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Research paper

Long-term stability of heat–humidity cured cellulose acetate phthalate coated beads

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Abstract

The objective of this study was to investigate the influence of stability storage conditions on the enteric release of heat–humidity cured cellulose acetate phthalate (CAP) coated beads. Theophylline beads were coated with 25 or 35% diethyl phthalate plasticized CAP dispersion (Aquacoat® CPD), and cured at a heat–humidity condition (50°C/75% RH) for 24 h. The cured beads were then stored in various container/closure systems (open glass containers, sealed glass containers with and without desiccant) and exposed to 40°C/75% RH for 6 months or 25°C/60% RH for 12 months. At accelerated conditions (40°C/75% RH), only beads stored in sealed glass containers with desiccant displayed stable release profiles throughout the exposure period. The beads stored in sealed glass containers without desiccant showed increased theophylline release in acidic media at 2 h, and did not maintain enteric resistance at 6 months. The release profiles of beads stored in open containers, directly exposed to 40°C/75% RH, were the least stable. The decrease in enteric protection of the beads stored at these two packaging conditions was correlated to an increased phthalic acid content in the films. At ambient storage conditions (25°C/60% RH), all samples possessed enteric release properties, irrespective of the container/closure system. Beads stored in sealed glass containers with desiccant remained the most stable compared to those at the other two packaging conditions. The results indicated that although humidity significantly contributed to coalescence of CAP coating during the curing process, the optimum packaging condition for the heat–humidity cured CAP coated beads was with desiccant to maintain the chemical stability of the CAP.

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

1. Introduction

Due to toxicity, cost and environmental concerns, aqueous coating systems have gradually replaced traditional organic coating systems. In comparing the enteric performance of some enteric polymers in the form of organic solutions, ammonium salt solutions and latex systems, Chang [1] reported that coated films from an aqueous dispersion of cellulose acetate phthalate (CAP, Aquateric®) provided insufficient acid resistance for theophylline beads. There were several reasons that could lead to such results: a different film formation mechanism from the aqueous dispersion compared to that from the organic solution or ammonia neutralized solution [2]; increased film permeability with aqueous based films [3]; sensitivity of film formation from aqueous dispersion to spraying parameters [4] and the large surface area of beads compared to the area of tablets or capsules. Our previous study [5], which investigated the influence of coating and curing conditions on CAP coated beads, demonstrated that film formation of CAP was sensitive to the coating temperature. Significantly improved films were formed at lower coating temperatures where the drying rate of the dispersion was slow. The findings were in agreement with Obara and McGinity's study [4] on CAP sprayed free films, in which the authors reported that the CAP free films formed when given sufficient moisture content. Furthermore, our study indicated that short-term exposure of CAP coated beads to both heat and humidity during the curing process greatly improved the coalescence of the films and produced enteric release profiles.

For heat–humidity curing to be a practical and applicable curing process for CAP coated beads, it is required that the enteric release profiles of these heat–humidity cured beads be maintained throughout the shelf-life of the finished drug product. In performing the release stability study, questions arise about what is the appropriate packaging configuration for these heat–humidity cured beads: exposing them to humidity or no humidity?

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In the CAP structure, the acetyl and phthalyl groups, which are responsible for the enteric properties, are susceptible to hydrolysis during storage, and the degree of hydrolysis increases as the storage temperature and humidity are increased [6,7]. Therefore, in consideration of the chemical stability of the polymer, the finished products should be kept in a low humidity environment to prevent ester cleavage. However, other aspects, such as the physical and mechanical stabilities, also influence the stability of films. The effect of humidity on the film properties of chemically stable polymers including Eudragit® RS 30D, ethylcellulose and hydroxypropyl methylcellulose (HPMC) has been investigated. In general, in a higher humidity environment, the hydroplasticization effect of the moisture reduced the T_g and increased the film flexibility, resulting in decreased drug release [8–11]. Karlsson and Singh [12] revealed that the physical properties of CAP films changed rapidly with changes in environmental humidity. Films tested at 70% RH were highly plastic and ductile compared to the films tested at 20% RH.

Humidity-induced film flexibility may be advantageous for CAP coated beads in order to sustain the increased stress during storage and maintain enteric resistance during dissolution testing. It is important to elucidate whether the chemical stability of the polymer or the physical stability of the film governs the enteric release of the heat–humidity cured beads as a function of shelf-life, so that an appropriate container/closure system can be chosen for stability testing.

So far, the enteric release profiles of heat–humidity cured beads have been maintained during exposure to 40°C/3% RH for 40 days [5]. Whether the presence of humidity is required to maintain the properties of coalesced films during long-term storage (6 months–1 year) is unknown. The objective of this study is to investigate the influence of stability storage conditions (e.g. temperature, humidity and container/closure system), on the enteric release of the heat–humidity cured CAP coated beads during long-term storage.

2. Materials and methods

2.1. Materials

The following chemicals were used as received: CAP aqueous dispersion (Aquacoat® CPD, FMC Corporation, Philadelphia, PA, USA), microcrystalline cellulose (Avicel® PH 101, FMC Corporation); theophylline anhydrous (Spectrum Quality Products, Inc., Gardena, CA, USA); lactose monohydrate (Foremost Farm USA, Baraboo, WI, USA) and diethyl phthalate (DEP; Eastman Chemical Company, Kingsport, TN, USA). The container was a 5-ml type I glass bottle and the closure was a white high density polyethylene (HDPE) plastic screw-cap with a foil liner (Saint Gobain Desjonqueres, France). Calcium sulfate anhydrous (Drierite; 1 g per container, W.A. Hammond Drierite Company Ltd, Xenia, OH, USA) was used as the desiccant.

2.2. Preparation of theophylline beads

Beads containing 25% theophylline, 50% microcrystalline cellulose and 25% lactose monohydrate were prepared by extrusion–spheronization according to the procedure described previously [5]. Dried beads in the 16- to 20-mesh size were used for coating.

2.3. Preparation of coating dispersion

Aquacoat® CPD was mixed moderately with a propeller-type mixer (Lightnin Series 20, Mixing Equipment Co., Inc., Rochester, NY, USA) and plasticized with 25 or 35% (w/w) DEP (based on total solids in the dispersion) for 24 h. Purified water was added to the dispersion after plasticization to dilute the total solids content to 15%. The dispersion was mixed for 15 min and filtered through a 120-mesh screen prior to coating.

2.4. Coating procedure

Theophylline beads, 250 g, were coated in a fluidized-bed coater (Strea-1, Niro Inc., Aeromatic-Fielderag Div., Columbia, MD, USA) with a Wurster insert. CAP dispersion was delivered by a peristaltic pump (Watson-Marlow, Concord, MA, USA). The coating parameters are summarized in Table 1.

2.5. Curing conditions

Coated beads were cured at the heat–humidity condition (50°C/75% RH) for 24 h. The beads were blended with 4% talc prior to the curing process to minimize tackiness. The heat–humidity cured beads were further dried at 40°C/3% RH for 3 days to decrease the moisture absorbed during the curing process.

2.6. Stability test

The beads were stored in different packaging configurations: sealed glass containers with desiccant, sealed glass containers without desiccant and open glass containers. The samples were exposed to 40°C/75% RH for 6 months or 25°C/60% RH for 12 months. The desiccant maintained

Table 1
The parameters employed for the coating of beads in the Strea-1 fluidized-bed coater

Outlet temperature	46°C
Air velocity	60–70 m^3/h
Nozzle diameter	1.2 mm
Spray rate	2.6 g/min
Atomizing air pressure	1.2 bar
Coating level	Theoretical weight gain of 30% based on total solids

the humidity within the glass containers at approximately 12%.

2.7. Dissolution

Drug release from the coated beads was evaluated according to the USP 24 Dissolution Method A for enteric-coated dosage forms. Specifically, 750 ml of 0.1 N HCl solution as the acidic media was equilibrated at 37°C in the dissolution apparatus (Vankel 6010, Vankel Industries, Inc., Edison, NJ, USA) at a paddle speed of 50 rpm. An accurately weighed aliquot of coated beads containing the equivalent of about 25 mg of theophylline was placed into each of the dissolution vessels. At 2 h, a 3 ml aliquot of the filtered dissolution media was withdrawn, and then the pH of the dissolution media was adjusted immediately to 6.8 by adding 250 ml of 0.2 M tribasic sodium phosphate to each vessel. Samples were withdrawn at 45 min following the pH adjustment.

2.8. Determination of theophylline concentration by reverse-phase high performance liquid chromatography (RP-HPLC)

An RP-HPLC method was developed to determine theophylline concentration in the dissolution samples in order to eliminate interference from possible increasing levels of the CAP degradation product phthalic acid present in the film after storage. The chromatographic system consisted of an LC-10-AT solvent delivery module and system controller, a Sil-10A auto injector and an SPD-M10A diode array detector (Shimadzu Corp., Columbia, MD, USA). A C_{18} column (Intersil 5μ, 150 × 4.6 mm, MetaChem Technologies Inc., Torrance, CA, USA) was used for separation. The mobile phase consisted of phosphate buffer (25 mM, pH 2.5) and acetonitrile in an 88:12 ratio. The flow rate was 1 ml/min and the detection wavelength was 270 nm. The retention time of theophylline was 4.8 min. At 6 min the acetonitrile concentration was increased to 60% to elute phthalic acid and DEP from the column, and the system was re-equilibrated at the starting mobile phase composition prior to the next injection. The total run time was 21 min. The linear range was from 1 to 31 μg/ml with a correlation coefficient of 0.9999. The recovery was 97.7 ± 1.1% and the relative standard deviation for six replicate injections was 0.67%.

2.9. Determination of DEP and phthalic acid content from coated beads by RP-HPLC

Extraction of DEP and phthalic acid from the coated film was performed using a method described previously [13], which was modified from Roxin et al. [7]. Specifically, an aliquot of 0.5 ml tetrahydrofuran was first added slowly to 130 mg beads in a centrifuge vial with stirring to dissolve the coating. CAP was then precipitated following the addition of 10 ml methanol with stirring. The mixture was centrifuged at 3000 rpm for 10 min. The DEP and phthalic acid concentration in the filtered supernatant was determined by RP-HPLC.

The same column and chromatographic system that was used for the determination of theophylline was employed for assay of DEP and phthalic acid. For DEP detection, the mobile phase consisted of phosphate buffer (25 mM, pH 2.5) and acetonitrile in a 40:60 ratio delivered at 1 ml/min. The detection wavelength was 220 nm and the retention time was 5.5 min. Theophylline and phthalic acid were eluted in less than 2.5 min, thus they did not interfere with the resolution of DEP.

Phthalic acid concentration was determined by using a mobile phase consisting of phosphate buffer (25 mM, pH 2.5) and acetonitrile in 83:17. The retention time of phthalic acid was 6.6 min. The mobile phase was delivered isocratically at 1 ml/min for the initial 7 min, and then the acetonitrile concentration was increased to 60% to elute DEP from the column. The column was then re-equilibrated at the initial mobile phase composition prior to the next injection. The total run time was 23 min. This method was modified from Bodmeier and Chen's method [14] to analyze phthalic acid from CAP films containing plasticizer and active drug.

The level of DEP and phthalic acid in the film was calculated by knowing the actual weight gain of the beads after coating.

3. Results and discussion

3.1. Accelerated stability study at 40°C/75% RH

The percentage of drug release in the acid and buffer stages from beads stored at 40°C/75% RH for 3 and 6 months is summarized in Table 2. At the 3-month storage period, reproducible release profiles were obtained from the beads stored in sealed glass containers with desiccant. The beads stored in sealed glass containers without desiccant showed a 2–3% increase in theophylline release in acidic media at 2 h, and a 5–6% increase in drug release in the buffer stage at 45 min compared to the initial dissolution profiles. However, for beads stored in the open glass containers directly exposed to 75% RH, the percentage of drug release at the end of the 2-h acid stage increased to more than 10%. Extending the stability test to 6 months, the beads stored in sealed glass containers with desiccant maintained similar enteric dissolution profiles to the initial dissolution profiles, however, those stored in the glass containers without desiccant did not pass the enteric test, resulting in more than 10% drug release at 2 h in acidic media (Table 2).

The phthalic acid levels in the coated films from beads stored in different container/closure systems at 40°C/75% RH for 3 and 6 months are given in Table 3. The beads stored in open glass containers contained the highest phthalic acid content (9.1%), while the phthalic acid level in the beads stored in sealed glass containers with desiccant remained low (1.9%). A correlation between the phthalic

Table 2
Percent theophylline released in acidic media at 2 h and in buffer media at 45 min from beads stored in different container/closure systems exposed to 40°C/75% RH for 3 and 6 months ($n = 3$)

DEP level	Release media	Initial	Container/closure system				
			Sealed glass containers without desiccant		Sealed glass containers with desiccant		Open glass containers
			3 months	6 months	3 months	6 months	3 months
25%	2 h in pH 1.2	4.5 ± 0.1	7.3 ± 0.4	14.7 ± 0.3	4.8 ± 0.4	5.2 ± 0.1	20.3 ± 0.9
	45 min in pH 6.8	77.3 ± 0.9	83.1 ± 2.5	93.1 ± 0.6	77.3 ± 0.6	79.1 ± 0.3	89.2 ± 0.9
35%	2 h in pH 1.2	4.4 ± 0.2	6.1 ± 0.2	12.8 ± 0.2	5.0 ± 0.2	4.9 ± 0.0	16.7 ± 0.7
	45 min in pH 6.8	78.0 ± 1.3	83.2 ± 2.5	92.5 ± 0.8	80.3 ± 2.3	80.8 ± 1.6	91.3 ± 0.6

acid level in the coated films from beads stored in different container/closure systems and the enteric performance of the beads is illustrated in Fig. 1. The data points fell into two regions: beads with a phthalic acid level of less than 6% demonstrated enteric properties with less than 10% drug release at 2 h in the acidic media, whereas for those samples that did not pass the enteric dissolution test, the phthalic acid content was greater than 6%. The correlation between the enteric resistance and the phthalic acid level in CAP coated films was in agreement to the 6% upper limit of phthalic acid reported by the manufacturer [15].

Phthalic acid can be produced from the hydrolysis of CAP or the hydrolysis of DEP. As shown in Tables 3 and 4, although phthalic acid levels from the beads stored in open glass containers and sealed glass containers with desiccant varied significantly (Table 3), similar amounts of DEP were recovered from these two samples (11.9 and 12.1%, Table 4). Therefore, the source of phthalic acid was not from the hydrolysis of DEP, but from a degradation product from CAP hydrolysis. Its level indicated the degree of CAP hydrolysis. Another hydrolysis product, acetic acid, was reported to evaporate during storage [7]. Therefore, its level would not reflect the extent of CAP hydrolysis and was not determined in this study. For beads stored in sealed glass containers with desiccant, the low humidity environment minimized the extent of polymer hydrolysis, resulting in low phthalic acid content and stable enteric resistance of the films. In contrast, a constant exposure to 75% RH for beads stored in open glass containers degraded the polymer extensively, producing phthalic acid over the 6% limit within a 3-month period at 40°C. The formation rate of phthalic acid in the coating layer of beads stored in sealed glass containers without desiccant was between the rates of the beads stored in the other two container/closure systems investigated. At this storage condition, the beads passed the 3-month accelerated stability test but failed the 6-month accelerated stability test. Our results were in agreement with Delporte's [6] aging study on CAP free films, in which the author demonstrated that the hydrolysis of CAP during storage was the primary reason for the deleterious enteric properties of the coating. He proposed that the phthalic acid molecules were uniformly distributed in the film through hydrogen bonding with the polymer. The dissolution of phthalic acid from the coating during exposure to acidic media may promote diffusion of drug.

The results from the accelerated stability test demonstrated that, although humidity facilitated the coalescence of CAP coated beads during the curing process, it should be avoided during long-term storage in the accelerated condition for these heat–humidity cured beads. The exposure of heat–humidity cured beads to low humidity environment during storage stabilized the chemical structure of the polymer, which played a key role in maintaining the enteric performance of the coating. The results were in good agreement with Plaizier-Vercammen and Suenens [16] who stated that CAP coated aspirin tablets should be protected from moisture during storage. Our results also indicated that the coalesced CAP film structures formed during heat–humidity curing remained unaffected during long-term exposure in a low humidity (<12%) environment.

Table 3
Phthalic acid (PA) content for beads stored at 40°C/75% RH for 3 and 6 months (35% DEP as plasticizer) ($n = 3$)

	Storage period	PA level in coated beads (%)[a]	PA level in coated films (%)[b]
	Initial	0.5 ± 0.0	2.6 ± 0.1
Sealed containers without desiccant	3 months	1.0 ± 0.0	5.6 ± 0.0
	6 months	1.5 ± 0.0	7.8 ± 0.1
Sealed containers with desiccant	3 months	0.4 ± 0.0	1.9 ± 0.0
	6 months	0.4 ± 0.0	2.0 ± 0.0
Open containers	3 months	1.7 ± 0.0	9.1 ± 0.1

[a] Percentage based on the weight of total beads.
[b] Percentage based on the weight of coated film on the beads.

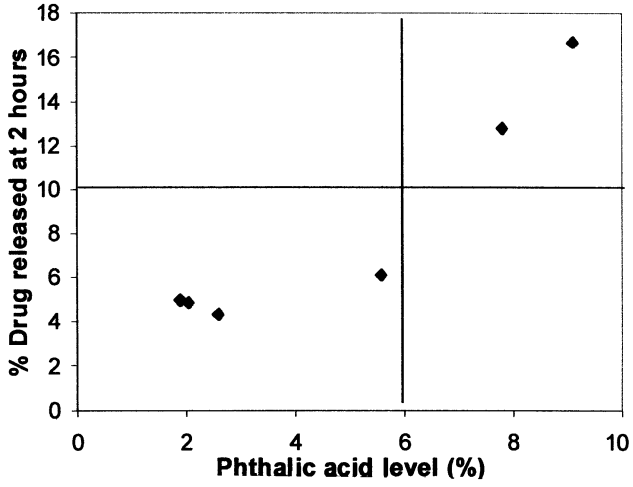

Fig. 1. Correlation between phthalic acid level in the coated films and percent drug release at 2 h in acidic media.

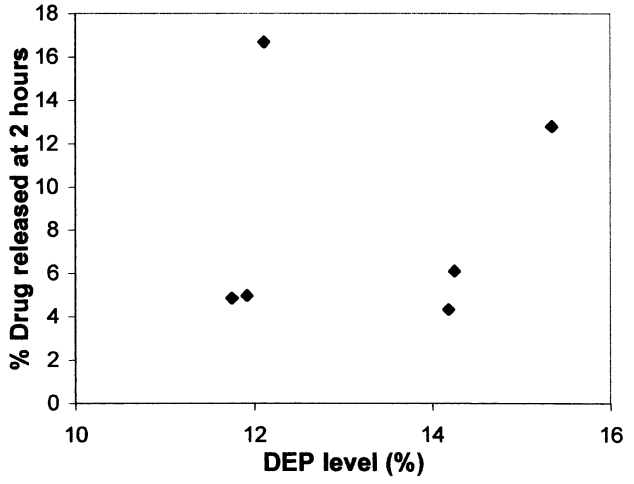

Fig. 2. Lack of correlation between DEP level in the coated films and percent drug release at 2 h in acidic media.

Although delayed disintegration and decreased drug release in the buffer stage from aqueous CAP coated tablets during storage was reported, due to the hydrolysis of CAP and the formation of insoluble cellulose acetate [17], these properties were not observed in this study with the coated beads. A consistent drug release in the buffer stage for beads stored in sealed glass containers with desiccant during storage was found. Although the beads stored in the sealed glass containers without desiccant had increased CAP degradant levels during storage, the release in the buffer media was slightly increased (Table 2) as compared to the retarded release found in tablets [17]. The thin layer of CAP films on the coated beads may dissolve rapidly in the buffer stage and allow steady drug diffusion, despite partial formation of the insoluble hydrolytic degradation product cellulose acetate. In addition, Delporte [6] reported that aged CAP films had a lower dissolution pH and a faster dissolution rate at pH 6 due to the interaction between phthalic acid and the polymer chains. This may also contribute to the increased drug release rate in buffer media observed from CAP coated beads stored in sealed glass containers without desiccant.

Only about 40% of the DEP was recovered from the beads coated with 35% DEP (the ratio of DEP to CAP total solids decreased from a theoretical value of 35 to 14% as shown in Table 4). The percentage loss of DEP was similar to that from beads coated with 10 and 25% DEP plasticized CAP reported previously [13]. Frohoff-Hulsmann et al. [18] also reported high volatility of DEP during coating and curing of ethylcellulose films. In this study, despite the loss of DEP during the coating and curing processes prior to storage, the DEP level was relatively stable (12–15%) during the 6-month accelerated stability test (Table 4). The slightly decreased plasticizer level in beads stored in sealed glass containers with desiccant and open glass containers may be due to adsorption of plasticizer by the desiccant and evaporation of DEP from the open-container storage condition. The level of plasticizer remaining in the beads stored in the different container/closure systems did not correlate with the release profiles of the beads as demonstrated in Fig. 2.

3.2. Stability test at 25°C/60% RH

Under this International Committee on Harmonization (ICH) storage condition, the influence of the container/closure system on drug release from the stored beads was much less compared to its influence on drug release stored at

Table 4
DEP content for beads stored at 40°C/75% RH for 3 and 6 months (35% DEP as plasticizer) ($n = 3$)

	Storage period	DEP level in coated beads (%)[a]	DEP level in coated films (%)[b]
	Initial	2.3 ± 0.1	14.2 ± 0.8
Sealed glass containers without desiccant	3 months	2.3 ± 0.1	14.3 ± 0.7
	6 months	2.5 ± 0.0	15.3 ± 0.1
Sealed glass containers with desiccant	3 months	2.0 ± 0.1	11.9 ± 0.7
	6 months	2.0 ± 0.0	11.8 ± 0.0
Open glass containers	3 months	2.0 ± 0.0	12.1 ± 0.1

[a] Percentage based on the weight of total beads.
[b] Percentage based on the ratio of DEP to the total CAP solids in the coated films.

Table 5
Percent theophylline released in acidic media at 2 h and in buffer media at 45 min from beads stored in different container/closure systems at 25°C/60% RH for 6 and 12 months ($n = 3$)

DEP level	Release media	Initial	Container/closure system				
			Sealed glass containers without desiccant		Sealed glass containers with desiccant		Open glass containers
			6 months	12 months	6 months	12 months	6 months
25%	2 h in pH 1.2	4.5 ± 0.1	5.2 ± 0.4	6.0 ± 0.3	4.8 ± 0.4	5.3 ± 0.2	5.8 ± 0.4
	45 min in pH 6.8	77.3 ± 0.9	81.0 ± 1.4	80.6 ± 0.8	79.2 ± 0.6	79.5 ± 0.4	81.9 ± 1.1
35%	2 h in pH 1.2	4.4 ± 0.2	4.8 ± 0.3	5.3 ± 0.0	4.4 ± 0.2	5.0 ± 0.2	5.3 ± 0.3
	45 min in pH 6.8	78.0 ± 1.3	79.2 ± 1.3	79.8 ± 0.7	78.2 ± 1.2	79.7 ± 1.1	79.4 ± 1.5

accelerated conditions. As shown in Table 5, at 6 months, all beads stored at 25°C/60% RH passed the enteric dissolution test, irrespective of the container/closure system investigated. However, the most similar release profiles compared to the initial data were obtained from beads stored in the sealed glass containers with desiccant, followed by those stored in the sealed glass containers without desiccant and those stored in the open glass containers. It followed the same rank order as those stored at 40°C/75% RH. This indicated that the relative humidity of 60% possessed a slight influence on the enteric release properties of the beads stored at ambient temperature.

From 6 to 12 months, the beads stored in sealed glass containers with and without desiccant displayed only minor increases in drug release. The results demonstrated that, at ambient storage conditions, the enteric properties of heat–humidity cured CAP beads remained stable for at least 1 year, with or without the presence of a desiccant. Delporte reported a slow phthalic acid formation rate for CAP films stored at room temperature and ambient humidity. From 6 to 12 months, the phthalic acid level was increased from 2 to 3% [6], both below 6%. Since the heat–humidity cured beads displayed enteric properties after 12 months at 25°C, it further confirmed that there was a correlation between CAP enteric performance and extent of hydrolysis.

3.3. Comparison of storage conditions: 40°C/75% RH and 25°C/60% RH

For beads stored in the sealed glass containers, the humidity within the headspace, which the beads were directly exposed to, was not influenced by the humidity external to the containers. Thus, beads stored in the sealed glass containers without desiccant at 40°C/75% RH and 25°C/60% RH were exposed to different environmental temperatures but similar headspace humidities. The beads stored in the sealed glass containers with desiccant at two storage conditions had similar but lower headspace humidities. Tables 2 and 5 show that beads stored in sealed glass containers with desiccant and exposed to similar low headspace humidities, displayed only a slight increase in drug release at 40°C (/75% RH) for 6 months compared to those stored at 25°C (/60% RH). However, for beads stored in sealed glass containers without desiccant, where the headspace humidity was higher, the drug release for those stored at 40°C (/75% RH) for 6 months was significantly greater compared to those stored at 25°C (/60% RH). The results indicated that protection of the coated beads from exposure to humidity improved the stability of the CAP coated beads to heat.

In conclusion, although CAP coated films required a short-term exposure to high humidity during heat–humidity curing process to coalesce and achieve enteric performance, the optimum long-term storage condition for heat–humidity cured beads was with desiccant to maintain the chemical stability of the CAP polymer and enteric properties of coated films. Stored in an appropriate container/closure system, the heat–humidity cured CAP coated beads retained their enteric resistance throughout long-term storage at both 25°C/60% RH and 40°C/75% RH storage conditions, making the heat–humidity curing process a viable process for CAP coated beads.

References

[1] 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. Technol. 14 (10) (1990) 62–70.
[2] F. Gumowski, E. Doelker, R. Gurny, The use of a new redispersible aqueous enteric coating material, Pharm. Technol. 11 (2) (1987) 26–32.
[3] 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.
[4] 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.
[5] R.O. Williams, J. Liu, Influence of processing and curing conditions on beads coated with an aqueous dispersion of cellulose acetate phthalate, Eur. J. Pharm. Biopharm. 49 (2000) 243–252.
[6] J.P. Delporte, Effect of aging on physical–chemical properties of free cellulose acetate phthalate films, Pharm. Ind. 41 (10) (1979) 984–990.
[7] P. Roxin, A. Karlsson, S.K. Singh, Characterization of cellulose acetate phthalate (CAP), Drug Dev. Ind. Pharm. 24 (11) (1998) 1025–1041.
[8] 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.

[9] 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.

[10] K. Amighi, A. Moes, Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets, Eur. J. Pharm. Biopharm. 42 (1) (1996) 29–35.

[11] C. Wu, Influence of non-traditional plasticizers and enteric polymers on the physicochemical and mechanical properties of polymeric films and film coated solid substrates, PhD Dissertation, The University of Texas at Austin, 1999.

[12] A. Karlsson, S.K. Singh, Thermal and mechanical characterization of cellulose acetate phthalate films for pharmaceutical tablet coating: effect of humidity during measurements, Drug Dev. Ind. Pharm. 24 (9) (1998) 827–834.

[13] R.O. Williams, J. Liu, The influence of plasticization on heat–humidity curing of cellulose acetate phthalate coated beads, Pharm. Dev. Technol. (2002) (in press).

[14] R. Bodmeier, H. Chen, Determination of the acidic degradation products, acetic, propionic, butyric, and phthalate acid in aqueous pseudolatexes of cellulosic esters by high performance liquid chromatography, Drug Dev. Ind. Pharm. 17 (13) (1991) 1811–1822.

[15] Aquateric® – Aqueous enteric coating, FMC Corporation, Philadelphia, PA, USA.

[16] 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.

[17] 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.

[18] M.A. Frohoff-Hulsmann, A. Schmitz, B.C. Lippold, Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxypropyl methylcellulose as coating material for diffusion pellets. I. Drug release rates from coated pellets, Int. J. Pharm. 177 (1999) 69–82.