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Thermal, mechanical and functional properties of cellulose acetate phthalate (CAP) coatings obtained from neutralized aqueous solutions

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Abstract

This study investigated the thermal, mechanical and functional properties of cellulose acetate phthalate (CAP) film coatings obtained from neutralized aqueous solutions. A novel salt forming agent, 2-amino-2-methyl-1-propanol (MAP), was used for the neutralization and dissolution of CAP in water. Triethylcitrate (TEC) was used as the plasticizer at 10–35% levels. Thermal and mechanical properties of free films plasticized with 10–35% TEC were evaluated by thermogravimetric analysis (TGA), thermal mechanical analysis (TMA) and dynamic mechanical spectroscopy (DMS). The physical stability of CAP/MAP films stored at 40 and 50°C was compared to ammoniated CAP films with respect to dissolution times in pH 6.8 buffer. Plasticized CAP/MAP films were also sprayed at three weight gains (6, 8 and 10%) onto acetylsalicylic acid (ASA) tablets (650 mg) using pan coating technology. The functional properties of the films were assessed for enteric integrity in 0.1 N HCl, drug release in pH 6.8 phosphate buffer and water permeability. Results have shown that CAP/MAP films plasticized with 25–35% TEC released $\leq 1\%$ ASA after 2 h in 0.1 N HCl and $> 95\%$ after 1 h in buffer, thereby demonstrating their excellent functional properties. These films had high permeability to water/acid which makes them unsuitable for acid-labile drugs, since water/HCl would penetrate rapidly into the tablet core and degrade the drug. Neither the T_g nor E' values differed significantly for films that showed satisfactory functional properties. Films were stiff and brittle with E' values in the range of $2\text{–}3 \times 10^9$ Pa and T_g values of 108–112°C. TEC appeared to have limited solubility in the CAP/MAP polymer with reduced plasticization effects at concentrations higher than 20–25%. CAP/MAP free films were found to be superior to ammoniated CAP films with respect to extent of aging when stored at 40°C. The results clearly showed the potential use of plasticized CAP/MAP films as an enteric film former for pharmaceutical products.

Keywords: Cellulose acetate phthalate; 2-Amino-2-methyl-1-propanol; Enteric coating; Plasticizers; Aqueous coating technology; Film coating, thermal properties; Mechanical properties

1. Introduction

Important functional properties of enteric film coatings are their water and drug permeabilities. Enteric coatings are primarily used to protect an acid-labile drug from the stomach acidity or re-

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duce gastric irritation. In the first case, the enteric film should have low water permeability. On the other hand, when the intent is to minimize gastric irritation, the film coating should have a low drug permeability during the acid stage. In both cases, the film must be readily soluble in the second stage of testing, i.e., alkaline buffer, so that the drug is readily available for systemic absorption.

Cellulose acetate phthalate (CAP) has been used for many years in organic solvent enteric coating technology. With the gradual elimination of all organic solvents used in the formulations of pharmaceutical drug products, there has been a growing need for aqueous-based coating processes. Since CAP has low water solubility, its formulation into an aqueous system is challenging. The polymer is insoluble in its non-ionized form which predominates in acid but becomes soluble as the phthalic acid groups become ionized above pH 6. CAP (Eastman Kodak Co., 1991) contains about 35% phthalyl and 24% acetyl groups. The methods proposed over the years to develop aqueous CAP coating solutions have focused primarily on the formation of soluble salts with ammonium hydroxide (Chang, 1990; Stafford, 1990; Eastman Kodak, 1991), sodium hydroxide or triethanolamine (Stafford, 1990). These solutions can be sprayed onto tablets after proper plasticization. Little attention has been given to these approaches, probably because of the alternative latex systems commercially available. However, CAP coating solutions have some advantages over latices since they are less prone to coagulation induced by shear and are more cost-efficient. In a search for a new pharmaceutically acceptable salt forming agent for CAP, it was found that 2-amino-2-methyl-1-propanol (MAP) solubilizes CAP in water. MAP is found in a number of OTC products containing pamabrom (Barnhart, 1989) which is 2-amino-2-methylpropan-1-ol 8-bromotheophyllinate (Reynolds, 1989), a mild diuretic that has been used for the relief of premenstrual tension. The goal of this study was to assess the potential use of plasticized CAP/MAP films as an enteric film former by studying their thermal, mechanical and functional properties. Thermal and mechanical properties of free films were evaluated by thermogravimetric analysis (TGA), thermal mechanical analysis (TMA) and dynamic mechanical spectroscopy (DMS). The functional properties of films sprayed onto acetylsalicylic acid (ASA) tablets were determined by monitoring drug release in 0.1 N HCl and pH 6.8 phosphate buffer using the methodology described under delayed-release (enteric-coated) articles (USP XXII).

2. Materials and methods

2.1. CAP / MAP and ammoniated CAP solutions

CAP (Eastman Chemical Co., TN) and MAP (95%, Aldrich Chemical Co., WI) were used as the polymer and salt forming agent, respectively. Triethylcitrate (TEC, Pfizer, NY) was used as the plasticizer. All percentages are expressed as % by weight. The amount of MAP required to dissolve the CAP was found to be 25%, based on CAP, corresponding to about a 25% acid group molar excess. Dissolution times of several hours were observed when lower amounts of MAP were used. The need for a molar excess of base has also been reported (Stafford, 1982) for the neutralization and dissolution of hydroxypropyl methylcellulose phthalate (HPMCP). The CAP solutions used for the free film evaluation and for the coating experiments were prepared as follows: CAP was initially dispersed in approx. 2/3 of the total amount of required water. The amount of CAP added was calculated to make an 8% solution after the final addition of water. Then, MAP was poured into the dispersion and the mixture agitated for 1 h to allow for complete dissolution of the polymer. TEC was added at 10–35% levels, based on CAP, and water was added to reach the final weight. Finally, the solution was agitated for a 30 min period to achieve plasticization of the polymer and then passed through a 420 μm (40-mesh) screen. The resulting plasticized CAP/MAP solution was clear, free from any insoluble material and used within 24 h following preparation. Ammoniated CAP solutions were prepared using the same method by adding a 30% ammonium hy-

droxide solution (American Chemical Ltd, Québec) at a 18% level, based on CAP.

2.2. Evaluation of free films

Unplasticized and plasticized polymer solutions were cast on poly(methyl methacrylate) film holders (62 cm^2) to make 0.15–0.2 mm thickness films. The films were allowed to dry at ambient conditions for 14–16 h. A final drying step was carried out in a convection tray dryer set at 45°C for 6–8 h. The dry films were finally detached from the holders and stored in a desiccator under calcium sulphate. The physical stability of ammoniated CAP and CAP/MAP films was evaluated by monitoring the time required for dissolution in a 50 mM sodium phosphate buffer adjusted to pH 6.8. Films that were plasticized with 20% TEC were placed (approx. 50 mg) in 20 ml glass vials and stored at 40 and 50°C stations over a 30 day period. At pre-determined time intervals, films were evaluated for dissolution in 10 ml of buffer under mild agitation (approx. 30 inversions per min).

2.3. Thermal and mechanical properties measurements

The residual moisture content of free films was evaluated by thermogravimetric analysis (Model RTG220, Seiko Instruments U.S.A. Inc., CA) under nitrogen (100 ml/min) at a scan rate of 10°C/min. Weight losses were recorded from values obtained between 30 and 130°C. Glass transition temperatures (T_g) were determined in duplicate by thermal mechanical analysis (TMA 120C, Seiko Instruments U.S.A. Inc., CA) using a penetration probe and by dynamic mechanical spectroscopy under tension (DMS200, Seiko Instruments U.S.A. Inc., CA). The TMA experiments were carried out under nitrogen at a scan rate of 5°C/min using a 10 g force. As heating progresses, the film softens and there is penetration of the probe. The glass transition temperature is determined at the intersection of the tangent drawn from the initial probe position and that drawn from the onset of maximum penetration rate. DMS experiments were carried out on films of approx. 11 × 6 mm in size. The films were clamped in the tension probe and heated at 4°C/min at a frequency of 1 Hz from 30 to 200°C under nitrogen (100 ml/min). The Young's storage modulus (E') and the T_g, measured from the loss tangent (tan δ) peak maximum, were determined as a function of plasticizer concentration.

Table 1
Film coating process parameters

Batch size	1 kg
Nozzle [a]	air, 67228-45; liquid, 2850
Inlet temperature	60°C
Air volume	250 scfm
Inlet air dew point	9–15°C
Spray rate	8–10 g/min
Atomizing pressure	1 bar
Pan differential pressure	−0.1 kPa
Pan speed	16 rpm
Outlet temperature	40–45°C
Drying	10 min at 2 rpm, heat on

[a] Flat spray, Spraying Systems Co., Quebec.

2.4. Tablet coating

ASA was used as a classical drug model to assess the enteric integrity of sprayed CAP/MAP films. ASA tablets (650 mg, proprietary formulation) were compressed with 16 × 9 mm (0.623 × 0.341 inch) oval plain punches. Tablet physical parameters such as weight, hardness (model HT300, Key, NJ) and thickness were measured. Tablet thickness was determined with a precision of ±0.001 mm using a digital micrometer (Mitutoyo, NJ). The tablets were coated (12 inch pan, Labcoat II system, O'Hara Manufacturing, Ontario) at 6, 8 and 10% theoretical film weight gains using process parameters shown in Table 1. Three levels of plasticizer (25, 30 and 35%) were evaluated for each film weight gain. Film thickness ($n = 20$) was determined by the same method as for the core tablets. Physical evaluation of films sprayed onto ASA tablets was performed by scanning electron microscopy (model JSM-820, Jeol U.S.A. Inc., MA).

2.5. Film coating functional testing and water permeability

The CAP/MAP films performance was evaluated with respect to enteric integrity and drug release in buffer according to the monograph of Aspirin Delayed-release Tablet (USP XXII). Using this methodology, coated tablets were placed into baskets (USP apparatus I) and rotated at 100 rpm in dissolution vessels containing 1000 ml of a 0.1 N HCl solution. After 2 h, samples (4–5 ml) were collected from the dissolution vessels and the amount of drug released was determined at 280 nm (model 8451A diode array spectrophotometer, Hewlett-Packard, CA), the isobestic point of ASA and salicylic acid. The tablets were then transferred into 1000 ml of a pH 6.8 sodium phosphate buffer (50 mM) and the amount of drug released was measured at 264 nm using 4–5 ml samples removed without replacement after 30, 60, 90 and 120 min. Amounts of ASA were determined in comparison with a standard solution having a known concentration in the same medium, as indicated in the monograph.

CAP/MAP sprayed films were also evaluated for their water/acid permeability with respect to exposure time in acid. Five tablets were placed in each dissolution vessel that contained 1000 ml of 0.1 N HCl at 37 ± 1°C. The agitation rate was set at 50 rpm using USP dissolution apparatus II (paddles). At pre-determined time intervals, tablets contained in each vessel were sampled, surface water removed, weighed and% weight gains determined.

3. Results and discussion

3.1. CAP/MAP films

The pH of the coating solutions ranged from 6.3 to 6.7. Table 2 lists the physical stability data for CAP/MAP and ammoniated CAP films. Ammoniated films showed a marked increase in dissolution time after 5 days of storage at 50°C. Insoluble, swollen and clear films were obtained after 12 days at 50°C. The hypothesis for this gradual polymer insolubilization is that the ammonium salt is in equilibrium with ammonia in the film. Ammonia could be responsible for the slow and gradual hydrolysis of the acetyl and phthalyl groups of CAP. The net result would be the formation of an insoluble cellulose ester. Even when stored at 40°C for 30 days, insoluble material was still present after 1 h exposure to a 50 mM, pH 6.8 sodium phosphate buffer. A salt forming agent such as MAP was evaluated because in theory, there is no equilibrium involved with a freely diffusible basic compound such as ammonia. An improvement in the physical stability was obtained using the MAP salt of CAP, when compared to ammoniated CAP. However, films stored at 50°C for 12 days disintegrated in 60–120 min with insoluble material present. When stored at 40°C for up to 30 days, the physical stability of these films was satisfactory with a small increase in dissolution time, i.e., 15–20 min compared to 60 min for ammoniated CAP films.

Table 2
Physical stability of CAP/MAP and ammoniated CAP films [a]

	CAP/MAP	Ammoniated CAP
Initial	< 5 min	< 5 min
5 days		
40°C	< 10 min	10–15 min
50°C	< 10 min	45–60[2] min
12 days		
40°C	< 10 min	< 10 min
50°C	60–120 [b]	> 24 h [c]
30 days		
40°C	15–20 min	1 h [b]
50°C	> 24 h [d]	> 24 h [e]

[a] Time required to dissolve approx. 50 mg of film in pH 6.8 sodium phosphate buffer.
[b] Disintegrated but insoluble material remaining in suspension.
[c] Brown discoloration, totally insoluble after 24 h, clear film after exposure to buffer.
[d] Swollen clear film but insoluble after 24 h.
[e] Brown discoloration, totally insoluble after 24 h, beige opaque film after exposure to buffer.

3.2. Thermal and mechanical properties of CAP/MAP films

Plasticizers are added to improve film characteristics and to reduce defects in film coatings. They lower the T_g of the polymer, which is de-

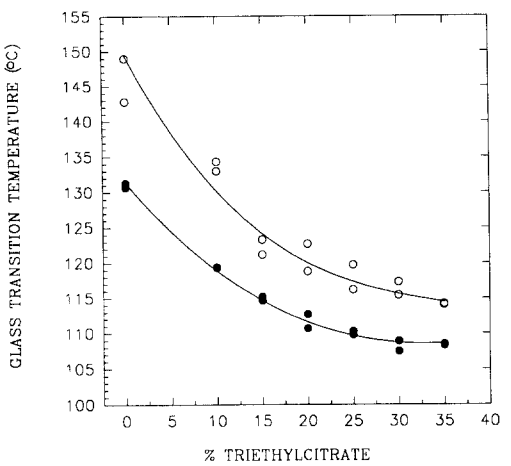

Fig. 1. Glass transition temperature of CAP/MAP free films with respect to TEC level: obtained by (○) TMA (duplicate) and (●) DMS (duplicate).

fined as the onset of molecular mobility of the polymer segments, by increasing the molecular free volume. The efficiency of plasticizers, which include water and solvents, is dependent on their miscibility with the polymer and their permanence. The latter requires that the plasticizers have low vapour pressures and low diffusion rates within the polymer. TEC was chosen as the plasticizer for CAP due to its pharmaceutical acceptability, good aqueous solubility and low volatility.

Fig. 1 shows CAP/MAP glass transition temperatures as a function of TEC concentration. The glass transition temperature of CAP/MAP films is approx. 146°C by TMA and 131°C by DMS. The TMA measurement is based on the penetration of a probe into the film and thus, measures the softening point. The DMS measures the onset of molecular mobility by imposing an oscillating tensile force on the polymer film at a set frequency, in this case, 1 Hz. The T_g values in the DMS experiments are obtained from the tan δ peak maxima. Since the glass transition is a thermodynamic and a kinetic process, it is dependent on the test method, test frequency, and heating rate. Different experimental techniques will give different T_g values, as can be seen in Fig. 1. The DMS provides a more realistic value of the true polymer T_g when measured at low frequencies (1 Hz) and low heating rates (Brandrup et al., 1989). Overall, the T_g values obtained by TMA and DMS show similar trends. The advantage of the TMA over the DMS is that the method is quick and easy (Masilungan and Lordi, 1984).

The T_g for CAP alone is reported to be between 171°C (Sinko et al., 1990) and 175°C (Eastman Kodak Co.). The CAP/MAP films have T_g values that are approx. 25–40 degrees lower than that reported for CAP films. This may be due to the salt formation between the carboxylic acid groups on CAP and the MAP. The effect may also be due to the presence of excess MAP (approx. 4% by weight) in the films which appears to act as an internal plasticizer. Residual moisture level of the films is important, since water could also be a plasticizer (Oksanen and Zografi, 1990). The moisture content of the films, evaluated by TGA, were similar and independent of plasticizer levels. Weight losses of 2.19, 1.94, 2.06, 1.37, 1.76, 1.56 and 1.72% were obtained for films that contained 0, 10, 15, 20, 25, 30 and 35% TEC, respectively.

The addition of TEC decreases the T_g of the CAP/MAP films but the plasticizer effect is reduced at levels higher than 20%. No further significant reduction of T_g are observed when TEC is added at 25–35% levels. This may be due to limited solubility of the plasticizer in the polymer. In contrast, the fact that there is no broadening of the tan δ peaks (Fig. 2) with increasing plasticizer concentrations, indicates that TEC is miscible with the CAP/MAP polymer. Nevertheless, TEC is not a very effective plasticizer for CAP, reducing the T_g by only 1 degree per wt%. Thus, TEC is miscible in the polymer but reaches a maximum solubility at about a 25% level, such that additional plasticizer has little effect on the T_g. Similar behaviour has been observed with other systems (Nielson, 1967; Ferry, 1980). One advantage of having films that have high T_g is that minimal aging is expected because the storage temperatures are well below the T_g. This has been observed for cellulose acetate films (Sinko et al., 1990).

Below the T_g, CAP/MAP films are stiff and brittle with high E' values in the range of $2–3 \times 10^9$ Pa. No differences in the E' values is ob-

served between plasticized and unplasticized films. As expected, there is a decrease in stiffness associated with the glass transition region.

3.3. Tablet coating

The core tablet weight, hardness and thickness were found to be 777 ± 8 mg (mean ± S.D.), 19.1 ± 0.5 Kp and 6.85 ± 0.04 mm, respectively. The tablet surface area as determined from punch drawings and tablet thickness was 3.07 cm^2. The minimum level of TEC that provided good film formation was found to be 25% by weight (based on CAP) as described earlier. This corresponded to the region where TEC exerted its maximum plasticization effect on the CAP/MAP polymer. Films that contained lower levels of TEC showed cracking at tablet edges. Subsequent coating trials were therefore carried out using CAP/MAP films that were plasticized with 25–35% TEC. Based on free film data, T_g values of 108–112°C were obtained by DMS for films of such compositions. The storage modulus values were also found to be similar (Fig. 2). It was surprising to find that a minimum concentration of 25% TEC was required to achieve satisfactory coatings since thermal and mechanical properties of free films plasticized with 20% TEC were not significantly different. The explanation could be that cast and sprayed films do not have the same properties

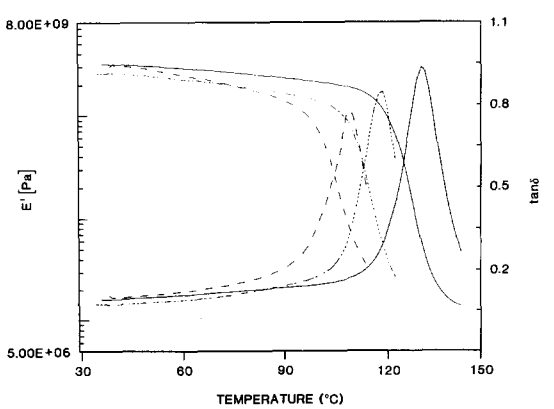

Fig. 2. Storage modulus, E' (Pa) and loss tangent (tan δ) with respect to temperature for CAP/MAP free films plasticized with (– – –) 10% TEC; (— —) 30% TEC; and (———) without plasticizer.

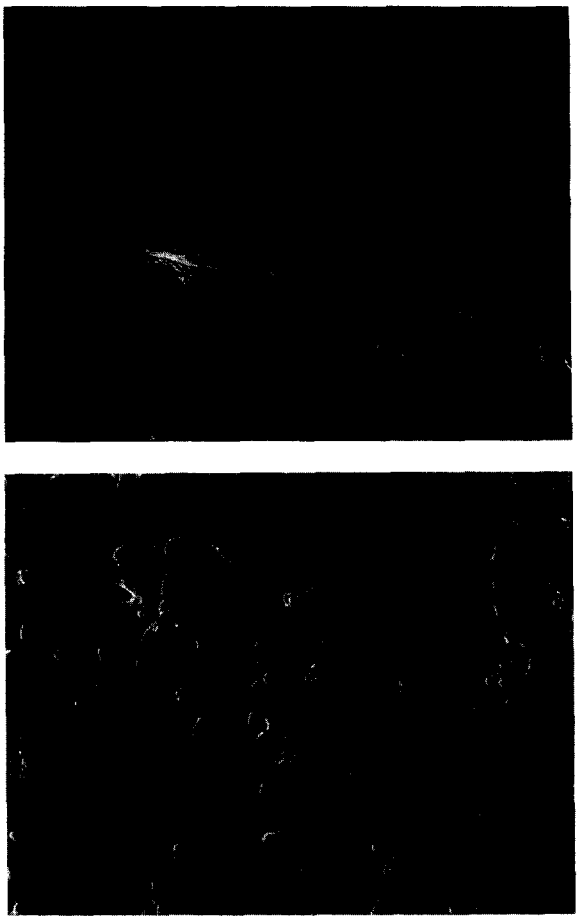

Fig. 3. Scanning electron micrograph of an ASA tablet coated with a CAP/MAP film (8% weight gain) plasticized with 30% TEC. (Top) Film cross-section, ×300, bar represents 35 μm; (bottom) film surface, ×1000, bar represents 10 μm.

because of the different film formation mechanisms involved. This could not be verified since the DMS experiments carried out on films that were cut and detached from coated tablets produced irreproducible data. Particles originating from the cores always adhered to the inner surface of the films causing significant problems.

Films that were sprayed onto ASA tablets were found to be homogeneous, dense and free from cracks and pores (Fig. 3). Film thicknesses ranged from 78–91, 123–135 and 143–175 μm for tablets that were coated with 6, 8 and 10% weight gains, respectively. The film thickness was measured on the tablet faces. However, it must be realized that

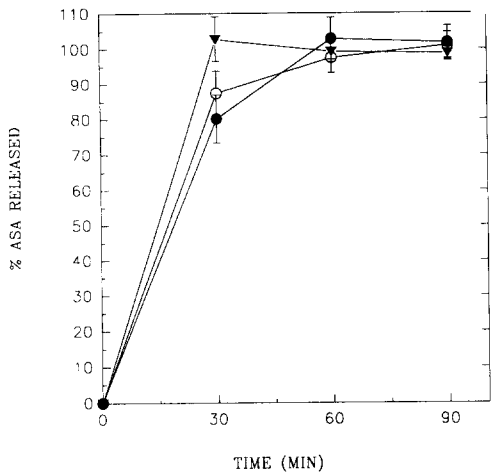

Fig. 4. % ASA released as a function of time in pH 6.8 sodium phosphate buffer. Films were plasticized with 25% TEC. (●) 10%, (○) 8% and (▼) 6% weight gains. Mean ± S.D. ($n = 6$). Film thicknesses were 165, 135 and 91 μm for 10, 8 and 6% weight gains, respectively.

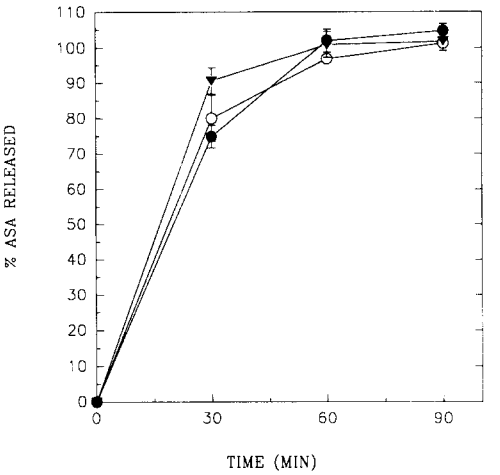

Fig. 5. % ASA released as a function of time in pH 6.8 sodium phosphate buffer. Films were plasticized with 30% TEC. (●) 10%, (○) 8% and (▼) 6% weight gains. Mean ± S.D. ($n = 6$). Film thicknesses were 175, 130 and 90 μm for 10, 8 and 6% weight gains, respectively.

the film thickness is alway less at tablet edges than on the faces. Film coating levels of less than 6% resulted in failures in the acid integrity testing due to incomplete coverage, especially at tablet edges.

3.4. Film coating functional testing

Core tablets released 95.4 ± 5.2% (S.D., $n = 6$) ASA after 30 min in acid, showing that the drug was readily available from the formulation. Regardless of film thickness and TEC level, all coated tablets released $\leq 1\%$ of ASA after 2 h exposure to acid, thereby demonstrating the excellent enteric integrity of the CAP/MAP films. Fig. 4–6 show percent ASA released with respect to time in pH 6.8 sodium phosphate buffer. Virtually 100% of ASA was released after 60 min, indicating solubilization of the film. For films that were plasticized with 25 and 30% TEC, there was a trend between the thickness and the amount of ASA released after 30 min. Tablets coated with films that were sprayed at a 6% weight gain level released the drug faster than those sprayed at 10% level. When TEC was used at a 35% concentration, > 90% ASA was released after 30 min at all weight gains. These functional tests results are consistent with the thermal and mechanical properties of the films that indicated similar behavior at these plasticizer levels. The results also demonstrated that all dosage forms conformed with compendial specifications of less than 10% drug release in acid after 2 h and more than 80% drug release in buffer after 90 min.

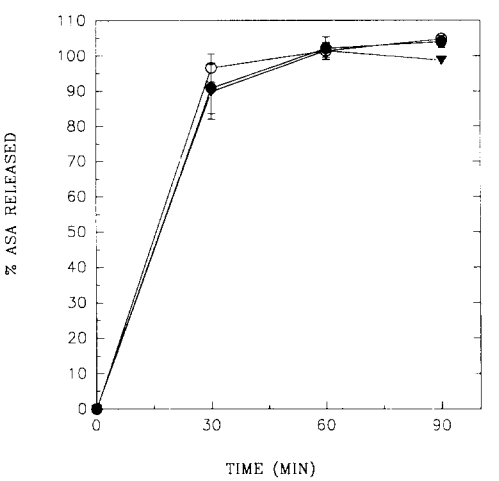

Fig. 6. % ASA released as a function of time in pH 6.8 sodium phosphate buffer. Films were plasticized with 35% TEC. (●) 10%, (○) 8% and (▼) 6% weight gains. Mean ± S.D. ($n = 6$). Film thicknesses were 143, 123 and 78 μm for 10, 8 and 6% weight gains, respectively.

Similar findings were reported when neutralized aqueous solutions of hydroxypropyl methylcellulose phthalate were used (Stafford, 1982). The enteric integrity was found to be comparable with that of films sprayed from organic solutions. Another report (Chang, 1990) described experiments where theophylline beads were coated with ammoniated CAP films. Satisfactory enteric integrity was shown but no dissolution data were available in buffer. However, the gradual insolubilization of ammoniated films after storage at 40 and 50°C (Table 2) appears to be a potential problem. In this respect, it has been shown in this study that CAP/MAP films might be superior to ammoniated films.

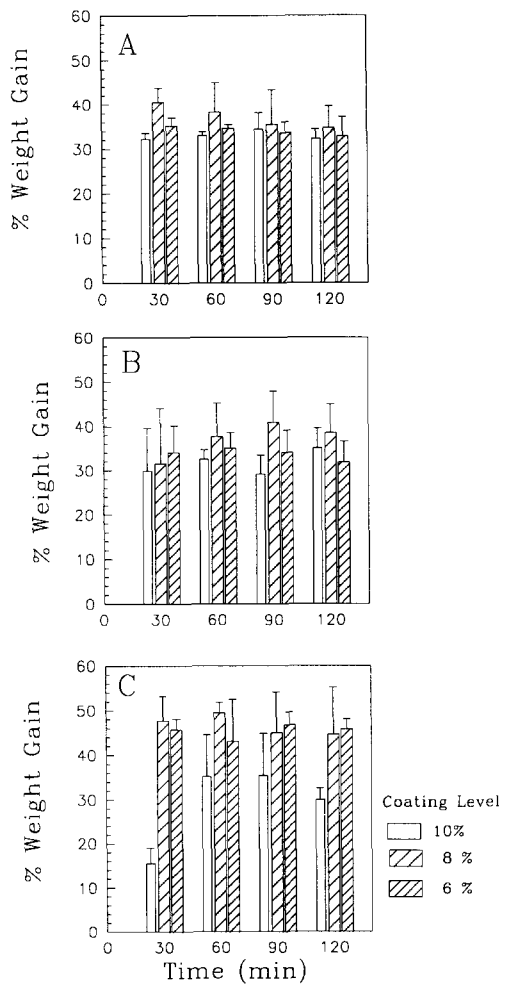

Fig. 7. Coated tablets% weight gains with respect to exposure time in 0.1 N HCl for films plasticized with (A) 25% TEC; (B) 30% TEC and (C) 35% TEC. Mean ± S.D. ($n = 5$).

Fig. 7 shows % weight gains with respect to exposure time in 0.1 N HCl for coated tablets. Most of the water/acid penetrated the coating within the first 30 min regardless of film thickness and plasticizer level. Percent weight gains were between 30 and 40% for films plasticized with 25 and 30% TEC. Films plasticized with 35% TEC and coated at 6% (78 μm) and 8% (123 μm) levels showed higher average weight gains, i.e., 40–50%. All tablets showed physical evidence of swelling after 30 min, nevertheless, the films were not permeable to ASA since $\leq 1\%$ was released after 2 h. The water permeability of these films was found to be much higher than for CAP films plasticized with diethyl phthalate and sprayed from an organic solution (Porter and Ridgway, 1982). Since CAP was deposited onto tablet surfaces as a water soluble salt form, it is not surprising that the water permeability of these films was found to be high. However, in the presence of acid, the phthalic acid groups are probably regenerated rapidly, otherwise the film would solubilize itself and release the drug. Physical evidence of this phenomenon indicated that after 2 h exposure to acid, the tablets and the films had swollen but the films were mechanically strong and insoluble.

4. Conclusion

This study described the thermal, mechanical and functional properties of neutralized aqueous solutions of CAP for enteric coating of pharmaceutical products. MAP was used as a novel salt forming agent for CAP. CAP/MAP free films showed less aging than ammoniated CAP films when stored at 40°C. Excellent enteric integrity and drug release in buffer were achieved when ASA tablets were coated with plasticized CAP/MAP solutions using conventional pan coating technology. These films had high permeability to water/acid which does not make them suitable for acid-labile drugs since water/HCl would penetrate rapidly into the tablet core and degrade the drug. Neither the T_g nor the E' values ob-

tained from free films experiments differed significantly for films that showed satisfactory functional properties at the 20–25% plasticizer levels. Films were stiff and brittle with E' values in the range of $2–3 \times 10^9$ Pa and T_g values of 108–112°C. TEC reduced the T_g of the CAP/MAP polymer by about 1 degree per wt% but appeared to have limited solubility resulting in reduced plasticization effects at concentrations higher than 20–25%. The results clearly indicated that CAP/MAP films warrant further investigations as an aqueous enteric coating system for pharmaceutical products. More work is required to determine if these films maintain their excellent functional properties with respect to aging. Also, the need for a subcoat and the film pigment carrying capacity are other important factors that would have to be explored before this system is envisaged in an actual product.

Acknowledgments

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