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Physico-chemical characterization of the ionic permeability of an enteric coating polymer

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Abstract

Cellulose acetate phthalate (CAP) is widely used as an enteric coating polymer. In this work, radiotracer and impedance measurements were performed in order to study the evolution in time of CAP films immersed in different solutions including artificial gastric juice. The membrane permeabilities demonstrate a strong dependence on the pH value, suggesting our film to behave like a cation-exchange membrane. A two-step transport mechanism is proposed to explain the variation of the experimental data with time. The effects of different plasticizers and solvents were also investigated, our observations showing the importance of using a hydrophobic plasticizer to improve the gastroresistance of the polymer.

Keywords: Cellulose acetate phthalate; Diethyl phthalate; Enteric coating film; Self-diffusion flux; Impedance spectroscopy; Ionic permeability; Plasticizer

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1. Introduction

One important purpose of enteric coatings is to maintain the stability of the drug which might otherwise to be subject to degradation if exposed to the gastric environment.

Since earlier studies suggesting cellulose acetate phthalate (CAP) as an enteric coating material (Malm et al., 1951), this polymer has been widely used in the pharmaceutical industry, thus far being one of the most often employed in the field of enteric film coating.

Nowadays, according to the existing codexes, the basis for determining the gastroresistance of a pharmaceutical dosage form is a modified disintegration test, requiring that the product remains physically intact for a specified period when exposed to simulated gastric juice. This test does not take the coating permeability into account.

The permeability of CAP coatings to some salts (Handbook of Pharmaceutical Excipients, 1986) and to artificial gastric juice (Kanig, 1954) is known, but a very limited number of works has

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discussed this fact from a physico-chemical point of view (Spitael and Kinget, 1977a,b).

When the film is permeable to HCl, an acid-labile substance, of enzymatic nature for example, can undergo the destructive action of gastric juice without tablet disintegration. This was reported by Whitehead (1988) for different commercial preparations of pancreatin and confirmed later (Bataille et al., 1990).

In a previous paper, the factors influencing the hydrogen ion permeability of an isolated film of CAP were investigated (Raffin et al., 1994). This permeability was greater when a solution of 0.034 M NaCl was used in the receiving side of the diffusion cell, instead of distilled water.

The purpose of this paper was to gain a better understanding of the influence of pH on the permeability of CAP film towards ions. Two experimental techniques were used: on the one hand, the direct measurement of the self-diffusion flux by radiotracers, the film being placed between two identical electrolyte solutions; and on the other, impedance spectroscopy which allows one to follow the variation with frequency of both the electrical resistance and the capacitance of the film. Different film thicknesses and various compositions in solvent and plasticizer were used for studying their effect on coating permeability.

2. Material and methods

2.1. Film preparation

The films were prepared by casting with a thin-layer chromatography applicator from 10% w/w of cellulose acetate phthalate (Eastman-Kodak Co., USA) solutions, according to a previously described method (Raffin et al., 1994).

In the present study, three different solvents were used (all solvents are reagent grade): acetone and two mixtures of ethyl acetate-isopropanol, 50:50 and 77:23 w/w (azeotrope).

Occasionally, triacetin (Merck Germany) and diethyl phthalate (Prolabo France) were added as plasticizers in a concentration corresponding to 30% w/w of the amount of the polymer.

Films of various thicknesses were investigated (14, 30, 50, and 70 μm). These values were measured using an MT 12 digital length gauge (Heidenhein Germany) with a precision of 0.5 μm.

2.2. Solutions

2.2.1. Composition of simulated gastric juice

The simulated gastric juice was prepared by dissolving 2.0 g of sodium chloride and 3.2 g of pepsin in 7.0 ml of hydrochloric acid and sufficient water to make 1000 ml. This test solution has a pH of about 1.2 (US Pharmacopeia, 1990). Therefore, the ionic concentration of the simulated gastric juice is 0.034 M Na^+, 0.063 M H^+ and 0.097 M Cl^-.

2.2.2. Composition of solutions used

Solutions containing only NaCl and HCl were used at different pH values ranging from 1.2 to 6. The pH variations induce changes in the ionic concentration of solutions. Thus, experiments were performed for two cases:

(1) The Na^+ concentration was kept constant (0.034 M) while the H^+ and Cl^- concentrations were varied;

(2) The Cl^- concentration was kept constant (0.097 M) while the H^+ and Na^+ concentrations were varied.

Therefore, at pH 1.2, the ionic composition of solutions was identical to those of the gastric juice; however, for other pH, the solutions had the following concentrations:

pH2 solution(1): $C_{Na} = 0.034$ M, $C_{Cl} = 0.044$ M
solution(2): $C_{Na} = 0.087$ M, $C_{Cl} = 0.097$ M,
pH3 solution(1): $C_{Na} = 0.034$ M, $C_{Cl} = 0.035$ M
solution(2): $C_{Na} = 0.096$ M, $C_{Cl} = 0.097$ M

From pH 3 to 6, the Na^+ and Cl^- concentrations were practically identical, either 0.034 M for solutions (1) or 0.097 M for solutions (2).

2.3. Flux measurements

Self-diffusion flux measurements were performed using radiotracers according to a previously described method (Sandeaux et al., 1991; Fares et al., 1994). The teflon cell comprised two identical compartments between which the membrane was interposed. The working area of the membrane was 12.6 cm^2. The volume of solutions was 40 ml in each compartment. Solutions at the same concentration on both sides of the membrane were stirred throughout the experiment with magnetic stirrers.

In one compartment (feed compartment), a very small volume (0.05–0.2 ml) of labelled compound was added. The changes of radioactivity in the other compartment (receiver compartment) were measured by sampling aliquots of solution at regular intervals and the number of ions crossing the membrane was calculated from the following relation:

$$n_t = \frac{CV(N_t^{\mathrm{R}} - N_{t-1}^{\mathrm{R}})}{N_t^{\mathrm{F}}} + n_{t-1} \qquad (1)$$

where n_t is the number of ions having diffused from feed to receiver compartment at time t, V denotes the volume of the solution in one compartment, C is the concentration of the diffusing ion, and N_t^{F} and N_t^{R} represent the numbers of disintegrations/min per ml in feed and receiver compartments at time t, respectively.

At equilibrium, the number of ions appearing in the receiver compartment varies linearly with time. The value of the flux was deduced from the slope of this straight line. Knowing the working area of the membrane, the flux was expressed in mol cm^{-2} s^{-1}.

^{22}NaCl and $H^{36}Cl$ were purchased from the Radiochemical Centre, Amersham, UK. The radioactivity of the samples was measured using two Packard spectrometers: γ-Auto-gamma 500 C for ^{22}Na, and β-Liquid scintillation analyser 1900 TR for ^{36}Cl.

2.4. Impedance measurements

Since cellulose acetate phthalate contains free carboxylic groups, CAP films can be compared with ion-exchange membranes (IEM) which are conductors. Their conductivity depends on the compositions of both the membrane material and the electrolyte solution with which the membrane is in contact.

As the electrical resistance of a conductor varies inversely with its area, the parameter which will be considered is the product (resistance) (area): R_s. The product of the resistance and the area is a constant which is a characteristic parameter of a membrane in contact with a given electrolyte at a given temperature.

There exist several techniques for measuring the electrical resistance of IEM: alternating current methods (AC) and direct current methods (DC). Most electrical resistance measurements are made with AC in order to avoid the effects of electrochemical polarization at the membrane-solution interface, and to provide information about transfer phenomena. A very convenient method consists in using a clip-cell with which the membrane can be easily put on and removed. In this case, the value of the membrane resistance is the difference between measured values with and without the membrane (Gavach et al., 1985). Unfortunately, this method cannot be applied to our ion-exchange polymer due to the very high value of its electrical resistance.

For more accurate measurements or for determining the resistance of the membrane out of equilibrium with the electrolyte solution, an alternative method is used, also involving AC. In this method, the membrane is removed from its equilibrium solution and after its surface is swept, directly clamped between two mercury half-cells (Gavach et al., 1989; Pourcelly et al., 1990). The impedance of the mercury-membrane-mercury system is measured over a large frequency domain and the equivalent circuit resistor-capacitor is deduced from the impedance spectra. This method, often used for IEM having a good electrical conductivity, could not be applied to the studied polymer because, due to its small thickness, it was very difficult to wipe only its surface without drying the material more deeply.

Consequently, an impedance method carried out in a four-electrode cell was used. In this cell illustrated in Fig. 1, the film was always in contact with the electrolyte solution and the Nyquist plots were recorded as a function of the hydration time. The electrical circuit was composed of a General Purpose Electrochemical System (GPES Autolab) from EcoChemie, monitored by a mi-

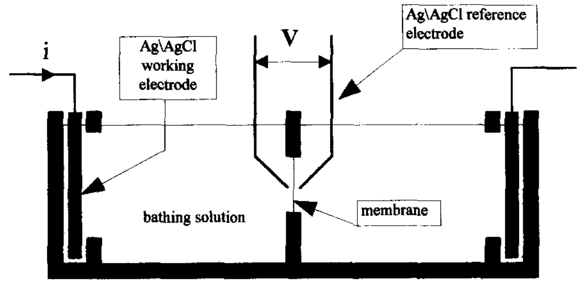

Fig. 1. Electrochemical cell used for the impedance measurements.

crocomputer. The frequency measurement ranged from 5 Hz to 50 kHz. Injection of charges was made through the two extreme Ag/AgCl electrodes and the voltage was measured between the Ag/AgCl probes.

The impedance of the membrane Z is a complex number which can be divided into a real and an imaginary part; the first one represents the resistive component (where voltage and current are in phase) and the second the reactive component (where current and voltage are out of phase, i.e., at $\pi/2$). Commonly, the in-phase component of the impedance is referred to as Z' and the out-of-phase component is called Z'' so that $Z(\omega) = Z'(\omega) - jZ''(\omega)$. Analysis of the data is made easier by displaying vectorially the impedance in the complex plane. The diagram where $Z''(\omega)$ is plotted vs $Z''(\omega)$ is called the Nyquist plot. For our membranes, the locus of the impedance in the complex plane is always a flattened semi-circle, and the resistance can be deduced from the intercept of the circle with the real axis. A set of Nyquist plots recorded for different hydration times is presented in Fig. 2. For low frequencies, the acquisition mode leads to shifts in the Nyquist plots because of the rapid decrease of the resistance with time. The equivalent circuit that would give the same diagram corresponds to a resistance-capacitance parallel circuit from which the values of the resistance and the constant-phase element (CPE) can be calculated through the relation:

$$Z = \frac{R}{1 + RY_0(j\omega)^{\alpha}} \tag{2}$$

where j is the complex operator, Z denotes the impedance, R the electrical resistance, Y_0 the frequency-independent real constant of the CPE, ω the pulsation and α a coefficient reflecting the non-homogeneity of the material; α ranges from 1/2 to 1 and for a pure capacitance, $\alpha = 1$. The different elements of the equivalent circuit were calculated from a special program (Boukamp, 1988/1989) using non-linear least-squares fitting of data.

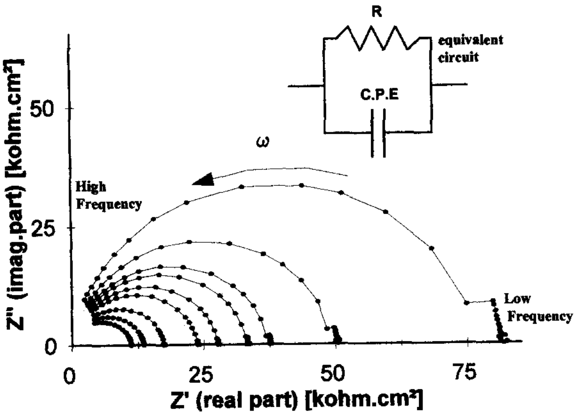

Fig. 2. Impedance spectra taken for different hydration times; the arrow points from low to high frequencies. Diameter of semi-circle decreases with time.

3. Results

3.1. Flux measurements

The Na^+ or Cl^- flux measurements were performed respectively with solutions (1) or (2) at varying pH (1.2–6). Only unplasticized films cast from the acetone solution were characterized by this method. The film thickness was 30 μm. The membrane samples were dry at the beginning of the experiment.

Fig. 3 shows an example of the variation in time of the number of Na^+ and Cl^- ions appearing in the receiver compartment. The resulting straight lines show that the unidirectional fluxes are constant during the time of the experiment. Nevertheless, for sodium ions, a constant flux is observed only after a time lag of about 50 min. In

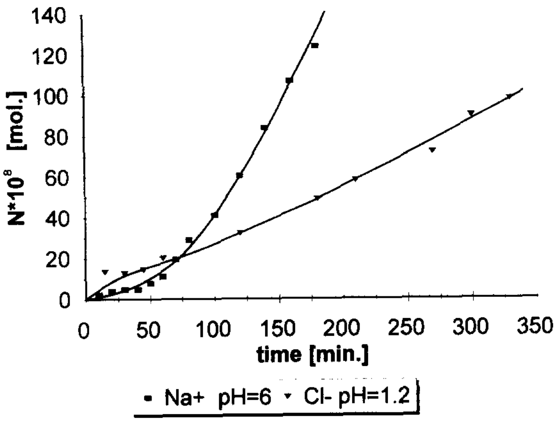

Fig. 3. Number of sodium and chloride ions appearing in the receiver compartment as a function of time.

order to check whether this time lag was due to film hydration, Na^+ flux measurements were performed at pH 6 (solution (1)), with a membrane sample previously equilibrated in this non-radioactive solution. The difference observed between the values obtained is not significant: 48 min for the dry film and 45 min for the hydrated one. Film hydration does not modify the time lag.

In Fig. 4, Na^+ and Cl^- fluxes are plotted as a function of pH. Throughout these experiments, the concentration of the ion whose unidirectional flux was measured was kept constant for all pH. One notes a great increase in sodium fluxes when the pH increases, while chloride flux decreases and becomes very low above pH 3.

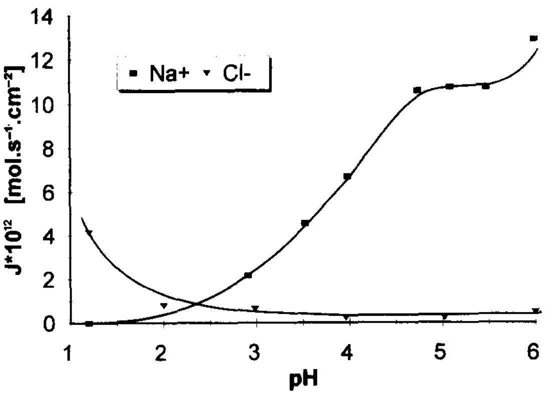

Fig. 4. Dependence of sodium and chloride steady-state fluxes on pH.

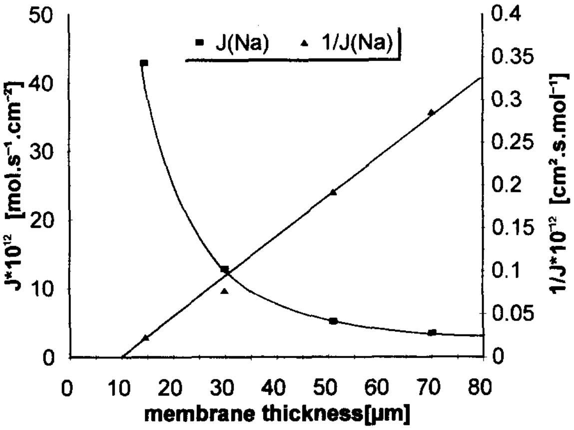

Fig. 5. Influence of film thickness on the steady-state sodium fluxes at pH 6.

It is known that the permeability of a film can be reduced by increasing its thickness (Okor and Anderson, 1986). Thus, the influence of the thickness on both sodium flux and time lag was studied at pH 6 and using solution (1). The corresponding results are presented in Fig. 5 and 6, respectively. Linear relationships are obtained with the time lag and the inverse of flux vs the thickness of the film.

3.2. Impedance measurements

The variations of the electrical resistance of the unplasticized film (30 μm) as functions of both pH of the equilibrating solution and hydra-

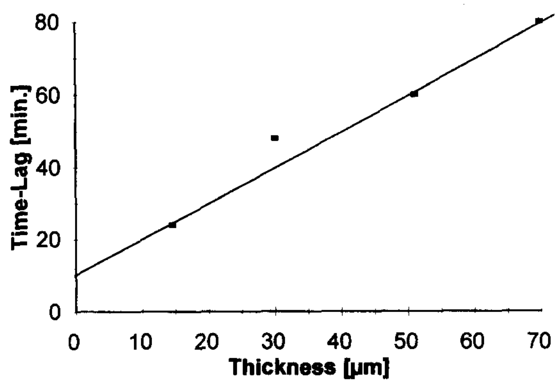

Fig. 6. Time lag of sodium flux (at pH 6) as a function of film thickness.

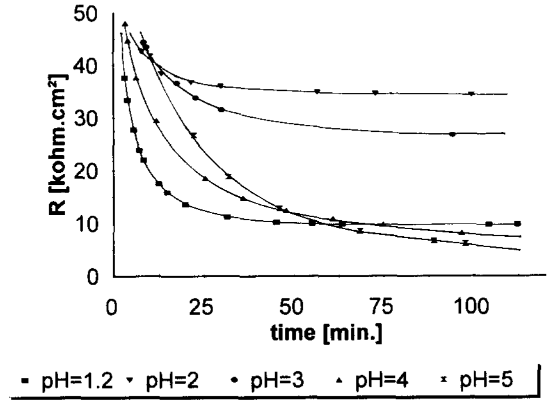

Fig. 7. Evolution with time of the electrical resistance *R* of the membrane for different pH values (solutions described in text).

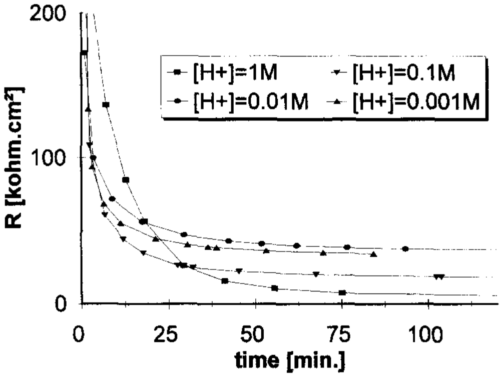

Fig. 9. Evolution with time of the electrical resistance *R* of the membrane in HCl solutions for different concentrations ranging from 0.001 to 1 M.

tion time are depicted in Fig. 7. The total amount of chloride ions in the equilibrating solution was kept constant, while the amount of Na^+ and H^+ ions was varied (solutions (2) described in section 2).

Fig. 8a and b shows the variation with time of the value of the two CPE components, i.e., the magnitude Y_0 of the constant-phase element and the exponent α, respectively (from Eq. 2).

Fig. 9 represents the variation of the electrical resistance when the membrane was only equilibrated with HCl solutions ranging from 0.001 to 1 M.

Lastly, Fig. 10 exhibits the influence of the plasticizing additive and casting solvent on the electrical resistance. The most important values of the resistance were obtained with diethyl phthalate, a hydrophobic plasticizing additive. As expected, in this particular case, the value of the capacitance does not vary with time. In contrast, the influence of the nature of the solvent was less significant.

4. Discussion

Since the CAP film bears carboxylic groups, its behaviour can be compared to those of a cation-exchange membrane bearing weak-acid groups. According to the pH values, the ion-exchanging sites can be either protonated (COOH) or depro-

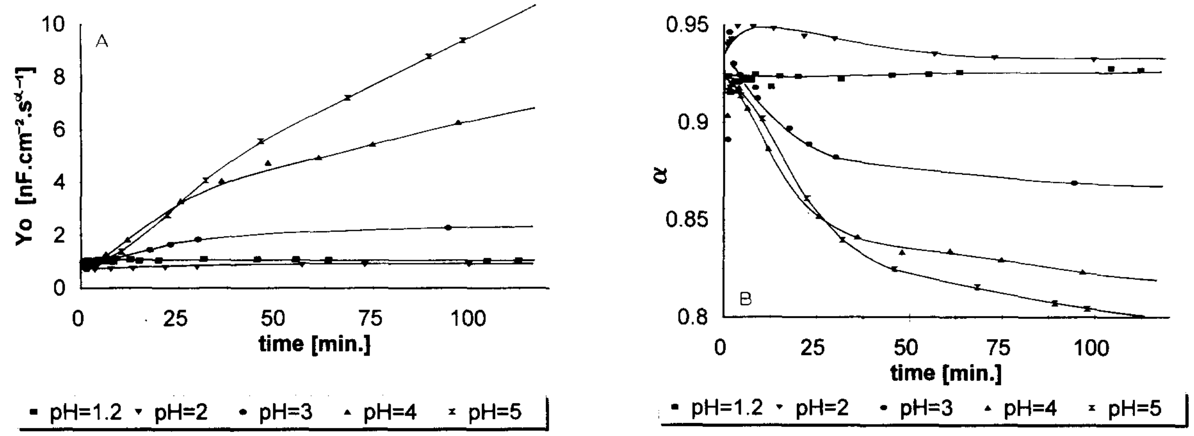

Fig. 8. (a) Magnitude Y_0 of the CPE as a function of time. (b) Exponent of α of the CPE as a function of time.

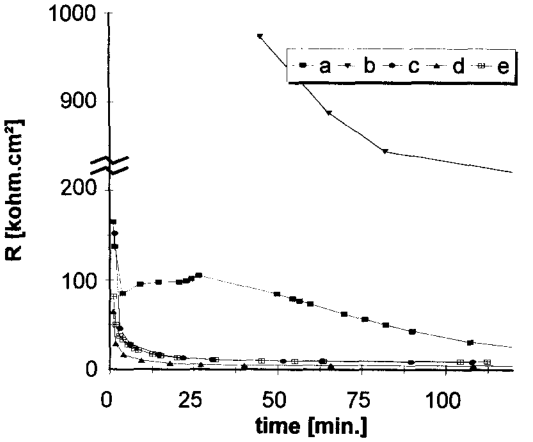

Fig. 10. Influence of formulation on the evolution in time of the electrical resistance. Influence of plasticizer: (a) triacetine, (b) diethyl phthalate. Influence of the solvent on unplasticized films: (c) diethyl acetate-isopropanol (azeotropic mixture); (d) ethyl acetate-isopropanol (50:50); (e) acetone.

tonated (COO^-). The results of flux and impedance measurements can be analysed taking into account the ionization of the fixed sites of the film. On the other hand, since the measurements were performed with a dry film, the transport mechanism must be related to the kinetics of film swelling.

4.1. Influence of pH on the transport mechanism through the CAP film

The comparison between results of diffusion fluxes (Fig. 4) and those of electrical resistances vs pH for long hydration times (Fig. 7) leads to similar conclusions:

At pH 1.2, J_{Cl^-} is greater than J_{Na^+}. At this pH value, all the fixed carboxylic sites of the membrane are protonated and the transfer of electrolyte is only due to HCl diffusion through the membrane. The electrical resistance of the membrane is relatively low and is due to the presence of partly dissociated HCl within the polymer film.

At pH 2, the carboxylic sites remain protonated but the interstitial solution contains less charge carriers than for pH 1.2.

Above pH 3, the carboxylic groups become more and more deprotonated, leading to large fluxes of Na^+ ions. This deprotonation is accompanied by a slight decrease in the resistance which can be explained by the occurrence of a second conduction mechanism by the sodium ions balancing the exchanging sites.

At about pH 5, one observes a plateau which seems to correspond to the complete deprotonation of the exchanging sites. Under these conditions, the electrical resistance is minimum because all the carboxylic sites are exchanging sites and charge transfer through the membrane is achieved by a hopping mechanism of sodium ions from one site to another.

Finally, at pH 6, the increase in J_{Na^+} may be attributed to a partial dissolution of the film. Previous studies showed that the dissolution pH of CAP was about 6–7 (Malm et al., 1951; Delporte, 1970).

Moreover, when the polymer film is only equilibrated with HCl solutions (Fig. 9), it does not bear ion-exchanging groups. Thus, the variation of its electrical resistance vs pH is not as important as with NaCl + HCl solutions because there is only one kind of transport mechanism. These results explain the greater permeability of CAP films to hydrogen ions when NaCl was added in test solutions (Raffin et al., 1994).

These previous facts are corroborated in Fig. 8 where the variations of the capacitance vs pH confirm that, for pH 1 and 2, i.e., without ion-exchanging sites, the capacitance is only that of a geometrical capacitance. When the deprotonation of carboxylic groups begins (from pH 3), the capacitance increases with time and this phenomenon is accentuated for pH 4 and 5 due to the presence of fixed charges in the membrane. A charged double layer at each solution-membrane interface follows from the creation of ionized exchanging groups. As the time constants are quite similar, we cannot distinguish between the two contributions (double layer and geometrical capacitance) and only one flattened semi-circle appears.

The electric resistance is inversely proportional to the conductivity, therefore it is related to the amount and mobility of charges carrying the electric current. Under the experimental conditions of this study, the following relation can be written:

$$\frac{1}{R}=K(C_{H^+}u_{H^+}+C_{Cl^-}u_{Cl^-}+C_{Na^+}u_{Na^+}) \quad (3)$$

where K is a constant, and C and u denote the concentration and mobility of all ionic species present in the film, respectively.

At pH 1.2, the carboxylic groups are protonated. The sodium concentration within the film is much lower than those of protons and chloride ions which have penetrated into the film during its swelling. Eq. 3 becomes:

$$\frac{1}{R}=K(u_{H^+}+u_{Cl^-})C_{HCl} \quad (4)$$

As shown in Fig. 7, at pH 1.2, the film is a conductor. The mechanism of transport occurs due to the solubilisation of HCl in the film followed by the diffusion of the H^+ and Cl^- ion-pair through the film. The flux values corroborate with such a transport mechanism. On the one hand, the chloride flux is greater than the sodium flux at pH 1.2 (Fig. 4), and on the other, a time lag is not observed for chloride flux (Fig. 3). This means that it is only the HCl partitioning at the membrane-solution interface which influences the rate of transport at acidic pH. Moreover, Eq. 4 also allows one to explain the increase in the electrical resistance at pH 2, for long hydration times (Fig. 7). Since the equilibrating solution contains 10-times less HCl, C_{HCl} decreases within the film, the sodium concentration maintains a negligible value, and R increases.

Above pH 3, the carboxylic groups become more and more deprotonated and the amount of sodium ions increases in the membrane, while that of chloride ions decreases. The fluxes of these last ions are close to zero. In contrast, the sodium fluxes increas greatly, making the film more conductive. The behavior of the CAP film becomes the same as that of a cation-exchange membrane from which the chloride anions are excluded.

When all the exchanging sites (COO^-) are balanced by Na^+ cations, the sodium concentration (C_{Na^+}) corresponding to the exchange capacity of the ion-exchange membrane is constant within the film. Therefore, the self-diffusion flux of sodium ions is constant and given by the following relation:

$$J_{Na^+}=\frac{D_{Na^+}C_{Na^+}}{e} \quad (5)$$

where D_{Na^+} denotes the self-diffusion coefficient of sodium ions in the membrane and e is the thickness of the membrane. This fact is verified for pH 4–5, when J_{Na^+} maintains a constant value (Fig. 4), and the values of the membrane conductivity are close.

4.2. Different steps of the transport mechanism

The mechanism of ion transfer between the solution and the film involves two steps: penetration of the electrolytic solution into the film and diffusion of ions within the membrane phase.

In Fig. 7, for a given pH, the decrease in electrical resistance which occurs at the beginning of experiments can be explained taking into account the film hydration, penetration of the electrolytic solution into the film increasing its ionic concentration and, therefore, its conductivity. Previous experiments (cf. Raffin et al., 1994) have shown that the films undergo an increase in weight of about 12–14% when equilibrated in the studied solutions. This gain is observed during the initial 15 min of contact between films and solutions, corresponding to the time in which we observe the decrease in the electrical resistance.

The self-diffusion flux can be related to the thickness of the membrane and of the boundary layer using the Helfferich equation (Helfferich, 1962):

$$\frac{1}{J}=\frac{e}{\overline{DC}}+\frac{2\delta}{DC} \quad (5)$$

where δ is the thickness of the boundary layer, and D and C represent the self-diffusion coefficient and the concentration of the diffusing ion, respectively. The bars refer to the membrane phase.

In Eq. 5, the first term represents the contribution of diffusion through the membrane while the second term refers to the contribution of diffusion through the boundary layer. For sodium ion, one can estimate the second term knowing $D_{Na^+} = 1.23 \times 10^{-5}$ cm^2 s^{-1} (Robinson and Stokes, 1955), $C_{Na^+} = 0.034$ M. The value of δ can be estimated to be close to 100 μm, as measured in previous works dealing with limiting current of polarization. The flux value deduced from the second term of Eq. 5 is about 2×10^{-5} mol cm^{-2} s^{-1}, much higher than the experimental value (about 10^{-12} mol cm^{-2} s^{-1}). This means that the limiting step of the transport mechanism is ion diffusion through the membrane phase. The presence of a time lag in sodium flux measurements, which does not occur in the chloride flux measurements (Fig. 3 and 6), also shows that the limiting step in the transport mechanism is not the penetration of solution into the film but the diffusion of ions through the film.

In Fig. 5, the extrapolation of the $1/J$ curve gives a value equal to 10 μm, which can correspond to an active thickness of the film which is lower than the real one. This result can be explained by the presence of a gel layer, on both faces of the film, through which the diffusion is much faster than in the central part. This heterogeneity, probably due to a difference in film hydration, was also observed with electrical resistance measurements (Fig. 2).

4.3. Influence of film formulation

Previous works showed that the composition of casting solvents affected the structure and hence the permeability of the resulting films (Spitael and Kinget, 1977a). Thus, we had expected that for the same solvent systems the electrical resistance would be different.

For acetone and the azeotropic mixture of ethyl acetate-isopropanol, the same values of electrical resistance were found, suggesting that these two solvent systems give films of similar quality. The films cast from the ethyl acetate-isopropanol (50:50 w/w) system presented only half of the resistance values of those mentioned above. This is explained by the greater volatility of ethyl acetate, which increases the isopropanol concentration in the solvent mixture. The polymer is not soluble in the alcohol and the films then obtained are more heterogeneous.

Nevertheless, the plasticizers seem to have a more important influence. Plasticized films have a greater electrical resistance than unplasticized ones. This may be explained considering the model where the plasticizer is distributed within the interstices of the polymer which decreases the penetration of the solution and hence the conductivity of the membrane (Lachman and Drubulis, 1964). For diethyl phthalate, this effect is very important because of its hydrophobic nature. This result is in agreement with various studies which show that hydrophobic plasticizers decrease moisture absorption and drug permeation through polymeric films. (Malm et al., 1951; Crawford and Esmerian, 1971; Spitael and Kinget, 1977b; Benita et al., 1986).

After hydration, films plasticized with triacetin present a small increase in electrical resistance. This value then decreases slowly with time, probably due to the leaching out of the hydrophilic plasticizer (Bodmeier and Paeratakul, 1992). The increase in resistance before leaching out may be a consequence of film fouling.

5. Conclusion

As a conclusion, this study has demonstrated the following:

Firstly, a coating film like the one studied, known to be gastroresistant, exhibits a real permeability at acidic pH, which is confirmed by the greater flux of chloride as well as by the electric resistance decreasing. This observation meets with the results of hydrogen ion diffusion previously obtained.

Secondly, the two methods were complementary in establishing the ionic permeability mechanism through the CAP film. Indeed, ion transfer through the CAP film is accomplished in two steps: penetration of the solution into the film and diffusion of ions within the film which is the limiting step. At acidic pH, as in gastric juice, the chloride ions cross the membrane with the protons, and ion transfer is only governed by a diffusion mechanism of the electrolytic solution. At neutral pH, ion transfer is achieved by a hopping mechanism of sodium ions from one exchanging site to another.

Finally, the solvent role is less important if compared to that of the plasticizer. Diethyl phthalate having a hydrophobic nature proved to be the best adjuvant for the formulation of a gastroresistant film, as shown by the very high resistance of the film at acidic pH.

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