS (%)	HPMC K4M (%)	PVP K-90 (%)	PEG 3350 (%)
Base mixture	90.9	9.1	–	–	–	–
Mixture A	83.2	8.4	8.4	–	–	–
Mixture B	83.2	8.4	–	8.4	–	–
Mixture C	83.2	8.4	–	–	8.4	–
Mixture D	83.2	8.4	–	–	–	8.4

2.6. Scanning electron micrographs

The surface and cross-sectional morphologies of the powder coated films and film coated tablets were observed with scanning electron microscopy (SEM, Model S-4500 FE, Hitachi, London, UK). Prior to analysis, the samples were sputter coated with gold:palladium (60:40; Sputter Coater Mod. K575, Emitech, Houston, TX, USA).

2.7. Drug release studies

Dissolution tests were conducted according to USP 26 Apparatus 2 guidelines (paddle method, Model VK7000 Dissolution Tester, VanKel, Cary, NC, USA) with 900 mL dissolution medium maintained at 37 ± 0.5 °C and agitated at 50 rpm ($n = 6$). The media studied included pH 1.0 (0.1 N HCl), pH 5.5 (50 mM acetate buffer), and pH 6.8 (50 mM phosphate buffer).

Samples were analyzed for drug content using a high performance liquid chromatography (HPLC) system with a photodiode array detector (Model 996, Waters, Milford, MA, USA) set at a wavelength of 281 nm. Samples were filtered using 0.45 μm nylon filters, and an autosampler (Model 717plus) was used to inject 10 μL samples. The data were collected and integrated using Empower® Version 5.0 software. The column used was an ODS-3 3 μm, 150 mm × 4.6 mm (Alltech Inertsil™, Deerfield, IL, USA). The mobile phase contained a mixture of water:acetonitrile:glacial acetic acid in volume ratios of 845:150:5 and 1.156 g/L of sodium acetate trihydrate. The retention time of the theophylline was 3.6 min. Linearity was demonstrated from 1 to 100 mg/μL ($R^2 = 0.998$) and injection repeatability was 1% relative standard deviation for six injections.

Table 2
The effect of curing time and temperature on the physical appearance of dry powder coated free films

Temperature (°C)	1 h	2 h	4 h	8 h	12 h	24 h
40	0	0	0	0	−	−
60	−	−	−	±	+	+
80	±	+	+	++	++	++
100	+	++	++	++	++	++

(0) no change in the layered powder; (−) coalescence of the powder, no film formation; (±) partial film formation; (+) film formation with opaque film; (++) transparent film.

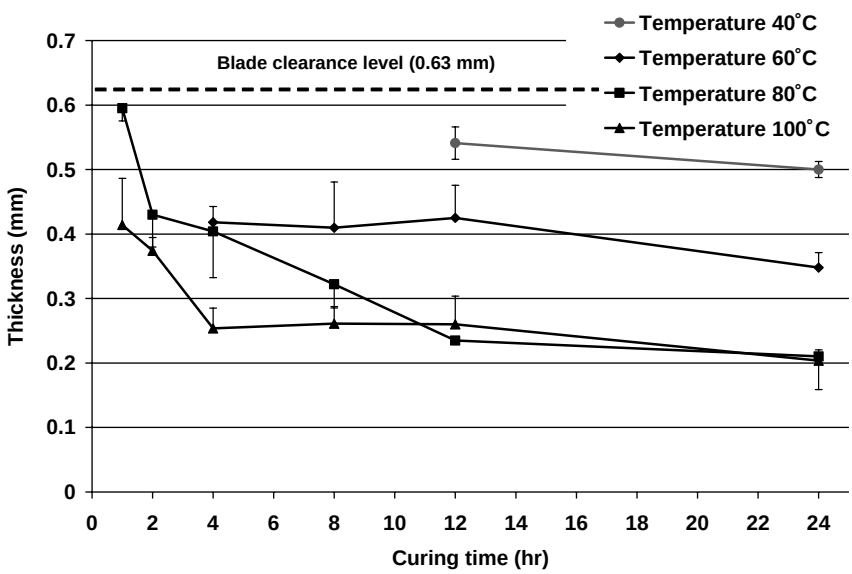

Fig. 2. Influence of curing time and temperature on thickness of free films prepared from Eudragit® E PO ($n = 3$).

3. Results and discussion

3.1. Studies on free films

In order to understand the film formation process and to determine the minimum film formation temperature (MFT) of the acrylic polymer coatings, free films of Eudragit® E PO powder were prepared and characterized. The free films were obtained by layering the dry polymer powder onto Teflon® plates, followed by curing the films in a static oven at temperatures between 40 and 100 °C. The degree of film formation was determined by observing the appearance and transparency of the cured layers (Table 2). Smooth and transparent films were obtained after curing for 8 h at 80 °C and 2 h at 100 °C. Maintaining the films for 8 h at 100 °C resulted in films that were slightly brown, suggesting degradation of the polymer. Partial coalescence of polymer powders was observed after 12 h at 40 °C and after 2 h at 60 °C. Nevertheless, curing for 12 and 24 h at 60 °C produced only opaque films.

The influence of curing time and temperature on film formation was determined by measuring the thickness of the layered free films (Fig. 2). A reduction in the thickness for the dry powder films was also considered an indication of coalescence of the polymer particles (Huang et al., 1997). As expected, the lowest curing temperature (40 °C) resulted in the slowest coalescence rate and the thickest powder layer. The powders cured at 60 °C showed a rapid rate of decrease in the thickness of the powder layer during the first 4 h, followed by slow coalescence of the powders with a reduction in the layer thickness of approximately 45% in 24 h. Curing at 80 °C produced a very fast coalescence of the polymer in the first 2 h (32% of thickness reduction), followed by a slower phase which reached a thickness of 0.24 ± 0.01 mm (63% of thickness reduction) after 12 h of curing. Curing for 24 h decreased the thickness to 0.21 ± 0.05 mm, with a final reduction of approximately 67%. The fastest rate of film formation was achieved at a curing temperature of 100 °C. Film thickness was reduced by about 35% in 1 h and by about 63% in 4 h, reaching a uniform layer of 0.25 ± 0.03 mm. After 24 h of curing, the film thickness reduction was approximately 68%.

The dependence of film formation on curing temperature was also studied using SEM analysis of the free films cured for 24 h at 40, 60, 80, and 100 °C. The powder cured at 40 °C showed partial coalescence of the micronized polymer particles and formation of a porous layer (Fig. 3A). Individual particles linked by solid bonds were evident throughout the cross-section of the film. At 60 °C the layer was more compact and with less voids (Fig. 3B). Although the polymer particles were still visible, the coating material was found to melt into a complicated three-dimensional structure (Fig. 3C). In addition, the cross-sectioned film showed the presence of a more dense polymer layer on the lower side of the coating (Fig. 3D). The characteristic film layer could be due to differences in the substrate interfaces. In addition, the weight of the upper powder layers exerted a force on the lowest powder layer. Photomicrographs of the powders cured at 80 and 100 °C were indicative of complete film formation, with a smooth, compact and uniform film layer (Fig. 3E–G). Moreover, the regular fracture of the cross-sectioned films confirmed the characteristic glassy behavior of the Eudragit® E PO films at room temperature, as shown in Fig. 3F. The influence of curing time on Eudragit® E PO free films cured at 80 °C was also examined (Fig. 4). The photomicrographs of the surface of the films confirmed that at least 8 h was necessary to achieve complete film formation of the polymer when cured at 80 °C.

3.2. Powder coating of theophylline tablets

The powder coating process for a solid substrate consisted of three phases: pre-heating, powdering, and curing (Fig. 5). In the first phase, the uncoated tablets were heated to a selected temperature. During the powdering phase, the polymer powder was transferred into the coating equipment, distributed onto the cores, adhered to the surface of substrate and a polymeric film coating layer was formed around the tablets. Powder adhesion onto the tablet surface was promoted by the partially melted polymer that generated binding forces between particles, and between particles and the tablet surfaces. During the curing phase, the temperature of the coated tablets was further increased to enhance coalescence of the coating powder particles and the formation of the final film.

The powder coating process was carried out using a laboratory scale spheronizer. Preliminary trials were conducted to optimize the configuration as well as the process parameters. The spheronizer disk selected

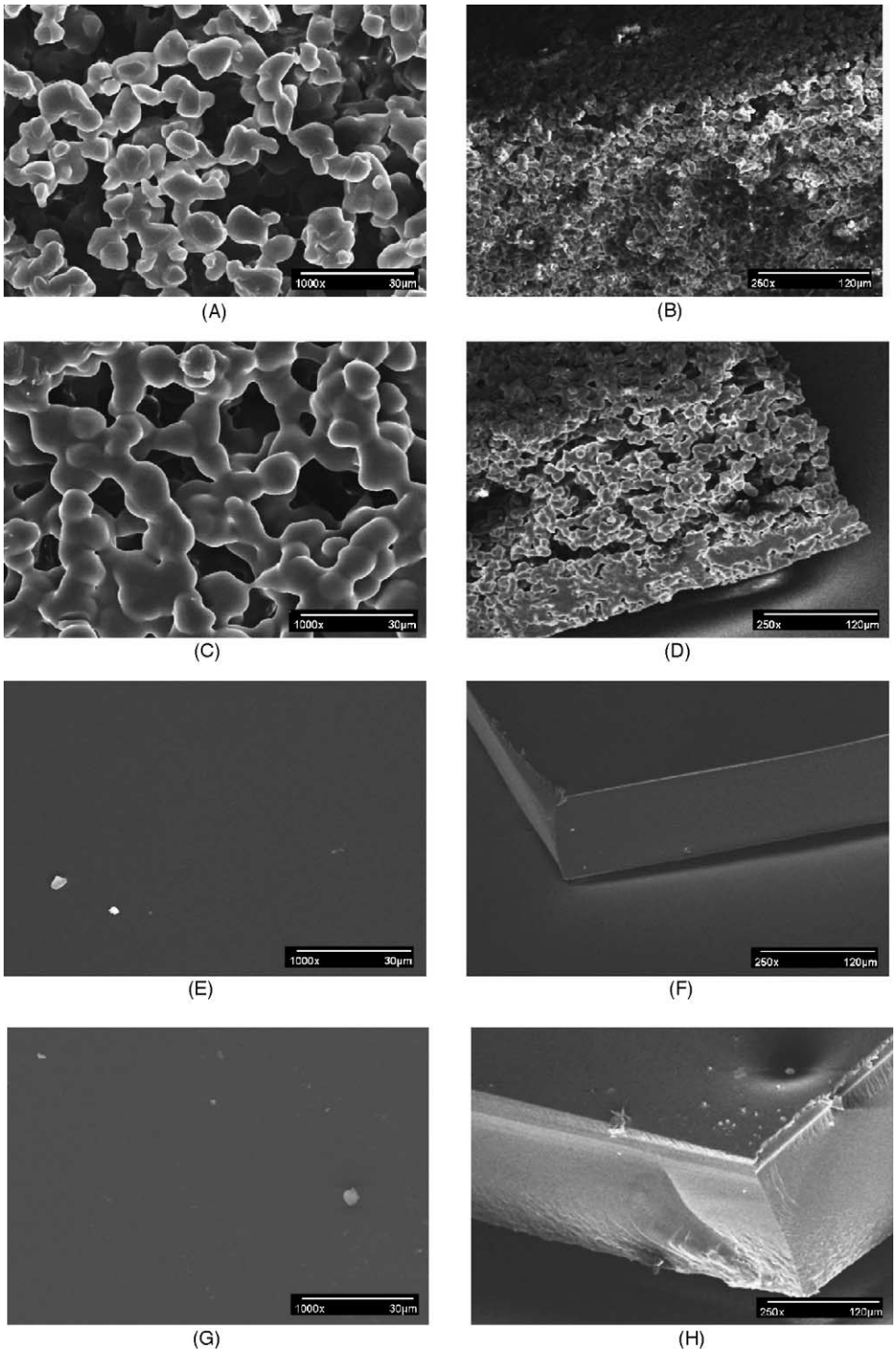

Fig. 3. Scanning electron micrographs of free films prepared from Eudragit® E PO cured for 24 h at 40 °C (A, surface; B, cross-section), 60 °C (C, surface; D, cross-section), 80 °C (E, surface; F, cross-section) and 100 °C (G, surface; H, cross-section).

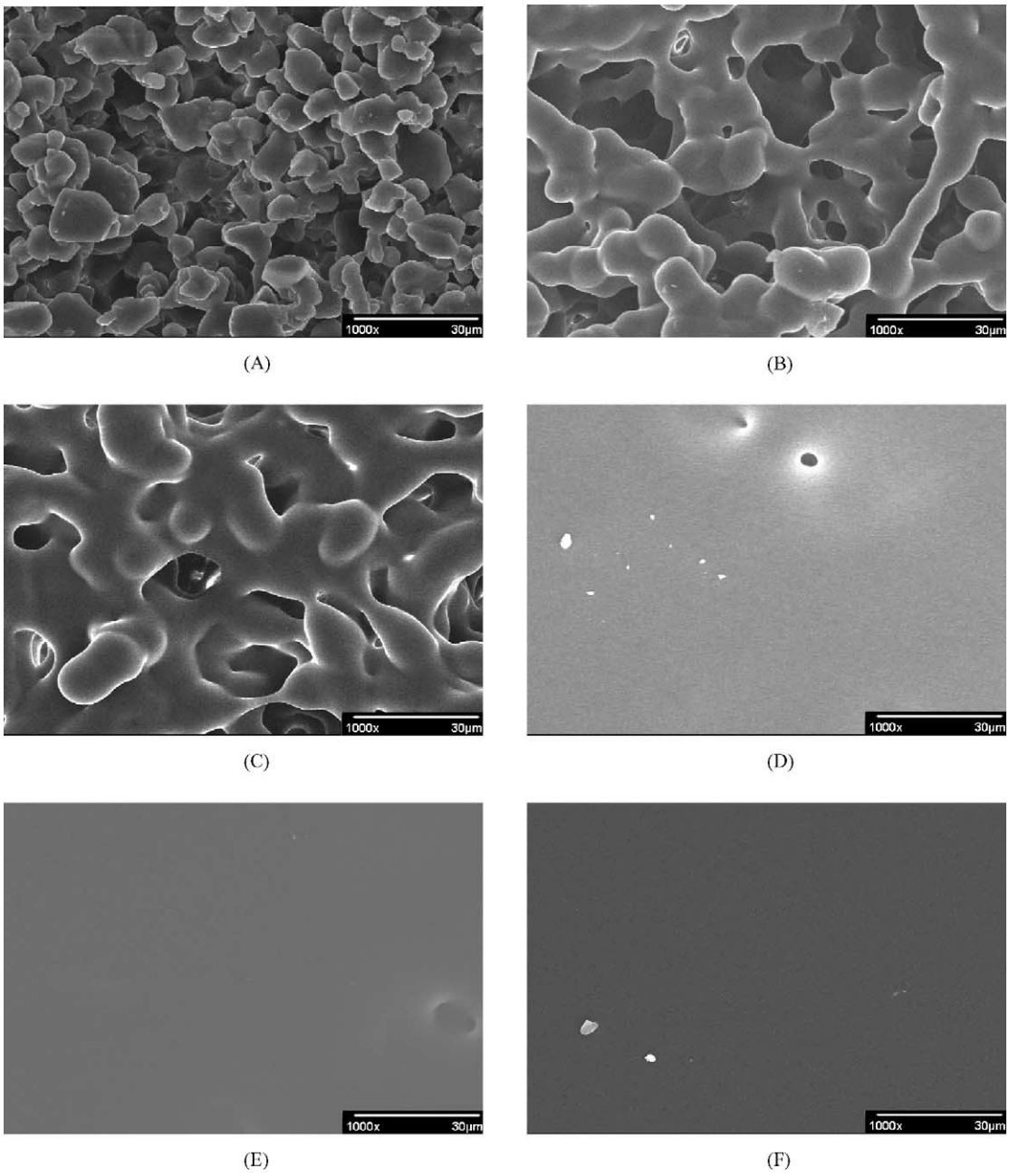

Fig. 4. Scanning electron micrographs of surface of free films prepared from Eudragit® E PO powder cured at 80 °C for 1 h (A), 2 h (B), 4 h (C), 8 h (D), 12 h (E), and 24 h (F).

was a smooth stainless steel disk having edges with a 45° angle of curvature to facilitate movement and tumbling of the cores and to prevent the loss of the coating powder. Disk rotation speed studies demonstrated that the tablets did not tumble and mix at low rotation speed, whereas higher rotation rates resulted in excessive friability of the cores and loss of the coating powder. The optimal rotation speed

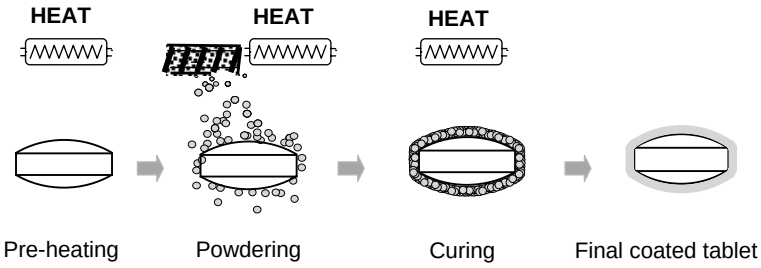

Fig. 5. Schematic representation of the powder coating process.

for the powder coating process was determined to be 190 rpm.

During the powder coating process, the temperature of the coating cores was found to be the most critical parameter. Coating trials employing a hot air gun as the heating source resulted in poor coating efficiency due to a significant loss of coating powder. Our studies demonstrated that the optimal heating source was an infrared lamp placed 3 cm above the top of the spheronizing chamber. A temperature probe immersed in the tablet bed continuously monitored the temperature while improving mixing of the coating tablets. During the powdering phase, temperatures below the T_g of Eudragit® E PO (50 ± 3 °C) resulted in no adhesion of the coating powder to the cores. On the other hand, temperatures above 70 °C caused irregular layering of the coating. The optimal temperature range for obtaining powder layering for Eudragit® E PO was between 55 and 60 °C.

Based on the results of the free films studies, the curing temperature was maintained at 80 °C for 12 h in order to form a continuous and compact film. Using the process parameters described in Table 3, tablets were coated at three levels, and the characteristics of the coated tablets and the processing times are reported in Table 4.

SEM analysis of cross-sectioned coated tablets before and after curing illustrated the efficiency of the curing conditions (Fig. 6). In particular, photomicrographs of the uncured coated tablets revealed a thick, porous layer, with polymer particles visible along the entire cross-section of the coating. Moreover, the thickness of the layer is appreciably different depending on position, with a thinner coating on the edge of the tablets. On the contrary, samples cured for 12 h at 80 °C produced more homogeneous coatings with compact and continuous film layers. The polymer particles melted into uniform films of constant thickness on the surface of the tablet.

The unpleasant flavor or odor of certain drugs and the difficulties related to swallowing bitter tasting dosage forms have been reported as the primary reasons for incompliance with drug therapy (Aronson and Hardman, 1992). Although the presence of artificial flavors and sweeteners can improve the palatability of a dosage form, the application of a coating around the drug particles or around the final dosage form has been demonstrated to provide a superior result by preventing the molecules from reaching the taste sensors. Dissolution testing was employed to assess the in vitro taste masking ability of the powder coating process. The pH of the saliva has been reported to be between 6.8 and 7.4 (Pedersen et al., 2002), and a

Table 3
Processing parameters used for powder coating of tablets

Processing parameters	Values
Batch size (g)	50
Disk rotation speed (rpm)	190
Temperature (°C)	55–60
Infrared lamp power (W)	130
Powder feeding rate (g/min)	0.5

Table 4
Processing times and coating levels of the powder coated tablets

	Weight gain (%)	Coating amount (mg/cm^2)	Process time (min)	
			Pre-heating	Powdering
Sample A	5.6	6.9	5	20
Sample B	8.2	10.1	5	24
Sample C	11.8	14.5	5	27

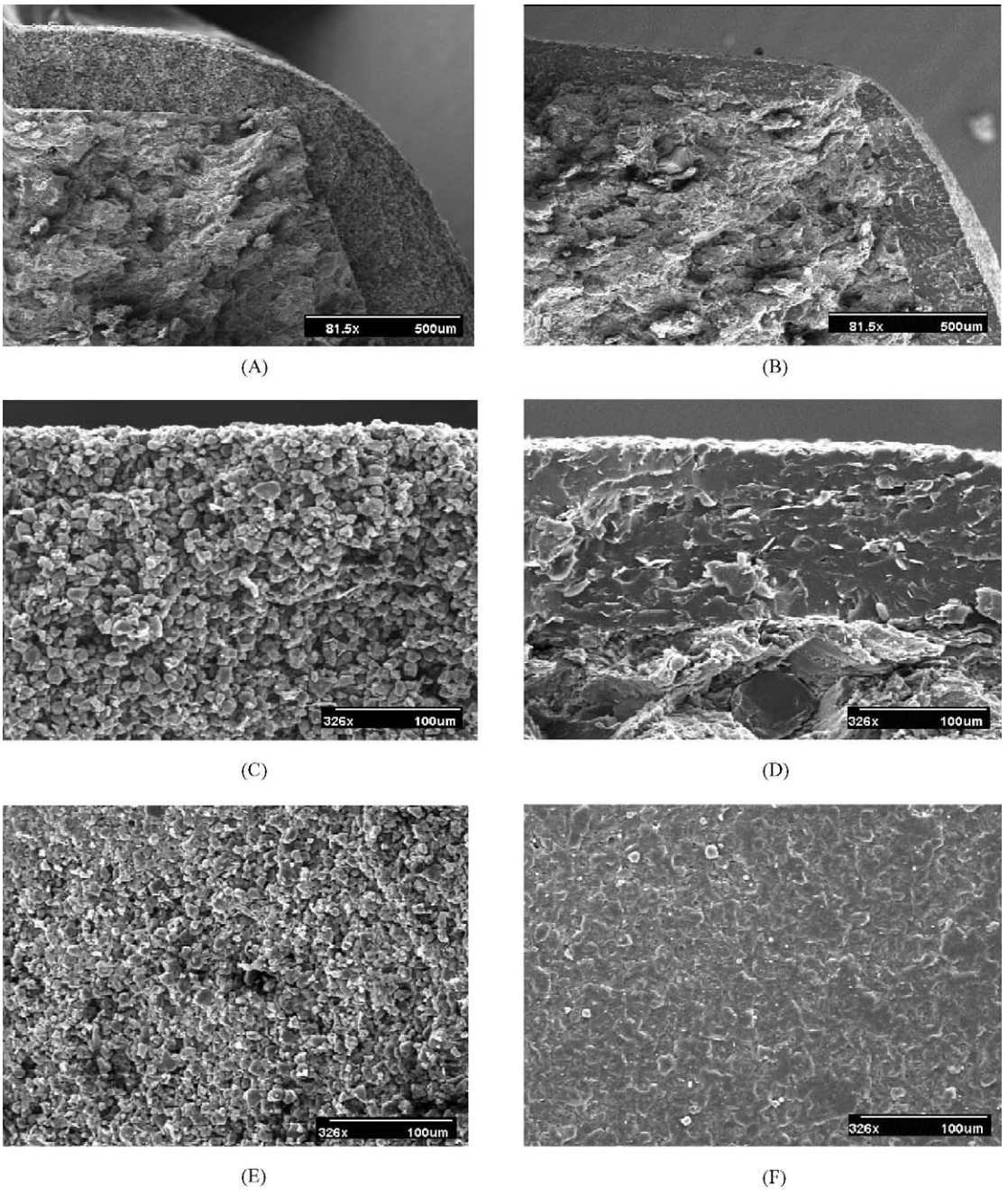

Fig. 6. Scanning electron micrographs of Eudragit® E PO powder coated tablets (14 mg/cm^2). Cross-section (A, C) and surface (E) of uncured tablet; cross-section (B, D) and surface (F) of tablet cured for 12 h at 80 °C.

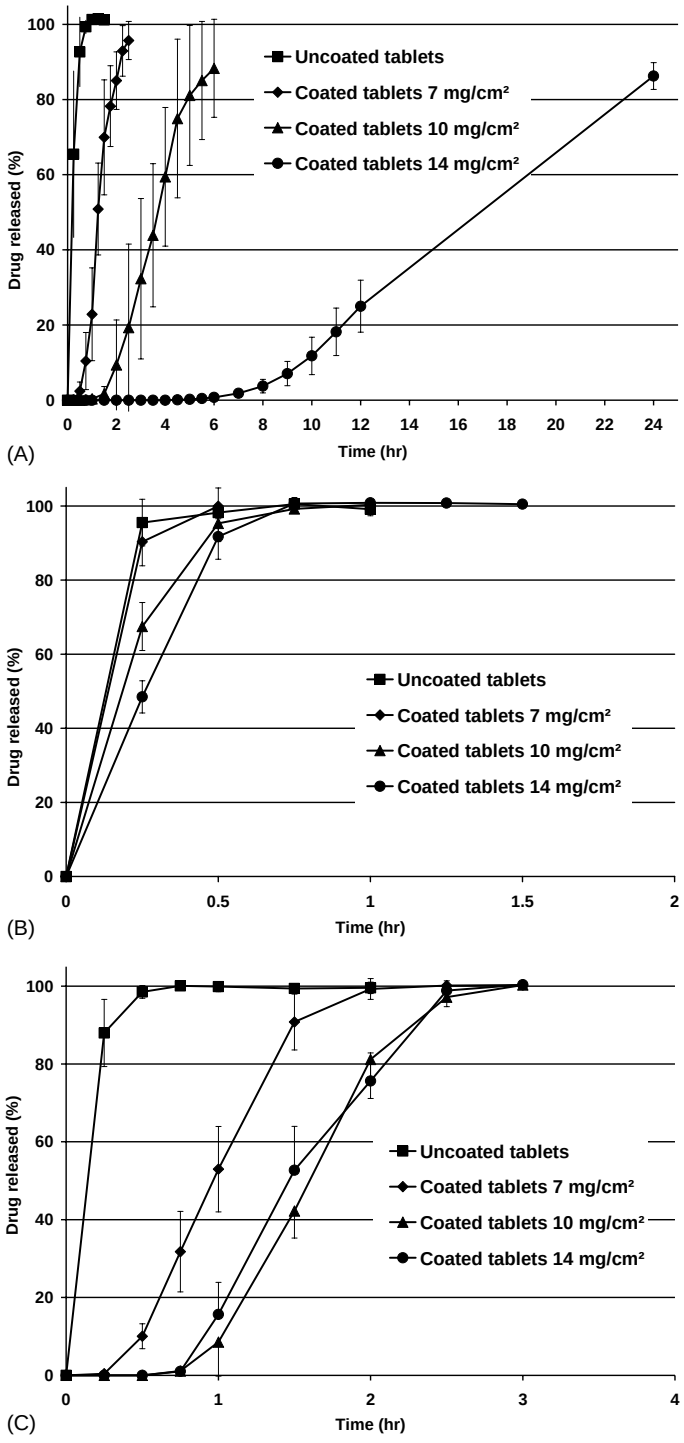

Fig. 7. Dissolution profiles of uncoated and powder coated theophylline containing tablets with increasing coating levels ($n = 6$): (A) pH 6.8 (50 mM phosphate buffer); (B) pH 1.0 (0.1 N hydrochloric acid); (C) pH 5.5 (50 mM acetate buffer).

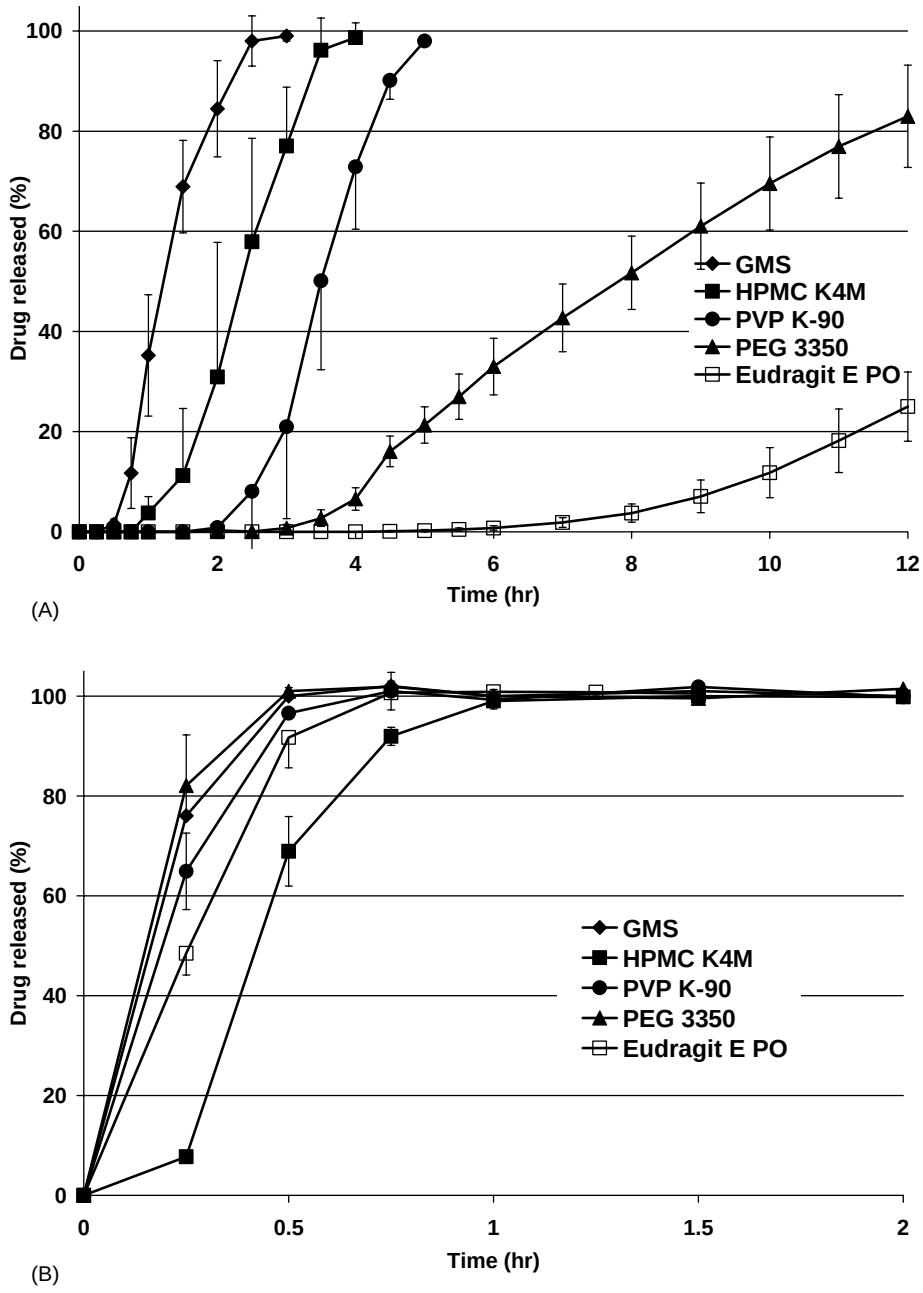

Fig. 8. Dissolution profiles of theophylline containing tablets powder coated with Eudragit® E PO including different hydrophilic polymers ($n = 6$): (A) pH 6.8 (50 mM phosphate buffer); (B) pH 1.0 (0.1 N hydrochloric acid).

delay in drug release of even only a few minutes can prevent the sensation of an unpleasant taste (Klancke, 2003). Furthermore, the use of a polymer soluble at gastric pH, such as Eudragit® E, would allow rapid release of drug for absorption in the gastrointestinal tract.

The dissolution profiles of coated samples obtained in pH 6.8 media confirmed the ability of the Eudragit®

E PO coating to delay the onset of drug release (Fig. 7). The sample with 7 mg/cm^2 of coating polymer retarded the onset of the drug release for 15 min, whereas the tablets with 10 mg/cm^2 delayed the release for 45 min and the tablets coated with 14 mg/cm^2 of polymer postponed the release for 5.5 h. Furthermore, since Eudragit® E PO is soluble in medium at pH below 5.5, the dissolution characteristics of the film coated tablets in pH 5.5 acetate buffer were studied. The 7 mg/cm^2 coated tablets produced a 15 min delay in the onset of drug release, while the 10 and 14 mg/cm^2 samples retarded drug release for 45 min. Tablets at all three coating levels also showed significant decreases in the drug release rate in the pH 5.5 dissolution medium. In contrast, each coated sample promptly released the drug in the dissolution tests performed in acidic medium as seen in Fig. 7B. The release rate was slightly decreased only for the coating levels of 10 and 14 mg/cm^2. However, in 30 min the percent of theophylline released was more than 90% for all three coating levels.

3.3. Influence of excipients in dry powder coating in dissolution

The influence of other powder excipients in the coating mixture on powder coating process and drug release was investigated. Hydrophilic polymers such as HPMC K4M, PVP K-90, and PEG 3350 as well as GMS were mixed to the Eudragit® E PO coating powders in mortar and pestle for 5 min prior to the powder coating process. The tablets were coated with the coating powder mixtures containing 10% of the hydrophilic material based on the amount of Eudragit®, which increased the weight of applied solids to approximately 13% (16 mg/cm^2 of coating).

In the case of low melting polymers (GMS and PEG 3350), the process yield was increased by the enhanced adhesion of the coating powders. Nevertheless, the addition of HPMC K4M and PVP K-90 did not cause any improvement.

The dissolution profiles reported in Fig. 8 demonstrate that the release behavior of the coated tablets in pH 6.8 medium was significantly affected by the presence of the hydrophilic polymers. Addition of hydrophilic polymers in the coatings increased the theophylline release rate from Eudragit® E PO powder coated tablets. The lag time of drug release was shortened when compared to the tablets coated with Eudragit® E PO alone. Drug release was delayed for only 30 and 60 min by the coating that contained GMS and HPMC K4M and the presence of PVP K-90 and PEG 3350 increased the onset of drug release for 2 and 3 h, respectively. However, only the inclusion of HPMC decreased the drug release in acidic medium while the other polymers slightly increased the drug release in the acidic medium. This is probably due to the gelling mechanism of HPMC.

4. Conclusions

The powder coating process was demonstrated to be an efficient method for film coating tablets using an acrylic polymer without solvents, water or liquid plasticizers. The coated tablets observed using SEM exhibited a continuous and uniform film coating. The results of dissolution testing indicated that film coating resulted in a delay in the release of the drug in pH 6.8 buffer media while no delay was observed in acidic medium. The delay provided by the powder coated films can be successfully exploited for taste masking, and possibly for other controlled release applications. The influence of tablet shape, processing methods and batch size on the powder coatings uniformity and reproducibility will be analyzed in future studies.

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