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Comparative evaluation of ammoniated aqueous and organic-solvent-based cellulose ester enteric coating systems: a study on free films

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Abstract

The permeability and mechanical properties of ammoniated aqueous and organic-solvent-based enteric films were evaluated with free films and with the films applied to tablets. The enteric coating materials studied were cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT) and hydroxypropyl methylcellulose phthalate (HPMCP, HP-50) plasticized with triacetin. Enteric films prepared from organic-solvent-based solutions showed lower permeability to basic drug (caffeine) and hydronium ions, and the permeability decreased in the sequence CAT, HP-50, CAP. As regards mechanical and stress-strain properties, ammoniated aqueous enteric films appeared to be somewhat weaker and more brittle than corresponding films prepared from acetone-based solutions. The results suggest very acceptable resistance of organic-solvent-based enteric films against short-term storage under tropical conditions.

Key words: Cellulose acetate phthalate; Cellulose acetate trimellitate; Permeability; Mechanical properties; Tropical conditions; Free film

1. Introduction

Interest in the use of aqueous-based film coating systems has been increasing steadily owing to the well-documented drawbacks (uneconomic, unsafe and toxic) associated with organic-solvent-based coating systems. For enteric film coating, aqueous latex and pseudolatex systems of various polymers have been widely used since the mid-1970's (Baudoux et al., 1990).

In the early 1980's, Stafford (1982) introduced a simple method of producing aqueous solutions of enteric coating systems from cellulose ester derivatives by neutralizing the free acid groups of the polymers with ammonium hydroxide. In this

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technique, ammonia ionises the free acid moiety on the polymer, forming a water-soluble salt of the polymer (Anon, 1988). An enteric film is formed when the coated drug preparation is exposed to acidic medium due to the transformation of the salt into the acid form.

There are only a few reports in the literature on the enteric properties of ammoniated cellulose ester derivatives (Chang, 1990; O'Connor and Berryman, 1992; Plaizie-Vercammen and Steppe, 1992). In these studies, the gastric resistance, dissolution properties, water permeability and stability of the films applied to various dosage forms were extensively investigated. Little is known, however, on, e.g., drug permeability, permeability to hydronium ions and mechanical strength of ammoniated aqueous films based on cellulose ester derivatives. For characterization of the effects of variables introduced by the film itself on film properties, the evaluation of free films has proved a very useful technique (Spitael, 1976; Okor, 1982).

According to Chang (1990), enteric films prepared from organic-solvent-based solutions showed considerably lower permeability to a basic drug, theophylline, as compared with films prepared from ammoniated aqueous polymer solutions. Furthermore, the permeation of water has been shown to be a greater concern for enteric coated products after conversion to ammoniated aqueous enteric coating formulations (O'Connor and Berryman, 1992). Consequently, and for the reasons mentioned above, it would seem reasonable to assume that aging under conditions of high temperature and high relative humidity (tropical conditions) will affect the enteric properties of ammoniated enteric coated products.

In the present study, the enteric properties of cellulose ester films prepared from ammoniated aqueous and organic-solvent-based solutions were evaluated with free films with special reference to morphological properties, drug permeability, permeability to hydrochloric acid (0.1 N), and mechanical properties. The effects of short-term stress storage conditions on the film properties were also investigated.

2. Materials and methods

2.1. Materials

The enteric coating materials studied were cellulose acetate trimellitate (CAT) (Eastman® C-A-T™, Eastman Chemical Co., U.S.A.), cellulose acetate phthalate (CAP) (Eastman® C-A-P™, Eastman Chemical Co., U.S.A.), and hydroxypropylmethylcellulose phthalate (HPMCP) (HP-50, Shin-Etsu Chemical, Japan). Purified water or acetone (E. Merck, Germany) mixed with purified water (97:3) was employed as solvent. Triacetin (Fluka AG, Switzerland), 25% (w/w) of the polymer weight, was used as a plasticizer.

2.2. Preparation of free films

The compositions of the polymer solutions used for free films and for tablet coating are summarized in Table 1. For preparation of aqueous solutions of CAT, CAP and HP-50, the polymers were neutralized with 25% ammonium hydroxide (E. Merck, Germany), and stabilized with magnesium carbonate (E. Merck, Germany) (Wyatt et al., 1992).

For preparing free films various amounts of the polymer solutions were poured onto Petri

Table 1
Compositions of the coating solutions used in preparation of free films and the coatings applied to tablets

	Ammoniated aqueous coating solutions (%)	Organic-solvent-based coating solutions (%)
Coating material		
CAT, CAP or HP-50	8.0	8.0
Solvent system		
Purified water	88.7	–
Acetone/water (97:3)	–	90.0
Additive		
Ammonium hydroxide (25%)	0.52	–
Magnesium carbonate	0.78	–
Plasticizer		
Triacetin	2.0	2.0

Percentages are expressed in terms of w/w.

dishes covered with polytetrafluoroethylene (Teflon®). The solvents were allowed to evaporate for 2 h at 50°C (aqueous solutions; at 40°C in short-term stability studies) or 20°C (organic-based solutions) and subsequently for 24 h at room temperature (20°C/40% RH). The films were allowed to stabilize in a desiccator at room temperature for at least 24 h before testing.

The dry thickness of the films was measured using a micrometer (Sony U30-F, Sony Magnescale Inc., Japan). For all film compositions, the accuracy of the thickness measurements was ± 5 μm. The limits that were accepted for the films were 85 and 115% of the desired film thickness. Films demonstrating large variations in thickness and unhomogeneous structure were rejected.

2.3. Storage conditions

For assessing stability under short-term stress storage conditions, enteric free films and coated tablets were exposed to conditions of high temperature (40°C) and humidity (70, 80, 90% RH) for 1 week. The relative humidities of 70, 80 and 90% were maintained with saturated copper chloride, potassium chloride and potassium nitrate solution in the bottom of a dessicator, respectively.

2.4. Film permeability

The permeabilities of the films (25–50 μm) were determined using two-compartment diffusion cells (Spectra/Por®, Serlabo, France) with continuous flow. The films were cut into pieces 5 cm in diameter and equilibrated in 0.1 N HCl at room temperature (20°C) for 1 h before being inserted into the cell. The effective surface area of the cell was 3.14 cm^2, and the volume of the half-cell was 1 ml. The donor side was filled with 100 ml of a solution of 0.1 N HCl containing caffeine 200 μg/ml (permeability test for a drug) or with 100 ml of a solution of 0.1 N HCl and NaCl 0.9% (w/v) (permeability test for 0.1 N HCl). The acceptor side was filled with 100 ml of a solution of 0.1 N HCl or purified water containing NaCl 0.9% (w/v), respectively. Both the donor and acceptor compartments of the cells were maintained at 37 ± 1°C using a constant temperature circulating bath. The drug concentrations and pH values in the receiver compartment were assayed spectrophotometrically (Ultrospec II 4052, LKB Biochrom, U.K.) and with a pH meter (PHM82, Radiometer Copenhagen, Denmark), respectively. At least four parallel determinations were performed.

Permeation coefficients were calculated on the basis of Fick's diffusion laws. The permeability of the films to caffeine was evaluated using the equation (Martin et al., 1983):

$$\ln(C_d) = \ln(C_d(0)) - P \times S \times t/V_d \quad (1)$$

In order to describe the permeability of the films to hydrochloric acid (0.1 N), the data were analyzed according to the following equations (Spitael and Kinget, 1977; Martin et al., 1983):

$$dM/dt = D \times S \times K \times C_d/h = P \times S \times C_d \quad (2)$$

which yields the following equations:

$$M = (P \times S \times C_d/h) \times t \quad (3)$$

$$M = C_r \times V_r = (P \times S \times C_d/h) \times t \quad (4)$$

$$C_r = (P \times S \times C_d/h \times V_r) \times t \quad (5)$$

where M is the number of moles permeating the film in time t, C_d denotes the concentration of the solution at the donor side, C_r is the concentration of the solution at the acceptor side, V_r represents the volume of the desorbing solution, S is the surface area of diffusion and h denotes the thickness of the film.

The calculations were performed with MathCAD® (MathSoft Inc., U.S.A.), version 3.1.

2.5. Mechanical strength

Measurements of the mechanical strength were carried out with a material testing apparatus (J.T. Lloyd Instruments Ltd, T 5002, U.K.). For testing, the films (50 ± 5 μm) were cut into strips of 8.0 × 1.5 cm. The extension rate was 10 mm/min. At least three parallel measurements were conducted.

2.6. Scanning electron microscopy

The surface topography and cross-section structure of the free films were determined by scanning electron microscopy (Jeol, JMS-820, Jeol Ltd, Japan).

2.7. Preparation and evaluation of coated tablets

A Korsch EK-0 (Korsch GmbH, Germany) single punch machine with biconvex 9 mm punches was used for preparing caffeine core tablets. The composition of the tablets was as follows: caffeine (Ph.Eur.), 4%; direct compression diluent (Cellactose, Meggle Milchindustrie GmbH, Germany), 95%; and magnesium stearate (Ph.Eur.), 1%. The tablet strength was set to 80 ± 5 N (Schleuniger-2E, Schleuniger GmbH, Germany). The core tablets were coated using a fluid bed coater (Aeromatic Strea 1, Aeromatic AG, Switzerland). The inlet air temperature was adjusted to 60 ± 1°C (35 ± 1°C for organic-CAP solution) and the outlet air temperature to 45 ± 1°C (28 ± 1 °C). The pneumatic spraying pressure was maintained at 1.0 bar. The flow rate was 110 m^3 h^{-1}. For each coating, the amount of coating was 15% of the total weight of the tablets (20 mg/cm^2). For the ammoniated-CAP coating, a subcoat of 2% HPMC was used in order to ensure adhesion and contact of CAP (Baudoux et al., 1990).

Drug permeability was determined employing the USP XXII rotating paddle method (Sotax AT6, Sotax AG, Switzerland). The dissolution medium was 900 ml of 0.1 N hydrochloric acid for the first 2 h, followed by phosphate-citrate buffer solution (pH 5.8 or 6.2) at 37°C. The rotation speed was 50 min^{-1}.

3. Results and discussion

3.1. Morphological properties

According to the literature, the formulation factors primarily affecting the structure and properties of pharmaceutical films include the properties of the polymer and solvent effects (Banker, 1966). Scanning electron micrographs show that the structure of the films was dependent on the solvent system used (Fig. 1). The structure of ammoniated aqueous enteric films was more porous and heterogeneous compared to that of organic enteric films.

Table 2
Permeation coefficients to caffeine of free enteric polymer films ($n = 4$–6)

Polymer	Thickness (μm)	Solvent	Permeation coefficient (P) ($\times 10^{-5}$) (cm s^{-1})
CAT	48	water	23.9
CAT	36	water	27.4
CAT	28	water	52.7
CAT	46	acetone/water	2.5
CAT	32	acetone/water	3.9
CAT	24	acetone/water	4.0
CAP	48	water	17.4
CAP	48	acetone/water	1.4
HP-50	46	water	5.7
HP-50	44	acetone/water	1.2

3.2. Film permeability to basic drug

The solvent used also affected the drug permeability properties of the enteric polymer films tested (Table 2). The films prepared from organic-solvent-based solution (acetone) were less permeable to caffeine than those prepared from ammoniated aqueous-based solutions. With both types of enteric films, diffusion was fastest with cellulose acetate trimellitate (CAT) and slowest with cellulose acetate phthalate (CAP). As seen in Table 2, the permeation coefficient (P) for CAT appeared to be dependent on film thickness. The variation in values may be explained on the basis of the difficulties in preparing homogeneous, non-porous free films with a thickness of 30 μm or less. The present results are in accordance with those of Spitael and Kinget (1977) who reported very low permeability to a water-soluble drug through organic cellulose ester films (CAP).

3.3. Film permeability to hydronium ions

Enteric films prepared from acetone-based solution showed very low permeability to hydro-

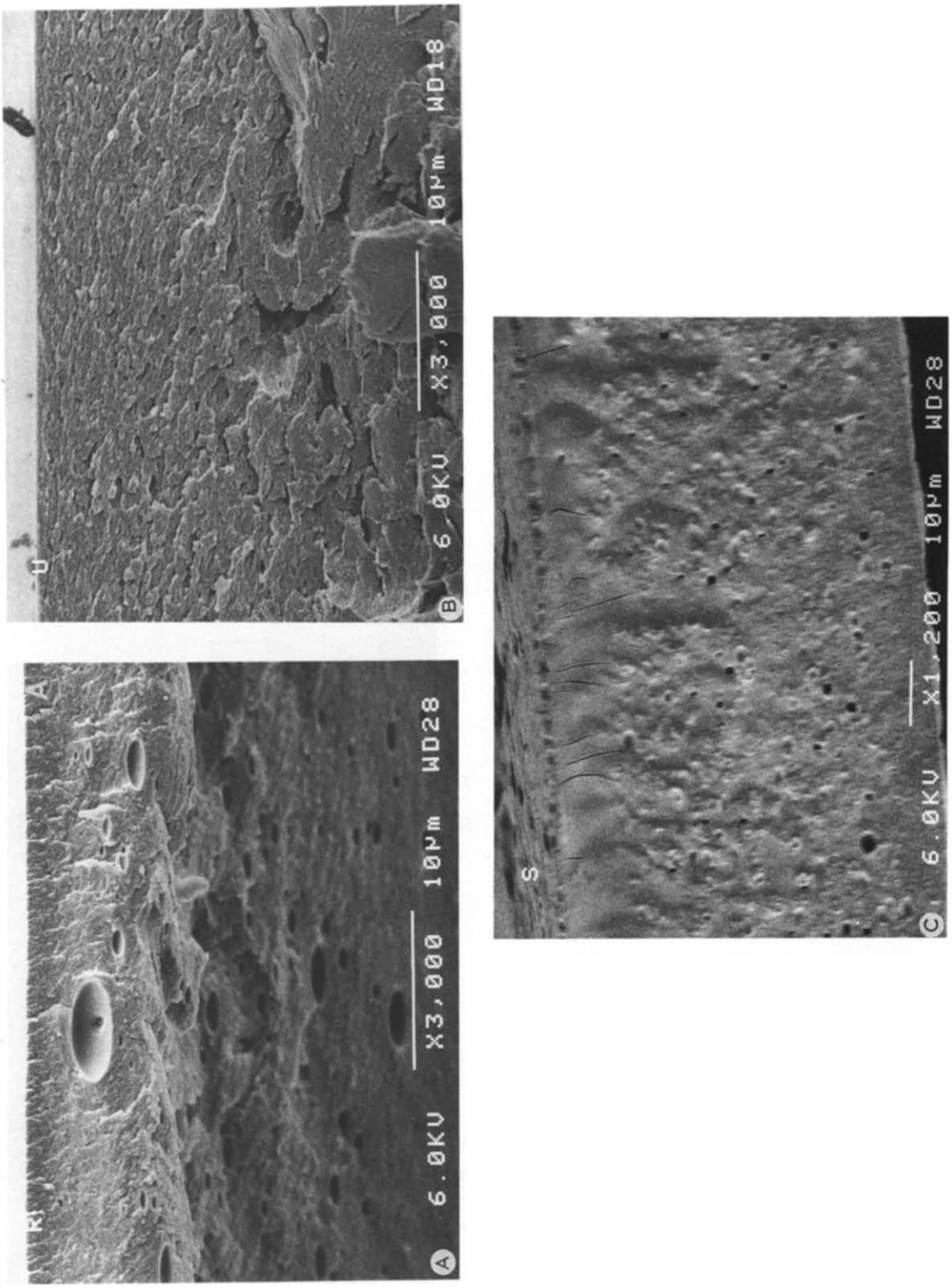

Fig. 1. Scanning electron micrographs of cross-sections of fresh ammoniated aqueous (A), fresh organic-solvent-based (B), and aged ammoniated aqueous (C) CAT films.

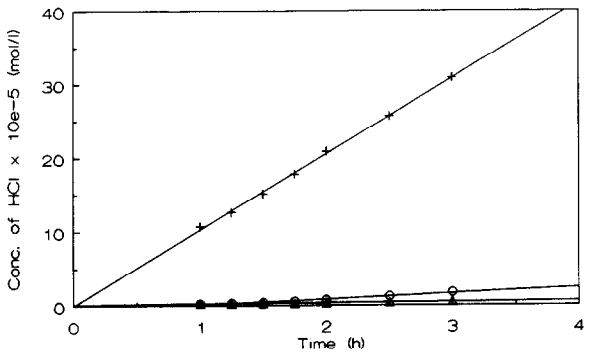

Fig. 2. Permeability of CAT, CAP and HP-50 (acetone/water 97:3) films to hydronium ions ($n = 4$–6). (+) CAT 45 μm, (△) CAP 50 μm and (○) HP-50 50 μm.

chloric acid (0.1 N), the permeability decreasing in the sequence CAT, HP-50, CAP (Fig. 2). Values for the slope of plots of hydronium ion (H_3O^+) concentration vs time were 1.0×10^{-4}, 6.3×10^{-6} and 1.0×10^{-6} mol l^{-1} h^{-1}, respectively. These findings are consistent with previous reports (Spitael, 1976; Chang, 1990) on gastric resistance properties of organic cellulose ester enteric coatings.

As shown in Table 3, the film thickness of CAT also demonstrated a clear effect on the permeability to hydronium ions. Therefore, sufficient amounts of CAT should be applied to drug products, for instance, in those cases where the

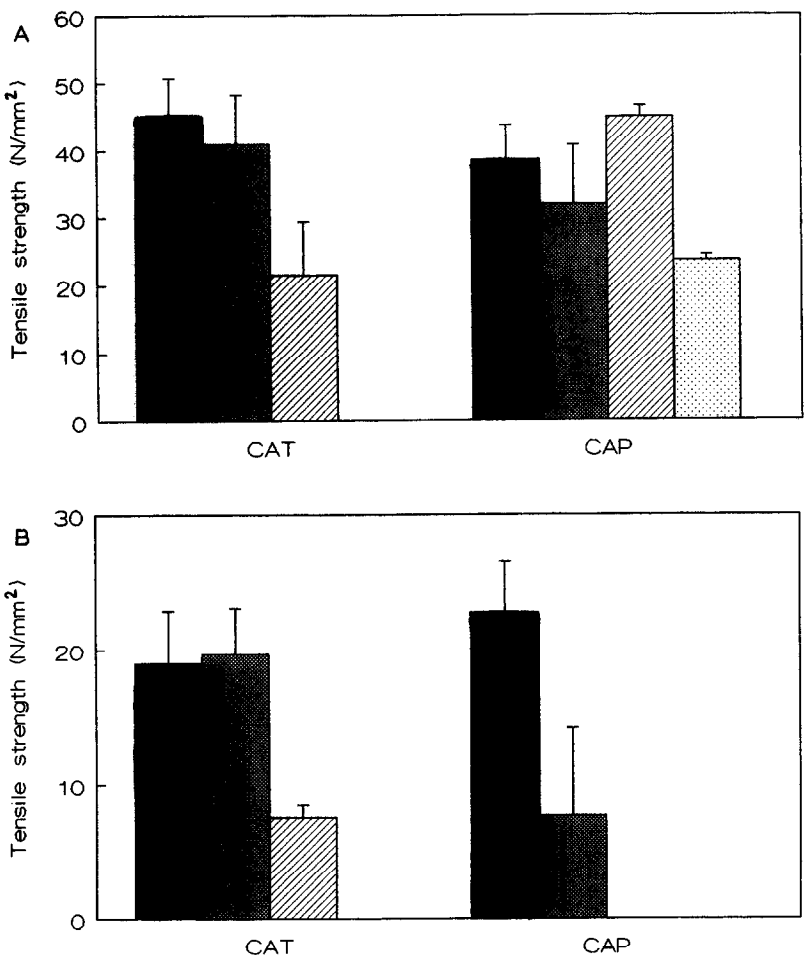

Fig. 3. Mechanical strength of fresh and aged organic-solvent-based (A) and ammoniated aqueous (B) CAT and CAP free films ($n = 3$). Bars: (filled) fresh; (stippled) 70% RH, 40°C; (diagonally hatched) 80% RH, 40°C; (dotted) 90% RH, 40°C.

Table 3
Slope values for plots of hydronium ion (H_3O^+) concentration vs time ($n = 3$–4)

Polymer	Thickness (μm)	Storage temperature and relative humidity (°C/% RH)	Slope value (k) (mol l^{-1} h^{-1})
Organic-CAT	45	fresh	1.0×10^{-4}
	35	fresh	1.7×10^{-4}
	25	fresh	2.6×10^{-4}
Organic-CAT	50	20/40	1.8×10^{-4}
Organic-CAT	50	40/70	3.6×10^{-4}
Organic-CAT	50	40/80	3.0×10^{-4}
Organic-CAT	50	40/90	2.9×10^{-4}
Organic-CAP	50	20/40	1.4×10^{-6}
Organic-CAP	50	40/70	1.8×10^{-6}
Organic-CAP	50	40/80	3.8×10^{-6}
Organic-CAP	50	40/90	3.7×10^{-6}

core units contain a highly pH-sensitive drug. This may be of particular value, for example, in the formulation of erythromycin or pancreatic enzymes containing oral preparations (Heinämäki, 1988).

Films prepared from ammoniated aqueous solution dissolved when purified water was used as a medium in the receiver side of the diffusion cells. According to the literature, ammoniated aqueous enteric film is formed when the film is exposed to acidic medium (Anon, 1988). This occurs when the enteric-coated drug product reaches the acidic environment of the stomach. On the basis of the present results, excessive amounts of water taken simultaneously with enteric-coated drug products of this type may be harmful with respect to their gastric resistance capability.

Storage under stress conditions appeared to increase the permeability of CAP films to H_3O^+ ions to a greater extent, as compared to CAT films (Table 3). This may be explained on the basis of the greater tendency of CAP to undergo hydrolysis, resulting in an increase in the free phthalic acid content, during storage under high temperature and high humidity conditions (Delporte, 1979; Eastman Kodak, 1991). Overall, however, the present results suggest excellent resistance of organic-solvent-based enteric films against short-term storage under tropical conditions.

3.4. Mechanical properties of the fresh and aged films

Determination of the mechanical and stress-strain properties of a film provides preliminary information on the ability of a coating to withstand strong environmental stresses (Banker, 1966). As demonstrated in Fig. 3, the tensile strength of organic enteric films was somewhat greater than that of the corresponding ammoniated aqueous films. Short-term aging under high temperature and high relative humidity storage conditions caused the mechanical strength to decrease with both organic-solvent-based and ammoniated aqueous free films (Fig. 3). The data show that the films aged at 40°C and 70% RH for 1 week appear to be slightly weaker than the corresponding fresh films, however, the difference is not statistically significant, while the films aged under higher relative humidity storage conditions (80 and 90% RH) were clearly weaker than the controls. With all types of films, loss of weight (2–8%) rather than an increase was observed during 1 week storage under tropical conditions. This may be due to triacetin evaporating during storage (Crawford, 1971; Gutierrez-Rocca and McGinity, 1993). This great loss of plasticizer

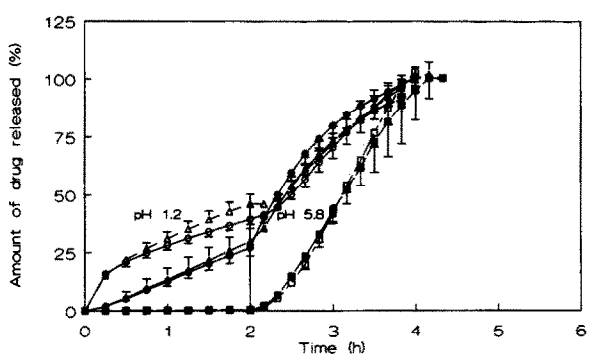

Fig. 4. Percentage of drug released from fresh (closed symbols) and aged (open symbols) enteric-coated tablets in 0.1 N HCl and in phosphate buffer solution at pH 5.8 and 6.2 ($n = 6$). (●, ○) Ammoniated-CAP, (▲, △) ammoniated-CAP with aqueous HPMC subcoat 2% and (■, □) organic-CAP.

is obviously mainly responsible for the impaired mechanical properties found with aged films.

3.5. Drug release from enteric-coated tablets

Fig. 4 shows the effect of short-term aging under tropical conditions on the gastric resistance and dissolution properties of cellulose ester enteric films applied to tablets. The results obtained with freshly coated caffeine tablets are in conformity with those in the case of the free films. The organic CAP coating showed virtually no loss of caffeine through the enteric coating during a period of 2 h. With ammoniated CAP coatings, premature drug release amounted to 15–25% in 2 h. Both types of ammoniated enteric coated tablets (with or without subcoat) clearly demonstrated a decrease in gastric resistance on aging for 1 week under tropical conditions.

4. Conclusions

Free films can be used in the preliminary testing of enteric film properties of ammoniated aqueous enteric coating systems. The diffusion of a water-soluble drug through the films prepared from ammoniated aqueous solutions is more rapid than that through the films prepared from organic-solvent-based (acetone) solution. As regards the mechanical properties, ammoniated aqueous enteric films appear to be weaker than the corresponding films prepared from acetone-based solutions. Aging under stress storage conditions (tropical conditions) can change the permeability and mechanical properties of ammoniated aqueous enteric films based on CAT or CAP. More research is needed in order to clarify the enteric and mechanical properties of enteric films prepared from ammoniated aqueous solutions.

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