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Permeability to hydrogen ions of an enteric coating polymer and interaction of film formulation factors

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Abstract

The influence of cellulose acetate phthalate film formulation on permeability to hydrogen ions was studied by measuring the permeability coefficients of free films in a diffusion cell. The effect of the studied factors and the interaction among them have been found to be significant. Aqueous and organic films have distinct behaviour; the former are considerably more permeable. Swelling experiments, X-ray diffraction and differential scanning calorimetry studies were carried out to clarify the differences observed in the permeability of the films. Copyright © 1996 Elsevier Science B.V.

Keywords: Aquateric; Cellulose acetate phthalate; Diethylphthalate; Enteric coating polymer; Free film; Permeability to hydrogen ions; Plasticizer

One of the essential functions of gastroresistant coatings is to prevent the decomposition of a labile drug by gastric juice (Chambliss, 1987).

A number of papers have been published showing that this protection can be insufficient due to the permeability of the coatings (Delporte, 1977; Porter and Ridgway, 1982), which can lead to destruction or loss of activity of the drug (Whitehead, 1988; Bataille et al., 1990).

In previous papers (Raffin et al., 1994, 1995), we studied the physicochemical factors that influence the ionic permeability of a cellulose acetate phthalate free film. Our results showed that at a pH of the same range as that of the gastric juice, the films of this enteric polymer are conductors of ions, due to the diffusion of H^+ and Cl^- across the polymer film. A clear effect of the type of plasticizer used was also observed, which showed that formulation has a very important influence on film permeability.

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In this study we confirm this influence by measuring permeability coefficients in a diffusion cell. The plasticizer can modify the physicochemical and mechanical characteristics of the film according to its hydrophilic or hydrophobic nature, influencing the film permeability to certain molecules (Jenkin et al., 1992). Also, the more advisable utilization of polymeric water dispersions due to the disadvantages of organic solvents (toxicity, inflammability) allowed us to compare the two kinds of film.

Films from organic solutions were obtained by casting a 10% (w/v) solution of cellulose acetate phthalate (CAP) (Eastman Kodak Company, USA) on glass plates. The solvents were: acetone, the 1:1 mixture and the azeotrope of ethylacetate and isopropanol. The plasticizers were triacetin (Merck, Germany) and diethylphthalate (Prolabo, France), corresponding to 30% in weight of the polymer. Films without plasticizer were also prepared. Two thicknesses were studied: 35 and 70 μm. Thickness was measured with a digital gauge MT 12 (Heidenhein, Germany) with a 0.5 μm precision.

Films from water dispersions (Aquateric, FMC, USA) were obtained with Petri dishes in an oven at 60°C. Plasticizers and polymer were in the same concentration as in organic solutions and 0.1% Polysorbate 80 (Merck, Germany) was added to prepare the dispersions. Because films 35 μm thick were not continuous, we used films of 70 and 100 μm thickness.

The diffusion cell was previously described (Raffin et al., 1994). United States Pharmacopeia (USP) artificial gastric juice without pepsin was used as permeant solution (US Pharmacopeia XXII, 1990). A solution of NaCl (2 g/l) was added in the receiving compartment of the cell, where the pH was measured at regular intervals over 4 h. The two compartments were stirred at 150 rpm speed. The temperature was 37 ± 0.5°C.

The permeability coefficient was calculated from the slope of the H^+ concentration in the receiving compartment as a function of time according to Fick's first law (Spitael and Kinget, 1977). Then, factorial analysis of variance (ANOVA) was carried out to show the existence of a possible interaction among the formulation factors.

In addition, the water uptake was determined by soaking the films in 300 ml of artificial gastric juice at 25°C for 20 h and weighing at regular intervals. The dry weight of the film was determined after 24 h in an oven at 110°C. The volume fraction of water in the films and the loss of leachable material were calculated according to Nixon and Wong (1990).

X-ray diffractograms were obtained with a diffractometer (Sigma 80) equipped with a horizontal CGR goniometer with copper anticathode ($K_\alpha = 1.5404$ Å) operated at a speed of $15°\theta$/h, with measurements between 5.0 and $20°\theta$ (Philips generator: 40 kV, 20 mA).

For differential scanning calorimetry (DSC), a Perkin-Elmer DSC-4/TADS system was used. Material (7–12 mg) was placed in aluminium pans and scanned from 30 to 200°C at a rate of 20°C/min under nitrogen current, using indium as a thermometric reference. The glass transition temperature was taken as the midpoint of the transition.

Permeability coefficients of films casted from organic solutions are presented in Table 1. The ANOVA showed that the plasticizer is the most significant factor. Fig. 1 shows that the presence of a plasticizer decreases the permeability of the film which can be explained by a reduction in porosity caused by an additional solvation exerted by these adjuvants (Porter and Ridgway, 1982). Diethylphthalate makes films less permeable: the permeability coefficient decreases 5-fold with this plasticizer against only 2-fold with triacetin.

These results confirm the impedance studies carried out before (Raffin et al., 1995). The evolution in time of the electrical resistance showed that unplasticized films are better conductors than films containing plasticizers and those plasticized with diethylphthalate have a greater electrical resistance than the others, denoting a more intense decrease in film permeability.

When thickness is increased, the permeability coefficients decrease, except for diethylphthalate films, where the permeability appears to be independent of the thickness. In addition, when the quantity of deposited polymer increases, the film is more homogeneous and the role of the solvent becomes insignificant (Chaumeil and Piton, 1973).

Table 1
Permeability coefficients of CAP films of different formulations (P.10E8) (cm/s)

	Pl-0		Pl-1		Pl-2	
	$E1$	$E2$	$E1$	$E2$	$E1$	$E2$
S1	40.95 (0.54)	16.75 (2.67)	4.78 (1.24)	7.64 (1.08)	11.08 (2.20)	0.01 (0.00)
S2	51.08 (6.64)	15.46 (0.01)	7.88 (0.21)	8.18 (0.72)	29.08 (1.52)	6.76 (1.74)
S3	32.53 (4.58)	17.06 (3.75)	0.01 (0.00)	4.18 (0.24)	25.38 (0.99)	8.02 (0.23)
A	—	—	—	29.26 (2.36)	—	31.52 (3.63)

Values in parentheses indicate S.D. for $n = 2$. Pl-0, without plasticizer; Pl-1, diethylphthalate; Pl-2, triacetin; E1, 35 μm; E2, 70 μm; S1, acetone; S2, 1:1 mixture; S3, azeotrope; A, aqueous dispersion (for $E = 100$ μm, $P = 13.26$ with Pl-1 and 20.95 with Pl-2).

Better results are obtained with acetone and the azeotropic mixture which have a constant composition during evaporation. The solubility of the polymer decreases in the 1:1 mixture of ethylacetate and isopropanol, due to the greater evaporation rate of the ester (Spitael and Kinget, 1977).

For water-based films, the only factor of significant influence on the permeability coefficient is film thickness. Films of 70 μm prepared from water dispersions with triacetin presented a permeability coefficient similar to 35-μm films obtained from organic solutions containing the same plasticizer. An increase of about 30 μm in thickness showed a more important effect on the permeability of organic films, which decreased 3-fold, while permeability coefficients of water dispersion films had a 1.5-fold reduction (Fig. 2). Hence, for the same thickness, the films obtained from Aquateric dispersions are more permeable than those prepared from organic solutions. This can be due to the greater porosity attributed to water dispersion films (Horvath and Ormos, 1989).

However, the role of plasticizer in aqueous films is very important even if no statistically significant difference was found for triacetin and diethylphthalate. The plasticizer is fundamental for polymer particle coalescence, and the affinity between the polymer and the plasticizer is expected to influence the quality of the films. Those containing triacetin are more homogeneous and transparent. Hydrophobic plasticizers like diethylphthalate may not be fully incorporated by polymer particles, resulting in an incomplete coalescence and consequently a very heterogeneous film (Bodmeyer and Paeratakul, 1994).

These results are corroborated by impedance measurements. Aquateric films exhibit a more marked decrease of their electrical resistance. In the case of diethylphthalate, the values reached 0.178 $k\Omega \cdot cm^2$ after 90 min in artificial gastric juice, against 889.1 $k\Omega \cdot cm^2$ for organic films. These films, when plasticized with diethylphthalate, are more efficient conductors than those with triacetin, showing that the plasticizer plays a fundamental role in film permeability of water-based films (Raffin, 1995).

In Table 2, the swelling characteristics of some films are presented. All the films presented swelling during the initial 15 min of contact between films and solution, the water uptake varying between 14 and 43% with regard to the weight of the dry polymer, with no significant weight gain after this step. Aqueous films exhibited a swelling rate 2-times greater than organic films (see water volumic fractions). They can be considered hydrophiles because of their high volumic fractions, above 0.3 (Zaikov et al., 1988). In addition, high values for ϕ_v are related to porous structures (Nixon and Wong, 1990), which is corroborated by the lower values found for aqueous film densities. This can fully explain the very important permeability of Aquateric films.

Otherwise, films casted from organic systems containing a plasticizer have an intermediate behaviour, with ϕ_v values lower than 0.2. These values confirm a decrease in porosity when a plasticizer is used. Nevertheless, no relationship can be established between permeability coefficients and ϕ_v values. So, the role of diethylphthalate in reducing film permeability cannot be attributed to any difference in water uptake.

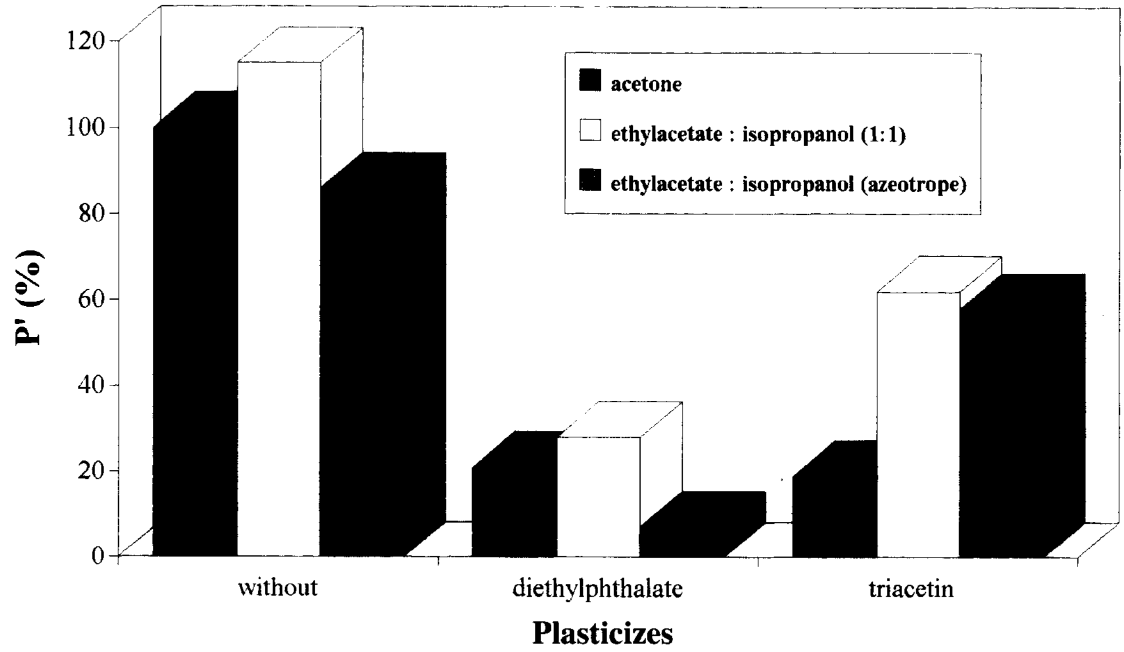

Fig. 1. Interaction between solvent and plasticizer on the permeability of CAP films. (*P'* is a relative value, considering the first column as 100%).

On the other hand, significant loss in weight was observed for plasticized films. The leaching out of hydrophilic plasticizers like triacetin has been reported in the literature (Bodmeyer and Paeratakul, 1992). As regards diethylphthalate, infrared spectra gave evidence for plasticizer hydrolysis due to the long contact with the acid solution used as gastric juice when heated. Phthalic acid forms the respective anhydride and water. The evaporation of water during film drying can explain the loss in weight of the films containing this hydrophobic plasticizer (Raffin, 1995).

Moreover, aqueous films plasticized with diethylphthalate presented a very great loss in their weight, suggesting that the hydrophobic plasticizer is not completely absorbed by the polymer and remains emulsified in the aqueous phase during latex preparation, which results in an incomplete coalescence of the spheres and a very heterogeneous film. Thus, this kind of adjuvant is not indicated for Aquateric films.

Although the CAP structure has been reported as essentially amorphous (Rona and Le Perdriel, 1974), organic films containing diethylphthalate gave evidence of a crystalline structure as shown in Fig. 3, suggesting that an interaction between this plasticizer and the polymer occurs. The similarity in structure of the plasticizer and the substituents of the polymer (phthalic acid) could have promoted the formation of crystalline zones, which have a 'physical reticulation' function, decreasing the mobility of polymeric chains in the amorphous regions.

Thus, the presence of crystallinity in diethylphthalate films can be another factor influencing the permeability of these films. The permeability is explained not only by the hydrophobic nature of film constituents but mainly by the interaction of the adjuvants and the polymer.

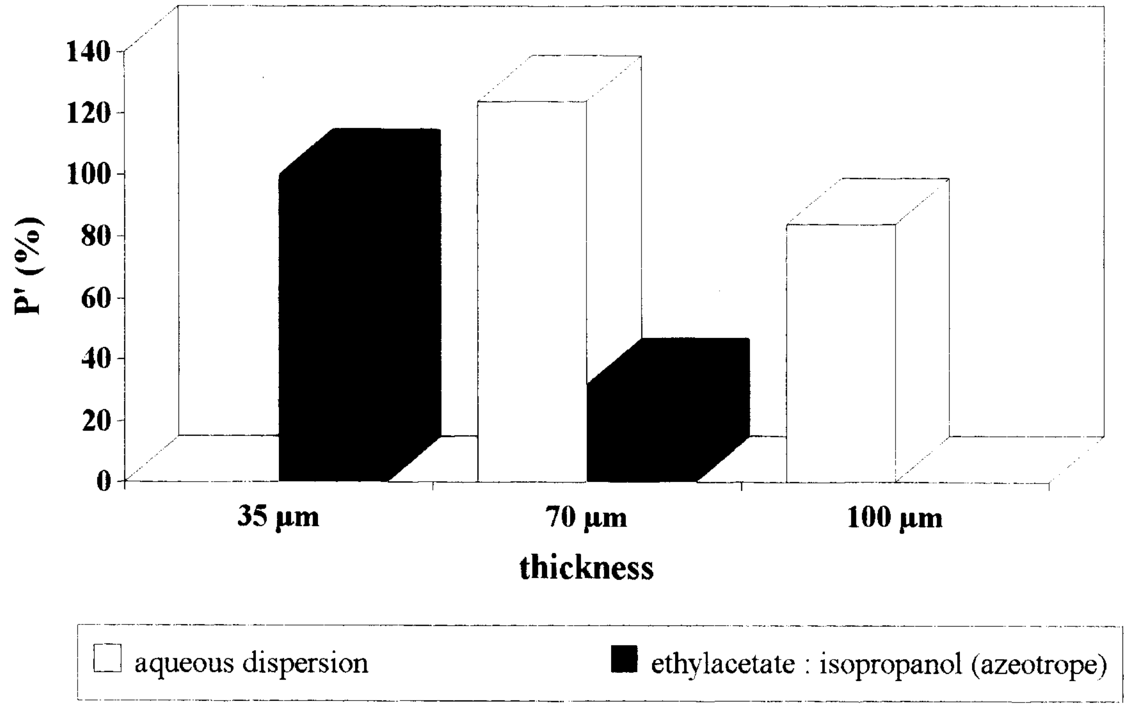

Fig. 2. Influence of film thickness on the permeability of aqueous and organic solvent-based films. (P' is a relative value, considering the first column as 100%).

The thermograms obtained showed the glass transitions as peaks of low intensity in the 140–180°C zone. Unplasticized films have a T_g of 170°C. A similar value was found in a complete study by Sakellariou et al. (1985).

Table 2
Volume fraction and loss in weight of films at swelling equilibrium

Film	Density (g/ml)	ϕ	Loss in weight (%)
O.Pl-0.E1	1.47	0.25	7.4
O.Pl-0.E2	1.36	0.19	5.4
O.Pl-1.E1	1.43	0.18	13.5
O.Pl-1.E2	1.37	0.13	21
O.Pl-2.E1	1.44	0.17	13.6
O.Pl-2.E2	1.38	0.16	13.5
A.Pl-1.E2	1.33	0.44	27.8
A.Pl-2.E2	1.35	0.35	17.3

O, ethylacetate:isopropanol azeotrope; A, aquateric; Pl-0, without plasticizer; Pl-1, diethylphthalate; Pl-2, triacetin; E1 = 35 µm; E2 = 70 µm.

The addition of a plasticizer decreases the T_g (151°C for films containing diethylphthalate and 147°C for those with triacetin). These high values indicate that the films are in the glassy state under our experimental conditions, though the decrease in T_g does not influence film permeability.

In conclusion, it appears from these results that the permeability of a polymer film can be affected by the use of different adjuvants and preparative conditions. The effect of plasticizers, solvents and film thickness as well as the interactions among these factors have a significant influence on film permeability. However, the coating systems must also be studied as protective films for dosage forms, which is the next step in our work, where it is planned to use an acidolabile substance to check the permeability of coated tablets.

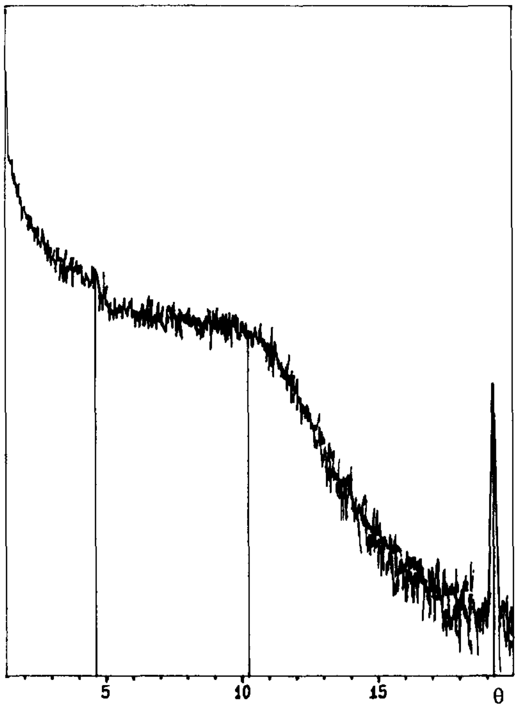

Fig. 3. X-ray diffractogram of a CAP film prepared from azeotrope–diethylphthalate solution.

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