ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 49 (2000) 243–252

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

Influence of processing and curing conditions on beads coated with an aqueous dispersion of cellulose acetate phthalate

Robert O. Williams III*, Jiping Liu

College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

Received 8 November 1999; accepted 18 January 2000

Abstract

The influence of fluidized-bed processing conditions, as well as curing parameters with and without humidity, on drug release from beads coated with cellulose acetate phthalate (CAP) aqueous dispersion was investigated. Theophylline beads prepared by extrusion–spheronization were coated with diethyl phthalate (DEP)-plasticized CAP dispersion (Aquacoat® CPD) using a Strea-1 fluidized-bed coater. The parameters investigated were plasticizer level, outlet temperature, spray rate during coating application and fluidizing air velocities using a half-factorial design. The processing temperature during coating applications was identified as a critical factor among the variables investigated. The release rate significantly decreased when the beads were coated at 36°C compared to those coated at 48°C ($P < 0.01$). Higher coating efficiencies and better coalescence of films were obtained at the lower coating temperature. Above the minimum film-formation temperature (MFFT), drug release in acid decreased as the coating temperature was decreased. Curing at 60°C significantly reduced the drug release for beads coated at 32°C, but had no significant effect on drug release for beads coated at temperatures above 36°C. Curing at 50°C in an atmosphere containing 75% RH (relative humidity), irreversibly converted poor film formation into better coalescence, and increased the mechanical toughness of films. Subsequent removal of the moisture absorbed from beads did not significantly alter the enteric profiles obtained through heat–humidity curing. The extent of coalescence via heat–humidity curing was dependent on the curing temperature, % humidity, curing time and coating temperature. The results demonstrated the importance of the selection of coating temperature for CAP-coated beads and the role of moisture on CAP film formation. Curing with humidity was found to be more effective than without.

Keywords: Cellulose acetate phthalate; Beads; Enteric coating; Curing; Humidity

1. Introduction

Cellulose acetate phthalate (CAP), a cellulose ester derivative, is used as an enteric polymer coating for delayed release products. It contains anhydroglucose units, with about half of the hydroxyl groups acetylated and about one fourth esterified with one of the two acid groups of phthalic acid [1]. CAP dissolves in buffered medium at pH values greater than 5.5. Due to safety, toxicity and environmental concerns, the traditional organic-based coating systems have gradually been replaced by aqueous-based coating systems. The ammonia-neutralized solutions [2,3] and pseudolatexes of CAP have been formulated [4,5] to accommodate such concerns. Currently, two CAP pseudolatex products are commercially available: Aquateric® is spray-dried CAP powder composed of CAP, Pluronic F-68, Myvacet 9-45 and Polysorbate 60; and Aquacoat® CPD, the most recently introduced product, is an aqueous dispersion of CAP containing 23% polymer, 7% poloxamer and 70% water.

In a latex dispersion, the polymer is dispersed as small particles rather than fully-entangled chains as it is in the solution. Particle deformation must occur in order to achieve coalescence. The driving force for fusion comes from the capillary forces caused by high interfacial tension between water and the polymer, and between water and air as water is evaporated. The plasticizer eases the relative movement of polymer chains by increasing the free volume or intermolecular space, and by reducing the minimal film-formation temperature [1,6,7]. This more complex mechanism of film formation may lead to the differences in functional performance of aqueous-based films compared to organic-based films. CAP films obtained from Aquateric® dispersion were reported to be more permeable than those

* Corresponding author. College of Pharmacy, The University of Texas at Austin, Pharmaceutics Division, Austin, TX 78712-1074, USA. Tel.: +1-512-471-4681; fax: +1-512-471-7474.

E-mail address: williro@mail.utexas.edu (R.O. Williams III)

0939-6411/00/$ - see front matter
PII: S0939-6411(00)00065-5

prepared from organic solutions [8]. Ammonia-neutralized CAP solutions rendered a more porous and heterogeneous film structure, and also produced films with increased swellability and permeability compared to those from organic solutions [9].

Studies on the application of CAP aqueous dispersions on coated enteric formulations with various active compounds, as well as studies with other enteric polymers, have been reported [10–15]. CAP and other cellulosic derivatives, such as hydroxypropyl methylcellulose phthalate (HPMCP) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), were more permeable than acrylic polymers due to their hydrophilicity and less dense molecular arrangements [15]. Studies showed that CAP, in the form of an aqueous dispersion, provided adequate acid resistance on coated products at sufficient coating levels [11–14]. Basic actives, such as sodium salicylate, may interact with CAP and create a micro pH greater than 5.5. A suitable subcoat layer was then required [11,12]. Most of these coating studies were carried out on tablets or gelatin capsules; however, few studies have been reported on beads. Beads possess advantages over tablets, such as low absorption variability and less propensity for dose dumping; however, since they have a much larger surface area, challenges abound for controlling drug release from this type of dosage form when coated with more permeable films. Chang [3] reported non-enteric performance of CAP (Aquateric®)-coated theophylline beads by the fluidized-bed process. The authors proposed that either the Pluronic F-68 in Aquateric® may have had an adverse effect, or the polymer was sensitive to the formulation variables, coating process and active substances.

Obara and McGinity studied the effect of processing conditions on the polymeric-free films prepared by spray method [16,17]. While the casting of the CAP dispersion resulted in transparent films, poor film formation was observed with the spray method. Powdered aggregate was obtained even though the surface temperature was maintained higher than the minimum film-formation temperature (MFFT). Rapid drying conditions may prevent the coalescence of the latex particles. Films were only formed using a high spray rate with a slow post-drying process to provide sufficient moisture content.

The objective of this paper was to investigate the effect of coating process variables on the in-situ enteric performance of beads coated with CAP aqueous dispersion. Theophylline was chosen as the model drug because of its non-ionic nature. Diethyl phthalate (DEP), a water insoluble plasticizer, was used as the plasticizer due to its effectiveness in reducing the glass transition temperature (T_g) of CAP, and its formation of less permeable films compared to films plasticized with water-soluble plasticizers [8]. Certain moisture requirements for film formation may not be achieved during spraying due to the existence of an upper-limit spray rate that can be applied on the beads without significant agglomeration. However, moisture can be supplied during the curing process. Therefore, another purpose of this study was to investigate the effect of curing under different relative humidities on drug release.

2. Materials and methods

2.1. Materials

The following chemicals were used as received: CAP aqueous dispersion (Aquacoat® CPD), Avicel® PH 101 (FMC Corporation, Philadelphia, PA); theophylline anhydrous (Spectrum Quality Products, Inc., Gardena, CA); lactose, monohydrate (Foremost Farm USA, Baraboo, WI); DEP (Eastman Chemical Company, Kingsport, TN); talc (Alphafil 500 USP; Luzenac America, Inc., Englewood, CO).

2.2. Preparation of theophylline beads

Beads were prepared by the extrusion–spheronization method. Theophylline, Avicel PH 101 and lactose in a 1:2:1 ratio were mixed for 20 min in a twin-shell dry blender (The Patterson–Kelley Co., Inc., East Stroudsburg, PA). Purified water was added slowly to the powder blend in the Kitchen Aid (Model KSM 90, Kitchen Aid, Inc., St. Joseph, MI) to prepare the wet mass. The wet mass was then passed through the extruder (Benchtop Granulator, Model No. 5666, LCI Corporation, Charlotte, NC) fitted with a 1.2-mm screen operated at a speed of 50 rev./min. The extrudates were immediately spheronized in a spheronizer (Caleva, Model 120, GEI Processing, Inc., Towaco, NJ) for 6 min. Wet beads between the sizes of 14- and 18-mesh were collected and dried for 48 h at 40°C. Dry beads between 16- and 20-mesh size were used for film coating.

2.3. Preparation of coating dispersion

Aquacoat® CPD was mixed moderately with a propeller mixer (Lightnin Series 20, Mixing Equipment Co., Inc., Rochester, NY). DEP was added slowly to the dispersion with stirring. The dispersion was continuously mixed for 1 h, and then mixed for an additional 23 h using a magnetic mixer (Corning, Model PC-320, Corning, NY). Purified water was then added to bring the total solids content to 15% and mixed for 15 min. The plasticized dispersion was filtered through a 120-mesh screen prior to coating.

2.4. Determination of MFFT

MFFT was quantitated using the method described by Obara and McGinity [17], which was modified from ASTM D2354-91 [18]. The temperature gradient of the MFFT bar spanned from 15 to 45°C. The air rate was 3 l/min as specified in ASTM D2354.

2.5. Coating procedure

Batches of 250 g of theophylline beads were loaded into a fluidized-bed coater (Strea-1, Niro Inc., Aeromatic–Fielderag Div., Columbia, MD) assembled with a Wurster insert. Coating dispersion was delivered by a peristaltic pump (Watson–Marlow, Concord, MA) and sprayed into the fluidized-bed via a 1.2-mm spray nozzle at the atomizing pressure of 1.5 bar. Coatings were performed at desired outlet temperatures by adjusting the inlet temperature setting. Beads were coated at two different plasticizer levels, outlet temperatures, spray rates and fluidizing air velocities, using a half-factorial design as shown in Table 1 (runs A–H). For each run, the initial spray rate was set at 1.4 g/min to reach a 3% coating, before switching to the targeted spray rates. Runs H through K, listed in Table 1, further investigated the influence of coating temperature, while other parameters were kept constant. Beads were coated at a theoretical weight gain of 30% for all batches. Unless specified, coated beads were post-column dried at the corresponding outlet temperature for 20 min. The coating efficiency was calculated by the following equation (Eq. (1))

$$(\text{weight of coated beads} - 250\ \text{g}) \times 100\%/75\ \text{g} \quad (1)$$

The degree of agglomeration was given by the following ranking system. Coated beads were sieved through a 14-mesh screen. Agglomeration between batches was compared by weighing beads retained on the sieve plus beads sticking on the Wurster column, if any present. The ranking system used was: '+', was given if the portion was within 5%; '++' for 5–10%; '+++' for 10–20%; and '++++' for 20–40%.

2.6. Curing conditions

An aliquot of coated beads from batches H–K were cured at 60°C for 12 h to study the effect of curing on beads coated at different temperatures.

A comparison of curing using heat-only (50 and 60°C), moisture-only (75% RH (relative humidity), saturated NaCl solution) and heat–moisture (50°C/75% RH) conditions was performed with batch H. For curing involving moisture, beads were blended with 2% talc to prevent sticking, if required, and placed in the desiccators containing saturated salt solutions.

Curing in the presence of different relative humidities was investigated with selected runs (batches H and K). Two curing temperatures, 40 and 50°C, and three relative humidities 51 (saturated NaBr solution), 65 (saturated KI solution) and 75% were studied for this purpose. Samples were taken out at 1, 2, 4, 8, 16 and 24 h and dried at 40°C for 24 h.

2.7. Dissolution

The enteric performance of the beads was evaluated by dissolution testing in 750 ml of 0.1 N HCl solution at 37°C, using the USP XXIII dissolution Apparatus II (paddle method; Vankel 6010, Vankel Industries, Inc., Edison, NJ) at a paddle speed of 50 rev./min. Accurately weighed samples containing the equivalent of about 25 mg of theophylline were used. Aliquots of 3 ml of the filtered dissolution medium were withdrawn at 10, 30, 60 and 120 min, and assayed by a diode array spectrophotometer (Model 8452A, Hewlett Packard Company, Wilmington, DE) at 270 nm.

Release in the pH 6.8 phosphate buffer was performed by the addition of 250 ml 0.2 M tribasic sodium phosphate (prewarmed to 37°C) immediately after the acid stage, and adjusting with 2 N HCl or NaOH to a pH of 6.8 ± 0.05. Additional samples were taken at 10, 20, 45 and 60 min and analyzed at 272 nm.

2.8. Scanning electron micrograph (SEM) of coated beads

The morphology of the surfaces was examined by scanning electron microscopy (Hitachi S-4100, Hitachi, Ltd., Ibaraki-Ken, Japan). Samples were gold-palladium coated for 60 s under an argon atmosphere using a Pelco Model 3 Sputter Coater (TED pella, Inc., Tusin, CA).

2.9. Preparation of free films by spray method

Free films were prepared by spraying Aquacoat® CPD

Table 1
Fluidized-bed coating conditions used for the experimental batches

Variable	Plasticizer level (%)[a]	Outlet temperature (°C)	Spray rate (g/min)	Air velocity (m^3/h)
A	(−) 30	(−) 36	(−) 2.0	(−) 50
B	(−) 30	(−) 36	(+) 3.2	(+) 90
C	(−) 30	(+) 48	(−) 2.0	(+) 90
D	(−) 30	(+) 48	(+) 3.2	(−) 50
E	(+) 35	(+) 48	(−) 2.0	(−) 50
F	(+) 35	(−) 36	(+) 3.2	(−) 50
G	(+) 35	(−) 36	(−) 2.0	(+) 90
H	(+) 35	(+) 48	(+) 3.2	(+) 90
I	35	36	3.2	90
J	35	40	3.2	90
K	35	32	3.2	90

[a] w/w; Based on total solids.

dispersion containing 35% DEP on a Teflon sheet. Hot air at 50°C, from a dryer, was blown over the surface to dry each layer between spraying. The thickness of the film was uniform and about 50 μm, which was close to the thickness of films applied on the beads in the fluidized-bed coater. The film was cut into two pieces and labeled A and B. Film A was cured at 40°C for 24 h. Film B was cured at 50°C/75%RH for 24 h, and then dried at 40°C for 24 h. Both films were conditioned at 23°C/50% RH for at least 7 days prior to the mechanical testing.

2.10. Measurement of mechanical properties

Mechanical properties of films A and B were tested using an Instron apparatus (Model 4201, Instron Corp., Canton, MA) based on the ASTM D882-95A guideline [19]. Films were cut into 13 × 140-mm rectangular specimens and five measurements were conducted for each film type. The test conditions were as follows: 1-KN load cell capacity; 5% amplification; 100-mm grip distance; 10-mm/min cross-head speed; and 80-mm/min chart speed. The mechanical properties, including tensile strength at break, % elongation at break and elastic modulus, were calculated from the load-time profiles.

2.11. Statistical analysis

Statistical analysis was performed using the SAS statistical package PROC GLM (SAS Institute, Cary, NC). Differences were considered to be significant at the level of $P < 0.05$.

3. Results and discussion

3.1. Effect of plasticizer levels and processing variables on drug release from coated theophylline beads

Fluidized-bed technology has been widely used for drying, granulating and coating pharmaceutical products. Its highly efficient drying capacity makes it ideal for coating beads and particles which tend to agglomerate when wet. The development of fluidized-bed technology also allows for the use of aqueous dispersions for coating beads, since it provides the higher energy needed to evaporate water. However, fluidized-bed coating is a complicated process. Many parameters will affect film formation, and are highly dependent on the characteristics of a given polymer. Therefore, it is necessary to investigate the processing conditions during product development.

Studies of free films produced by the spray method indicated that aqueous CAP film from Aquateric® was sensitive to drying conditions [17]. In this study, the influence of processing variables on film formation from beads coated with Aquacoat® CPD was investigated. Three important processing variables, including outlet temperature, spray rate and air velocity, along with plasticizer level, were evaluated by a half-factorial design. The release profiles of beads from batches A–H are shown in Fig. 1. The release was modeled using first-order kinetics. The first-order release rate, % agglomeration and coating efficiency are summarized in Table 2. The data was analyzed by SAS proc GLM, and the ANOVA tables are shown in Table 3. Temperature was found to be a critical parameter affecting drug release ($P < 0.01$). As seen in Fig. 1, all batches coated at 48°C released about 80% of theophylline within 30 min in acidic medium. Coated beads lost their integrity after 15 min, indicating that the film was not acid-resistant. The MFFT of CAP dispersion containing 35% DEP based on latex solids was experimentally determined to be 29 ± 1°C, thus the temperature of 48°C was well above the MFFT and within the normal coating range of 10–20° above the MFFT. However, the SEM picture in Fig. 2A reveals that coalescence had not taken place under this coating temperature. At ×5000 magnification, uncoalesced polymer particles could be seen on the surface of beads. It seemed that, at such a high temperature, the atomized droplets were dried while impinging onto the surface of the beads, and prevented further spreading and coalescence. Yang and Ghebre-Sellassie [20] reported similar results using ethylcellulose dispersion coated at a bed temperature of 50°C. Although the coating temperature was well above the T_g, the authors reported that films did not form because the evaporation rate of water may have overcome the diffusion of water from between the polymer particles to the surface, and prevented the development of capillary forces required for particle deformation.

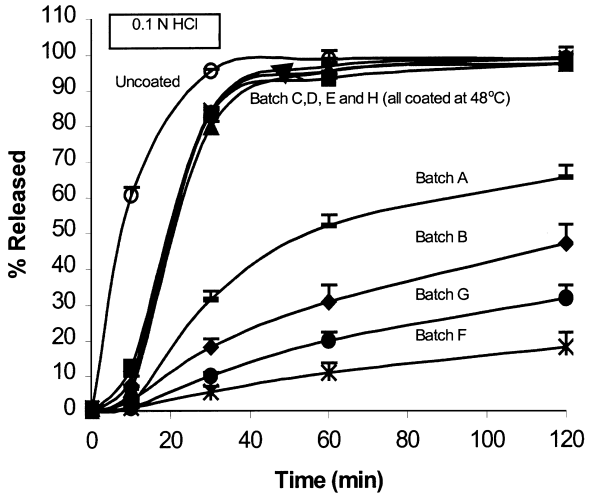

Fig. 1. Dissolution profiles of theophylline beads coated at various coating conditions. (○) Uncoated beads; (−), batch A; (◆), batch B; (■), batch C; (▲), batch D; (×), batch E; (), batch F; (●), batch G; (+), batch H.

In comparison, all batches coated at 36°C showed lower drug-release rates. Although there was not a statistically significant impact of the other three variables on the release rate, the release was retarded to different degrees for the batches coated at 36°C. The SEM picture in Fig. 2B reveals the presence of cracks on the surface of beads coated with

Table 2
Summary of data from half-factorial experiments

Batch	1st order release rate	Coating efficiency (%)	Degree of agglomeration
A[a]	0.0090	89.6	+
B[a]	0.0053	88.5	++
C	0.0499	79.1	−
D	0.0594	82.0	−
E	0.0660	82.9	−
F[a]	0.0017	92.3	++++
G[a]	0.0033	88.1	+
H	0.0585	80.5	−

[a] Batches coated at 36°C.

30% DEP-plasticized CAP. This implied that the polymer coating was under-plasticized. The slowest release was found with batch F (35% DEP at a spray rate of 3.2 g/min and air velocity of 50 m^3/h). The SEM picture in Fig. 2C demonstrates improved coalescence of the film. This condition represented a 'wet' environment for CPD-coating, in which the temperature and air velocity were low, while the spray rate was high. The overall drying rate was slower and led to better film formation. This finding was consistent with the studies of free films reported by Obara and McGinity [17]. Using an IR moisture sensor, Watano et al. also reported that drug release from Eudragit L-30D- or Eudragit RS-30D-coated granules was decreased as the moisture content in the tumbling fluidized-bed process was increased [21,22]. The reduction in drug release was due to a higher coating efficiency, as a result of reduced spray-drying of atomized coating droplets at higher moisture contents. As shown in Table 2, the coating efficiency for CAP-coated at 36°C was about 5% more compared to the batches coated at 48°C. Both temperature and air velocity had a statistically significant influence on the coating efficiency ($P < 0.05$). Because of insufficient drying, low drug release of theophylline in batch F was accompanied by significant agglomeration, while all four batches coated at 48°C showed no agglomeration. This was due to the appearance of spray-drying and failure to coalesce. It was noted that at the 36°C-coating temperature, although the release rate was lower, none of the batches investigated displayed less than 10% release in the acidic media.

3.2. Effect of temperature and curing conditions

Two more levels of temperature around 36°C, but above the MFFT, were conducted to further investigate the effect of temperature and search for the optimized point. In this study, the plasticizer level was 35%, the spray rate was 3.2 g/min, in order to avoid a lengthy spray process, and the air velocity was 90 m^3/h in order to reduce agglomeration. Comparing between batches F and I, which were at the same coating temperature, this combination reduced the %

Table 3
ANOVA tables for first-order rate constant and coating efficiency[a]

Dependent variable: first order rate constant					
Source	d.f.	SS	MS	*F*-value	Pr > *F*
Model	4	0.00580260	0.00145065	39.76	0.0062
Error	3	0.00010944	0.00003648		
Total	7	0.00591204			
R-square		C.V.	Root MSE	Mean	
0.981488		19.09118	0.0060399	0.03163750	
A	1	0.00000435	0.00000435	0.12	0.7526
B	1	0.00575128	0.00575128	157.65	0.0011
C	1	0.00000136	0.00000136	0.04	0.8592
D	1	0.00004560	0.00004560	1.25	0.3450
Dependent variable: coating efficiency					
Model	4	162.81000000	40.70250000	144.51	0.0009
Error	3	0.84500000	0.28166667		
Total	7	163.65500000			
R-square		C.V.	Root MSE	Mean	
0.994837		0.621637	0.5307227	85.37500000	
A	1	2.64500000	2.64500000	9.39	0.0548
B	1	144.50000000	144.50000000	513.02	0.0002
C	1	1.62000000	1.62000000	5.75	0.0960
D	1	14.04500000	14.04500000	49.86	0.0058

[a] A, Plasticizer level; B, outlet temperature; C, spray rate; D, air velocity.

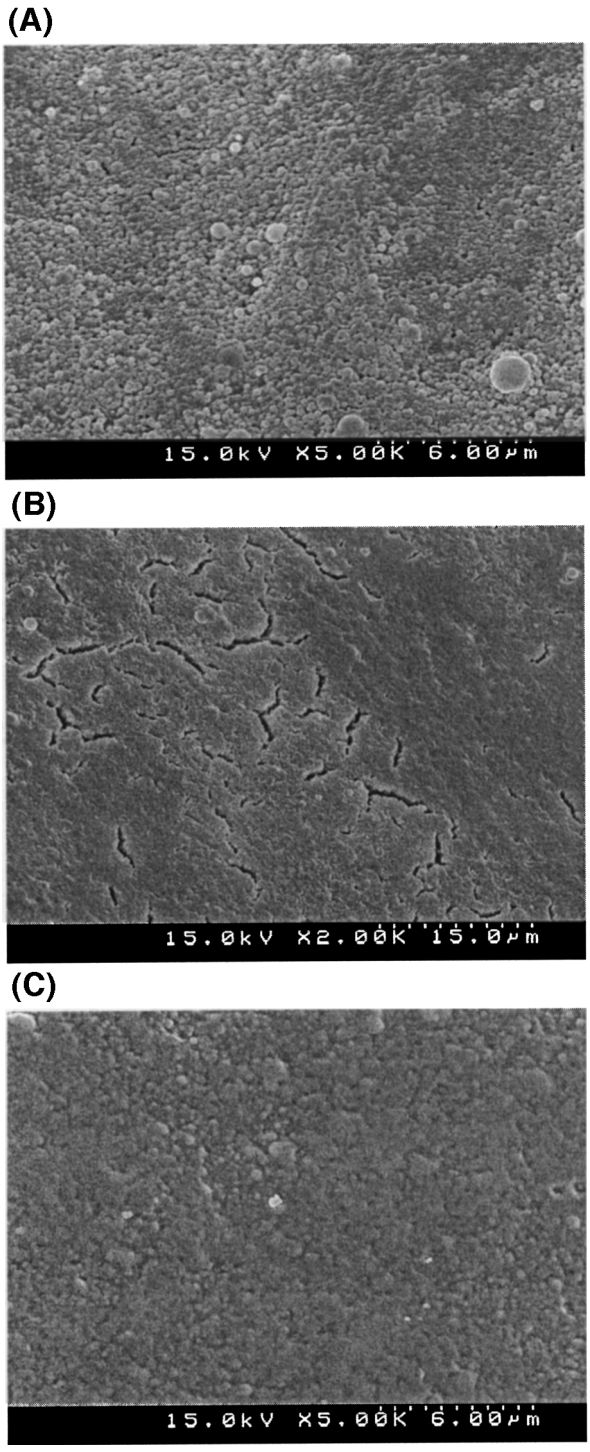

Fig. 2. SEM pictures of the surface of coated beads. (A) Batch H (batches C, D and E shared similar features); (B), batch A (batch B showed similar features but less cracking); (C), batch F.

agglomeration by more than 67%. The drug release was slightly higher because the air velocity was increased.

Dissolution profiles of batches H–K are shown in Fig. 3 (solid line). As the temperature was decreased, the release rate of theophylline decreased. The results indicated that at 32°C, the temperature was not low enough to impede film formation; in fact, lowering the coating temperature enhanced coalescence. The low water evaporation rate possibly gave more opportunities for the polymer particles to coalesce before the film was dried. The polymer particles were able to move freely, which led to the formation of a continuous and well-packed film [22]. Since moisture was present in the film and water molecules could function as a plasticizer, release of the drug may vary when moisture that remained in the coating layer was gradually evaporated. The temporary plasticization with water may lead to increased release when water is removed, but if coalescence continues during water evaporation, the drug release will decrease further. The % release of theophylline at 2 h for beads coated at 32°C, before and after either drying at 40°C for 24 and 48 h, or stored at 0% RH for 5 days, is compared in Fig. 4. The results indicated that the dissolution was further reduced as the water evaporated, which suggested that coalescence continued during the drying process.

On comparison of the four coating temperatures investigated, temperatures above 40°C were not suitable for CAP-coating on beads. A lower coating temperature was the better choice because more acid-resistance was demonstrated from the drug-release profiles. It was also found that beads coated at 36°C, but post-column dried at 48°C, displayed nearly a 10% increase in drug release in acid medium at 2 h. Hence, it would be preferable to perform the drying of beads at lower temperatures in the fluidized bed, or in an oven at 40°C, to prevent sticking during storage.

Since no enteric profiles were obtained in the above-mentioned studies, curing was investigated for the effect in obtaining enteric-release profiles. Curing is the thermal treatment after coating to provide additional heat for further coalescence, and has been suggested for use with polymers with a high T_g, such as CAP. The results shown in Fig. 3 (dashed line) reveal the dissolution profiles of beads

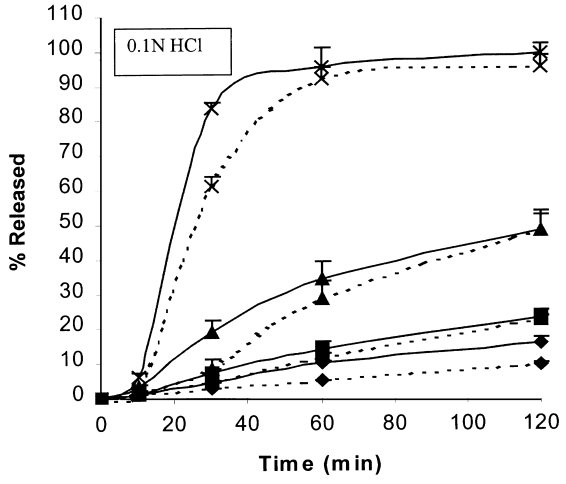

Fig. 3. Dissolution profiles of theophylline beads coated at various temperatures. (◆) 32°C; (■), 36°C; (▲), 40°C; (×), 48°C. The solid line represents uncured beads and the dashed line represents cured beads.

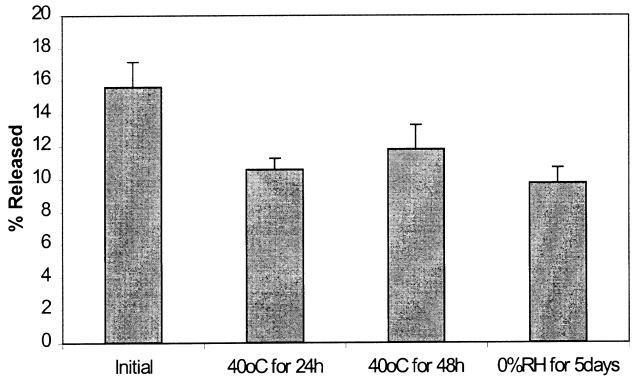

Fig. 4. Percent release of theophylline at 2 h in 0.1 N HCl for batch K dried at different conditions.

subjected to curing at 60°C for 12 h. It was found that the curing step only reduced the drug release from beads coated at 32°C ($P < 0.05$). The beads in this batch were found to be aggregated after the curing step, therefore, 2% talc was blended with the beads before placing them in the oven. After the curing step, the release of theophylline after 2 h in acid media decreased to less than 10%. For beads coated at 36, 40 and 48°C, curing only slowed down the initial release rate, but there was no significant difference in the % release at 2 h compared to the uncured beads ($P > 0.05$). These results indicated that curing was dependent on the coating temperature. The residual moisture retained in the coating layer of beads coated at 32°C may play a role in the coalescence during curing. It was proposed that heat was not the only factor required for the coalescence of CAP films, and curing was not able to proceed without sufficient moisture present in the film coating. Therefore, the following study was performed to compare curing with and without the presence of moisture.

3.3. Effect of humidity on the curing process

During bead coating, the spray rate was controlled to avoid heavy agglomeration. Therefore, the moisture requirement for CAP film formation, as suggested in Obara and McGinity's study on spray films [17], may not be reached during spraying of the coating onto the substrate. In order to verify the influence of moisture on CAP film formation, batch H was heat-cured at 75% RH. This also provided information to study the conversion of a poorly coalesced film, due to lack of moisture at high coating temperatures, by providing additional moisture during curing.

Dissolution profiles of batch H cured at various heat-only conditions (50°C for 24 h; 60°C for 24 and 48 h), moisture-only condition (75% RH at room temperature for 24 h) and the combination of heat–moisture conditions (50°C/75% RH for 24 h) are compared in Fig. 5. With the heat-only curing condition, the release of theophylline was immediate in acid media and similar to the uncured beads. No significant differences were shown for curing at higher temperatures or longer times. Theophylline was completely released at 2 h in acid media, as shown in Fig. 5. With the moisture-only condition, similar results were found. However, interestingly, beads cured at 50°C/75% RH were found to be aggregated with shinier surfaces, which indicated that film coalescence may have occurred. The experiment was repeated by blending beads with 2% talc and cured at the same conditions to prevent sticking. A dramatic change in the dissolution profiles was found, and enteric profiles with a drug release of less than 10% in acid media were obtained (Fig. 5). It was observed that the film remained intact during the 2-h exposure to the acid media. More than 80% of theophylline was released in the buffer stage at 45 min. Surprisingly, beads from batch H coated at a 20%-coating level and subjected to same curing process, showed similar release profiles. This suggested that the coating level could be reduced due to the formation of a higher quality film.

The weight gain of beads was 1.4% during the curing process at 50°C/75% RH, which suggested that water molecules were absorbed into the film. Since water is a well-known plasticizer, it would plasticize the film and increase the film quality. However, the plasticization is temporary, due to its low boiling point and subsequent evaporation. Therefore, it was necessary to investigate the effect of removing the water from the cured beads on drug dissolution in acid media. The heat–moisture cured beads were dried at 40°C for 24 h. Dried beads weighed slightly less than uncured beads, which indicated that the moisture absorbed was removed. As seen in Fig. 5, the enteric-dissolution profiles were reproducible after the absorbed moisture was removed by heat. Also, it was found that increasing

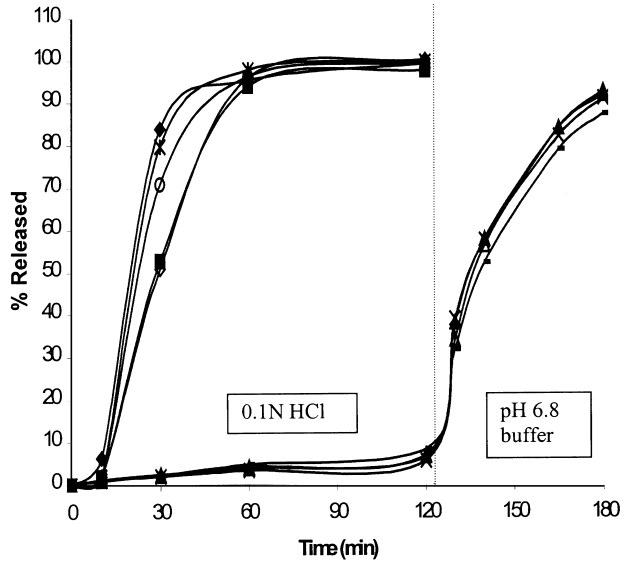

Fig. 5. Release profiles of batch H subjected to different curing process. (◆) Uncured; (*), 50°C for 24 h; (■), 60°C for 24 h; (◇), 60°C for 48 h; (○), 25°C/75% RH for 24 h; (▲), 50°C/75% RH for 24 h; (△), 50°C/75% RH for 24 h + 40°C for 24 h; (−), 20%-coating level, 50°C/75% RH for 24 h + 40°C for 24 h; (×), No talc, 50°C/75% RH for 24 h + 40°C for 24 h.

the drying time to 7 days at 40°C did not change the dissolution profiles significantly ($P < 0.05$). Similar dissolution results were found at 40 days. The results indicated that both temperature and humidity were necessary to obtain good film quality during curing for poor film formed at high coating temperatures, and the restoration was a long-term effect even after moisture was removed.

When the beads were examined by SEM, the surface was covered with talc particles. To exclude the potential effect of talc on the dissolution, beads from batch H were carefully placed onto a Teflon plate and heat–humidity cured. The dissolution test in acid media was conducted on the beads without the prior use of talc. The results shown in Fig. 5 indicated that the release was slightly lower than in beads with talc. This indicated that talc functioned as an anti-sticking agent without altering the release of the drug from the beads. During curing, some talc particles adsorbed onto the surface may affect the film continuity, but this only slightly influenced the drug release. SEM demonstrated that, after heat–humidity curing, uncoalesced surface features, as seen previously in Fig. 2A, had been transformed into a smooth and coalesced film without defects (pictures not shown). The morphology of the film remained the same when the moisture that was absorbed during curing was removed. Similar morphological changes were observed for HPMCAS-coated beads when stored in an open container at 40°C/75% RH [10].

In order to determine the change of mechanical properties after heat–humidity curing, free films were prepared by the spray method. The freshly-made film was observed to be semi-transparent, and film A, which was dried at 40°C for 24 h, retained the same appearance. Film B, which was cured at 50°C/75%RH for 24 h and then dried at 40°C for 24 h, became completely transparent after curing. The representative displacement-load profiles of films A and B are shown in Fig. 6. Mechanical properties obtained from the displacement-load profiles demonstrated significant differences in the tensile strength, % elongation and elastic modulus between films A and B ($P < 0.05$). Heat–humidity curing produced films with increased tensile strength, % elongation and elastic modules, with the effect more pronounced on the elongation (increased by 3.3-fold). Similar trends were reported for ethylcellulose, another cellulosic polymer, when stored at 45°C/75% RH [23]. In a previous study [24], heat-curing decreased the % elongation and increased the tensile strength and elastic modulus of CAP-cast films. Moisture was reported to be an effective plasticizer, leading to films with increased % elongation, and reduced tensile strength and elastic modulus [25]. This study showed that curing while exposed to 75% RH combined the effects of heat and plasticization, which together increased the toughness of the CAP films. This explained why coated beads were able to remain intact in the acid media during dissolution. Dramatically-reduced drug release in the acid media also indicated the critical role of mechanical strength and ductility on being acid-resistant for CAP films.

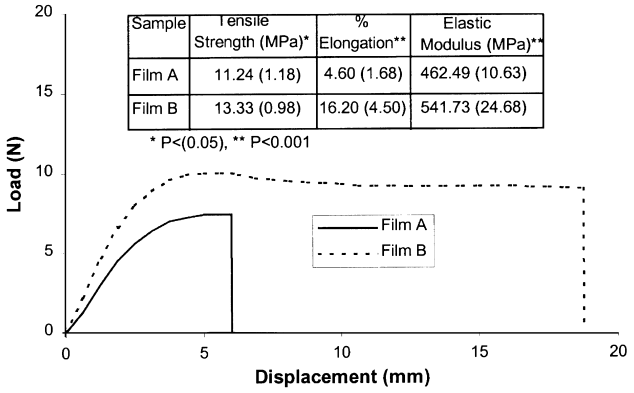

Fig. 6. Representative load-displacement profiles of films A and B.

Without sufficient moisture in the coating layers, capillary forces were not sufficient to deform the polymer particles, leaving dried particles on the surface of the polymer coating. The semi-transparent appearance of the free film may be the result of some uncoalesced polymer particles formed during spraying. When these dried particles were exposed to heat with sufficient moisture, water molecules were absorbed by the coating. Water molecules, very efficient plasticizers, interacted with polymer chains by competing for bonding sites, i.e. free hydroxyl groups, to increase the mobility [23]. The fraction of DEP that remained in the form of emulsion droplets in the coating dispersion without interacting with the polymer, may undergo redistribution between the polymer and water phases, leading to a greater fraction of DEP associated with the polymer. With sufficient heat provided, the coating layer became soft. Polymer particles were mobile and coalesced to form a continuous film. When moisture was removed from the cured beads, it was DEP which maintained the film integrity.

In order to maintain the stability of the drug and CAP, it is preferred to conduct the curing process at a lower temperature and humidity for shorter periods of time. To identify the minimum temperature and humidity required for allowing film coalescence, beads from batch H were cured at 40 and 50°C with humidities of 51, 65 and 75% for 24 h, and beads from batch K were cured at 40 and 50°C at a humidity of 75%. The % theophylline released at 2 h in acid media is summarized in Table 4. For batch H, 51% RH was shown to have no effect on decreasing the theophylline release at either curing temperature, as well as the curing condition at 40°C/65% RH. The weight of beads was decreased, which indicated no interaction between the coating and the water molecules. Beads from batch H cured at 50°C with 65 and 75% RH for 24 h exhibited enteric-release dissolution profiles. Curing at 40°C/75% RH decreased the theophylline release significantly from 99.17 to 14.33%, which indicated that coalescence occurred; however, under such conditions, curing times longer than 24 h were required in order to achieve complete coalescence. As beads from batch K had better film formation than those from batch H, 40°C was

Table 4
Percent release of drug from coated beads after curing for 24 h at various temperatures and humidities[a]

Temperature (°C)	40			50		
Humidity (%)	51	65	75	51	65	75
Batch H	100.20 (0.40)	100.17 (0.38)	14.33 (0.30)	99.73 (0.98)	8.69 (0.59)	6.67 (0.18)
Batch K	–	–	8.59 (0.54)	–	–	6.39 (0.46)

[a] Standard deviations shown in parentheses.

found to be sufficient to reduce theophylline release to less than 10% in acid media. For beads from batch H cured at 50°C/65% and 50°C/75% RH, the minimum time to reach reproducible release profiles was evaluated. Fig. 7 shows that for beads cured at 75% RH, the time to achieve reproducible release profiles was about 4 h; however, at 65% RH, almost 24-h curing time was required to obtain similar release profiles. These results indicated that the effect of curing with moisture was dependent on the exposure temperature, exposure humidity, curing time and history of coating conditions.

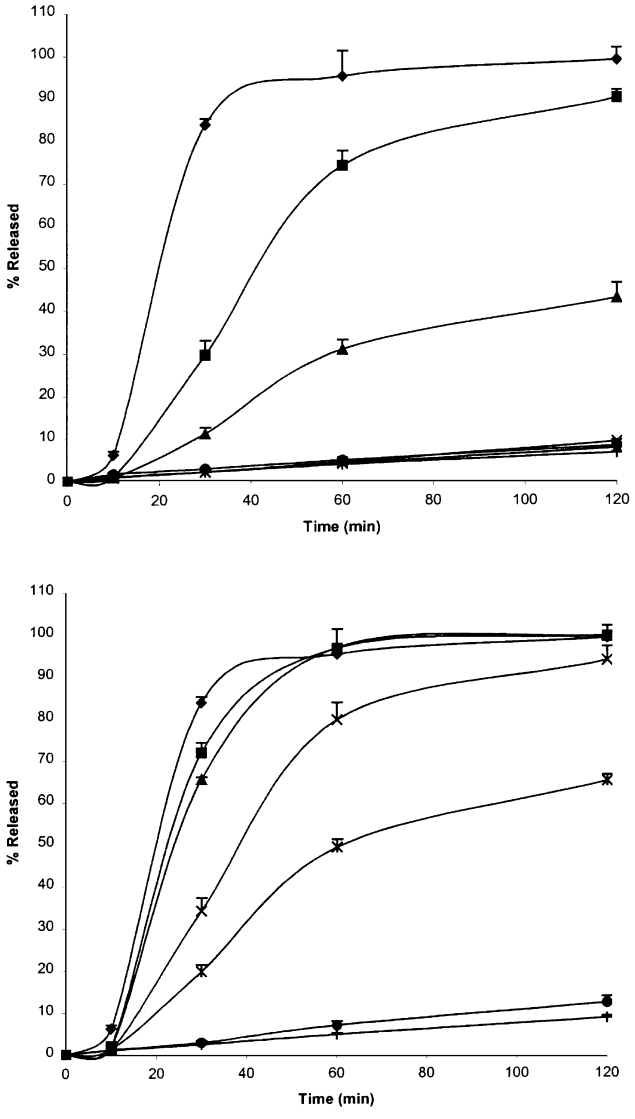

Fig. 7. Release profile of batch H cured at: (top), 50°C/75% RH; and (bottom), 50°C/65% RH for different periods of time. Curing times: (◆), 0 h; (■), 1 h; (▲), 2 h; (×), 4 h; (∗), 8 h; (●), 16 h; (+), 24 h.

In summary, the effects of fluidized-bed processing and curing conditions were evaluated for beads coated with an aqueous CAP dispersion. The coating temperature was found to be a critical parameter. Above the MFFT, the lower the coating temperature, the better the enteric film was formed. Heat-only curing had no significant effect on reducing the drug release, except for the batch coated at the lowest temperature. Exposure of the beads to elevated humidity during curing enhanced coalescence of the film and the mechanical strength of film. The degree of improvement was dependent on the curing temperature, % humidity, curing time and the history of coating conditions. These findings supported the importance of controlling the processing and curing conditions to enhance post-coating polymer coalescence for beads coated with aqueous CAP.

References

[1] T.A. Wheatley, C.R. Steuernagel, Latex emulsions for controlled drug delivery, in: J.W. McGinity (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Dekker, New York, 1997, pp. 1–54.
[2] M.S. Gordon, A. Fratis, R. Goldbium, D. Jung, K.E. Schwartz, Z.T. Chowhan, In vivo and in vitro evaluation of four different aqueous polymeric dispersions for producing an enteric coated tablets, Int. J. Pharm. 115 (1995) 29–34.
[3] R.-K. Chang, A comparison of rheological and enteric properties among organic solutions, ammonium salt aqueous solutions, and latex systems of some enteric polymers, Pharm. Tech. 14 (10) (1990) 62–70.
[4] Aquacoat® CPD–Aqueous enteric coating, FMC Corporation, Philadelphia, PA, USA.
[5] Aquateric® – Aqueous enteric coating, FMC Corporation, Philadelphia, PA, USA.
[6] F. Gumowski, E. Doelker, R. Gurny, The use of a new redispersible aqueous enteric coating material, Pharm. Tech. 11 (1987) 26–32.
[7] C.A. Entwistle, R.C. Rowe, Plasticization of cellulose ethers used in the film coating of tablets, J. Pharm. Pharmacol. 31 (1979) 267–272.
[8] F. Raffin, C. Duru, M. Jacob, Permeability to hydrogen ions of an enteric coating polymer and interaction of film formulation factors, Int. J. Pharm. 145 (1996) 247–252.
[9] J.T. Heinämäki, A.I. Colarte, A.J. Nordström, J.K. Yliruusi, Comparative evaluation of ammoniated aqueous and organic-solvent-based cellulose ester enteric coating systems: a study on free films, Int. J. Pharm. 109 (1994) 9–16.
[10] K. Thoma, K. Bechtold, Influence of aqueous coatings on the stability

of enteric coated pellets and tablets, Eur. J. Pharm. Biopharm. 47 (1999) 39–50.
[11] I. Cherretté, J.A. Plaizier-Vercammen, Evaluation of a water dispersion of Aquateric for its enteric coating properties of hard gelatin capsules manufactured with a fluidized bed technique, Pharm. Acta Helv. 67 (1992) 227–230.
[12] J. Plaizier-Vercammen, G. Suenens, Evaluation of Aquateric, a pseudolatex of cellulose acetate phthalate, for its enteric coating properties on tablets, S.T.P. Pharm. Sci. 1 (1991) 307–312.
[13] R. Bianchini, M. Resciniti, C. Vecchio, Technological evaluation of aqueous enteric coating systems with and without insoluble additives, Drug Dev. Ind. Pharm. 17 (1991) 1779–1794.
[14] F. Gumowski, E. Doelker, R. Gurny, The use of a new redispersible aqueous enteric coating material, Pharm. Tech. 11 (1987) 26–32.
[15] S. Scheiffele, K. Kolter, G. Schepky, Studies comparing Kollicoat MAE 30 D with commercial cellulose derivatives for enteric coating on caffeine cores, Drug Dev. Ind. Pharm. 24 (1998) 807–818.
[16] S. Obara, J.W. McGinity, Properties of free films prepared from aqueous polymers by a spraying technique, Pharm. Res. 11 (1994) 1562–1567.
[17] S. Obara, J.W. McGinity, Influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique, Int. J. Pharm. 126 (1995) 1–10.
[18] American Society for Testing and Materials (ASTM), Guideline, D 2354-91: Standard Test Method for Minimum Film Formation Temperature (MFFT) of Emulsion Vehicles.
[19] American Society for Testing and Materials (ASTM), Guideline, D 882-95a: Standard Test Method for Tensile Properties of Thin Plastic Sheeting.
[20] S.T. Yang, I. Ghebre-Sellassie, The effect of product bed temperature on the microstructure of Aquacoat-based controlled-release coatings, Int. J. Pharm. 60 (1990) 109–124.
[21] S. Watano, K. Yoshikawa, K. Miyanami, Evaluation of aqueous enteric coated granules prepared by moisture control method in tumbling fluidized bed process, Chem. Pharm. Bull. 42 (1994) 663–667.
[22] S. Watano, I. Wada, K. Miyanami, Modeling and simulation of drug release from granule coated with an aqueous-based system of acrylic copolymer, Chem. Pharm. Bull. 43 (1995) 877–880.
[23] D. Hutchings, S. Clarson, A. Sakr, Studies of the mechanical properties of free films prepared using an ethylcellulose pseudolatex coating system, Int. J. Pharm. 104 (1994) 203–213.
[24] R.O. Williams, T.A. Wheatley, J. Liu, Influence of plasticization and curing conditions on the mechanical properties of aqueous-based cellulose acetate phthalate films, S.T.P Pharm. Sci. 9 (1999) 545–553.
[25] M.E. Aulton, M.H. Abdul-Razzak, The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems. Part 1: the influence of plasticizers, Drug Dev. Ind. Pharm. 7 (1981) 649–668.