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Characterization and drug-permeation profiles of microporous and dense cellulose acetate membranes: influence of plasticizer and pore forming agent

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Abstract

The use of pore forming agents and plasticizers are efficient ways to obtain membranes for controlled drug permeation through polymeric membranes. The challenge of the present study was to combine these two strategies to obtain cellulose acetate (CA) membranes, where poly(caprolactone triol) (PCL-T) was used as a plasticizer and water, dissolved in a casting solution, was used as a pore forming agent. First, the influence of water on membrane morphology, porosity and the permeation coefficient of a model drug (paracetamol) was analyzed. The influence of different amounts of PCL-T on the permeation coefficient of the CA membranes was then evaluated. Finally, both strategies were combined to obtain porous CA/PCL-T membranes. The membrane microstructure was analyzed using scanning electron microscopy (SEM), the CA crystallinity was determined via differential scanning calorimetry (DSC), and membrane permeability was investigated using paracetamol. The addition of water, a non-solvent, during the membrane casting process was found to be a simple and effective way to change membrane porosity and consequently the drug-permeation profile. When small quantities of non-solvent were used to obtain low porosity membranes, the presence of a plasticizer agent could be used to better modulate drug permeation. Combining the addition of PCL-T with the use of a non-solvent resulted in a series of CA membranes with paracetamol-permeation coefficient values in the range of ca. 10^{-7} to 10^{-5} cm s^{-1}.

Keywords: Cellulose acetate; Poly(caprolactone triol); Plasticizer; Porous membrane; Drug permeation

1. Introduction

Polymeric materials are important for controlling the drug diffusion from delivery systems. Examples of drug delivery systems using membrane controlled diffusion are: membranes for transdermal delivery (Guy, 1996; Kalia and Guy, 2001), coating films formed around a core containing drug material (Narisawa et al., 1994a,b), a polymeric matrix containing dispersed drug (Siegel and Langer, 1990), microspheres, nanospheres, etc.

Factors such as porosity, tortuosity, surface area, thickness and crystallinity play an important role in controlling the rate of drug permeation through a membrane. In general, two important methods are used to modify the characteristics of the membrane

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and consequently the drug permeation: the pore forming agent (Narisawa et al., 1993; Lin and Lu, 2002) and the presence of a plasticizer (Rao and Diwan, 1997; Siepmann et al., 1999; Wang et al., 2002). Porous membranes could be created by: (i) leaching out of polymeric additives (Lin and Lu, 2002); (ii) using a non-solvent to promote polymer phase separation (Narisawa et al., 1993; Stamatialis et al., 2000) or; (iii) dispersing drug particles in the membrane (Tongwen and Binglin, 1998; Bawa et al., 1985; Siegel et al., 1989; Siegel and Langer, 1990).

Plasticizers are generally used to improve the mechanical properties of a polymer matrix. However, previous studies have shown that a plasticizer can also modify the drug permeation through a membrane. This behavior occurs because the plasticizer agent can weaken the intermolecular forces between the polymer chains, increasing the free volume (Kumar and Gupta, 1998). Thus, the drug permeability through the membrane may be affected by the addition of a plasticizer (Rao and Diwan, 1997; Siepmann et al., 1999; Wang et al., 2002). Some examples of plasticizers commonly used include phthalate and phosphate esters, fatty acids, citrate and glycol derivatives (Hyppölä et al., 1996; Phuapradit et al., 1995; Wang et al., 2002; Rao and Diwan, 1997; Tarvainen et al., 2003).

In general, pore forming agents or plasticizers are applied to obtained polymeric systems with controlled drug permeation. However, the combination of both strategies to obtain membranes for drug permeation has not been extensively studied until now (Appel et al., 1992; Kelbert and Bechard, 1992; Verma et al., 2003) and this is the challenge of the present study. Cellulose acetate (CA) was chosen as the membrane forming polymer, poly(caprolactone triol) (PCL-T) as the plasticizer and water as the non-solvent in order to generate pores in the CA/PCL-T membranes.

The present study was conducted in order to analyze the influence of the effects of non-solvent and plasticizer on the membrane microstructure, CA crystallinity and membrane porosity (determined using paracetamol-permeation profiles). First, the influence of different amounts of water in the polymer casting solution on membrane porosity and consequently on the paracetamol-permeation profile was analyzed. Next, a relationship between different PCL-T contents and the drug-permeation coefficient for dense membranes was determined. Finally, these two formulation variables (plasticizer and non-solvent) were combined to obtain a series of membranes that have defined drug-permeation profiles. In addition, equations which describe the relationship between the amount of PCL-T used and the permeation coefficient were obtained.

2. Materials and methods

2.1. Materials

The following chemical products were obtained from commercial suppliers and used as received: Cellulose acetate, with ca. 40% of acetyl content, $M_n = 37\,000\,\mathrm{g\,mol^{-1}}$ (Fluka, New York, USA), poly(caprolactone triol), $M_n = 300\,\mathrm{g\,mol^{-1}}$ (Sigma-Aldrich, St. Louis, USA), acetone (Vetec, Rio de Janeiro, Brazil) and paracetamol (Natural Pharma, São Paulo, Brazil).

2.2. Preparation of the membranes

Membranes were prepared by the solvent casting method. To prepare dense membranes, cellulose acetate and PCL-T were dissolved in acetone in a concentration of 9.65 wt.% of the polymers in different proportions (1.25 g of CA/PCL-T and 11.7 g of acetone). The solutions were shaken at room temperature for 24 h in sealed vials to avoid contact between the acetone solution and ambient humidity. Five milliliters of the polymer solution were poured into a Petri dish (Teflon) and the solvent was evaporated at room temperature in a desiccator under low pressure in order to avoid moisture. Membrane-forming solutions with 0, 10, 20, 30, 40 and 50 wt.% PCL-T were used. After the membrane formation, the residual acetone was removed in a vacuum oven at room temperature for 24 h and the membranes were stored in a desiccator until analyzed.

For preparing porous membranes water was used as a non-solvent agent. The same amounts of CA and PCL-T mentioned above were dissolved in acetone/water solution in sealed vials. Solutions with 1.5, 3.0 and 4.0 wt.% of water (in relation to total mass of the polymer solution) were used. The solvent was evaporated under ambient conditions. To eliminate sol-

vent residues the membranes were dried in the same way as described above.

2.3. Morphological analysis

A scanning electron microscope (Philips XL30) was used to observe the morphology of the surface and cross-section of CA and CA/PCL-T membranes coated with a thin layer of gold. To observe the cross-section, the samples were fractured under liquid nitrogen.

2.4. Determination of the membrane porosity

The apparent volume of the membranes, V_T, was calculated from the thickness and the surface area of the membrane. The total volume of the membrane, V_M, was defined based on the polymer mass of the membranes and the corresponding polymer density. The membrane density (δ) was calculated as described by Narisawa et al. (1993). The average thickness (X), membrane weight (w) and known membrane area (S) of at least nine samples of each composition were measured and the density value was obtained by the relation $\delta = w/SX$. The porosity (ε) of the membranes was then calculated from the apparent and the total volumes according to Eq. (1) (Yamane et al., 1998). At least six samples of each membrane were used to determine the porosity.

$$\varepsilon = \frac{V_T - V_M}{V_T} \quad (1)$$

2.5. Determination of melting enthalpy

In order to evaluate the influence of the amount of PCL-T used on CA crystallinity, and consequently on the drug-permeation profile, the melting enthalpy of CA/PCL-T membranes was determined. Using differential scanning calorimetry (DSC-50, Shimadzu), membrane samples of ca. 5 mg were heated from room temperature to 250 °C at a heating rate of 10 °C min^{-1}. The enthalpy was determined from the area of the CA melting peak at ca. 230 °C.

2.6. Determination of the weight loss of the CA/PCL-T membrane in buffer solution

Approximately 0.15 g of each dense membrane was first dried at room temperature in a vacuum oven until constant weight was achieved. The membranes were then maintained in 40 ml of phosphate buffer solution pH 7.4 at 37.0 ± 0.5 °C for 12 h. The membranes were dried again in a vacuum oven until constant weight was achieved. The weight loss was determined by the difference between the membrane weight before and after immersion in buffer solutions. Each experiment was repeated at least three times for the dense membranes (prepared in the absence of water).

2.7. Swelling of the dense cellulose acetate membrane

Approximately 0.1 g of dense CA membrane was first dried at room temperature in a vacuum oven until constant weight. The membrane was then maintained in distilled water for 24 h under stirring. The membrane was quickly dried with paper to remove excess water on the membrane surface and weighed to determine the amount of absorbed water. To be sure that the CA membrane did not lose weight during this procedure, the membrane was dried again in a vacuum oven to eliminate the absorbed water and the weight observed was compared to the initial weight.

2.8. Permeation of paracetamol through the membranes

Permeation experiments were performed using a horizontal side-by-side diffusion cell at 37.0 ± 0.5 °C. The membranes, previously equilibrated with phosphate buffer pH 7.4 for 1 h, were clamped between two compartments of equal volumes (7 ml, diffusion area 6.8 cm^2). The average membrane thickness was measured with a micrometer and the value was 70 ± 5 μm. The saturated paracetamol solution at pH 7.4 and the aqueous buffer solution were placed in the donor and receptor cell compartments, respectively. The cell was shaken horizontally at the rate of 120 rpm to minimize the boundary effect. The total volume of the receptor solution was removed after pre-determined time intervals and replaced with new buffer solution at 37 °C. The concentrations of paracetamol were determined by UV-Vis spectrometry at 244 nm (Perkin-Elmer, UV-Vis Lambda 11/Bio). All experiments were performed at least in triplicate.

2.9. Analysis of the data

Applying Fick's first law of diffusion under sink conditions, the permeation rate of the drug was defined by Eq. (2) (Martin, 1993), where Q (g cm^{-2}) is the amount of diffused drug at time t (s) per unit surface area; C_d (g cm^{-3}) is the concentration of drug in the donor cell and P (cm s^{-1}) is the permeation coefficient.

$$\frac{Q}{t} = PC_d \quad (2)$$

3. Results and discussion

3.1. The influence of water on the properties of cellulose acetate membranes

First, the CA membranes were prepared by dissolving the polymer in acetone in the vials covered only with a glass plate. After 6–7 h the solution was cast onto a Petri dish (Teflon). With this procedure, a poor membrane reproducibility was obtained. The ambient humidity influenced the membrane appearance. During polymer dissolution in acetone, small amounts of water vapor can dissolve in the casting solution. Since the evaporation rate of acetone during casting was faster than that of water, the concentration of non-solvent increased gradually and CA phase separation took place (Laity et al., 2001; Vaessen et al., 2002).

To avoid the presence of dissolved water in acetone, the polymer casting solutions were prepared in the sealed vials and the acetone was allowed to evaporate under low pressure. Dense membranes were obtained with this procedure.

In order to better analyze the effect of water on the CA membrane porosity and on the paracetamol-permeation coefficient, CA membranes were prepared with different water contents in the casting solutions (1.5, 3.0 and 4.0 wt.%). With this procedure, porous membranes were produced.

In Fig. 1 the effect of water content on membrane porosity and on paracetamol-permeation coefficient (P) is shown. An apparent linear increase in porosity with water concentration in the casting solutions was observed. As mentioned before, water acts as a non-solvent and a process including coacervation and gelation takes place during drying of the cast films, forming the porous membranes. Similar behavior was observed by Narisawa et al. (1993, 1994a,b) with ethyl cellulose membranes prepared with a mixture of ethanol and water.

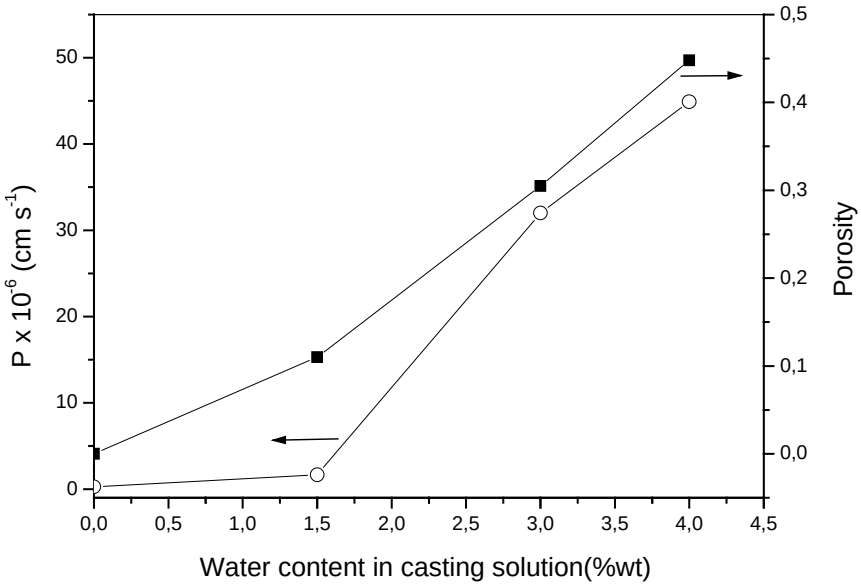

Fig. 1. Variation in the permeation coefficent of paracetamol (○) and the porosity of CA membranes (■) prepared with different water contents in the casting solution. The error bars have the same size as or are smaller than the symbols.

Fig. 1 shows also that the permeation coefficients of the membranes prepared without water (dense) and with 1.5 wt.% of water were quite low, and a significant increase in *P*-values was observed only when 3.0 and 4.0 wt.% of water were used. This could be explained by the percolation theory proposed by Siegel and Langer (1990). Based on this theory, the diffusion of a drug molecule through a membrane could be hindered due a mechanism called random pore topology which contributes a certain tortuosity. In addition, these pore structures could form many blind alleys or "dead-ends." These characteristics hinder the permeation of a molecule through a porous membrane due to the absence of interconnecting pathways. When the porosity is increased above the percolation threshold, the dead-end pores fraction starts to reduce and interconnecting pores are formed, resulting in an increase in permeability.

This argument could be applied to the present data. The permeation coefficient of the membrane prepared with 1.5 wt.% of water did not increase in the same way as that of the other membranes, despite the linear increase in porosity. Based on the observed data, it is possible to suggest that the membrane pores prepared with 1.5 wt.% of water are isolated, and do not contribute to paracetamol permeation. On the other hand, the CA membranes prepared with 3.0 and 4.0 wt.% of water may possess interconnecting pores, resulting in higher permeation coefficients.

Similar behavior was observed for ethyl cellulose membranes prepared in the presence of ethanol/water casting solution and poly(ε-caprolactone) membranes prepared with PEG (Narisawa et al., 1993; Lin and Lu, 2002).

Fig. 2 presents the SEM micrographs of the surfaces (Fig. 2A–D) and cross-sections (Fig. 2E–H) of CA membranes prepared with different amounts of water in the casting solutions. The membranes prepared in the absence of water showed a smooth surface, without pores, as observed in the cross-sections (Fig. 2A and E, respectively). This occurred because only acetone was used and during membrane casting the polymer molecules were immobilized in a glassy state and no pores were formed.

With the addition of 1.5 wt.% of water in the casting solution the membrane surface became less smooth (Fig. 2B) and it was possible to observe pores in the cross-section (Fig. 2F), which were formed due to the presence of water. These pores have no connections with the membrane surface, consistent with the low paracetamol permeation presented in Fig. 1. However, with higher concentrations of water (3 and 4 wt.%) a significant increase in porosity was observed on the membrane surface (Fig. 2C and D). At the same time, there were larger pores observed in the cross-sections (Fig. 2G and H), which could lead to the increase in paracetamol permeation previously discussed.

3.2. The influence of PCL-T on the properties of CA membranes

Fig. 3 shows the profiles of paracetamol permeation through CA membranes plasticized with different amounts of PCL-T. There is a significant influence of PCL-T content on the permeation of paracetamol which is explained by the free volume theory of diffusion. The presence of plasticizer reduced the polymer–polymer interactions (Kumar and Gupta, 1998), increasing the mobility of the polymer chains and, consequently, the paracetamol permeation. All the permeation profiles exhibited straight lines, indicating that the paracetamol permeation obeyed Fick's law.

Table 1 summarizes the melting enthalpy (ΔH_m), loss of weight of the dense CA/PCL-T membranes after immersion in buffer solution and the paracetamol-permeation coefficient (*P*) of the dense membranes. The *P*-values of the CA/PCL-T membranes prepared with 1.5 wt.% of water are also presented in Table 1and discussed later in Section 3.3.

The permeation coefficient of paracetamol increased with higher amounts of PCL-T in the membrane up to 40 wt.%. Interesting, there is only a small variation between the values of P for the membranes with 40 and 50 wt.% of plasticizer. This behavior is apparently related to the phase separation between CA and PCL-T in this composition.

As mentioned above, PCL-T decreases the attractive forces between the CA molecules, increasing the chain mobility. Through the analysis of the melting enthalpy of CA/PCL-T membranes, it is possible to conclude that PCL-T also reduces the crystallinity of CA. It is well known that the crystalline region in a polymer matrix hinders solute permeation due to the low segmental mobility of the polymer (Mulder, 1997). With the introduction of 10 wt.% PCL-T, the melting enthalpy decreases, suggesting a significant

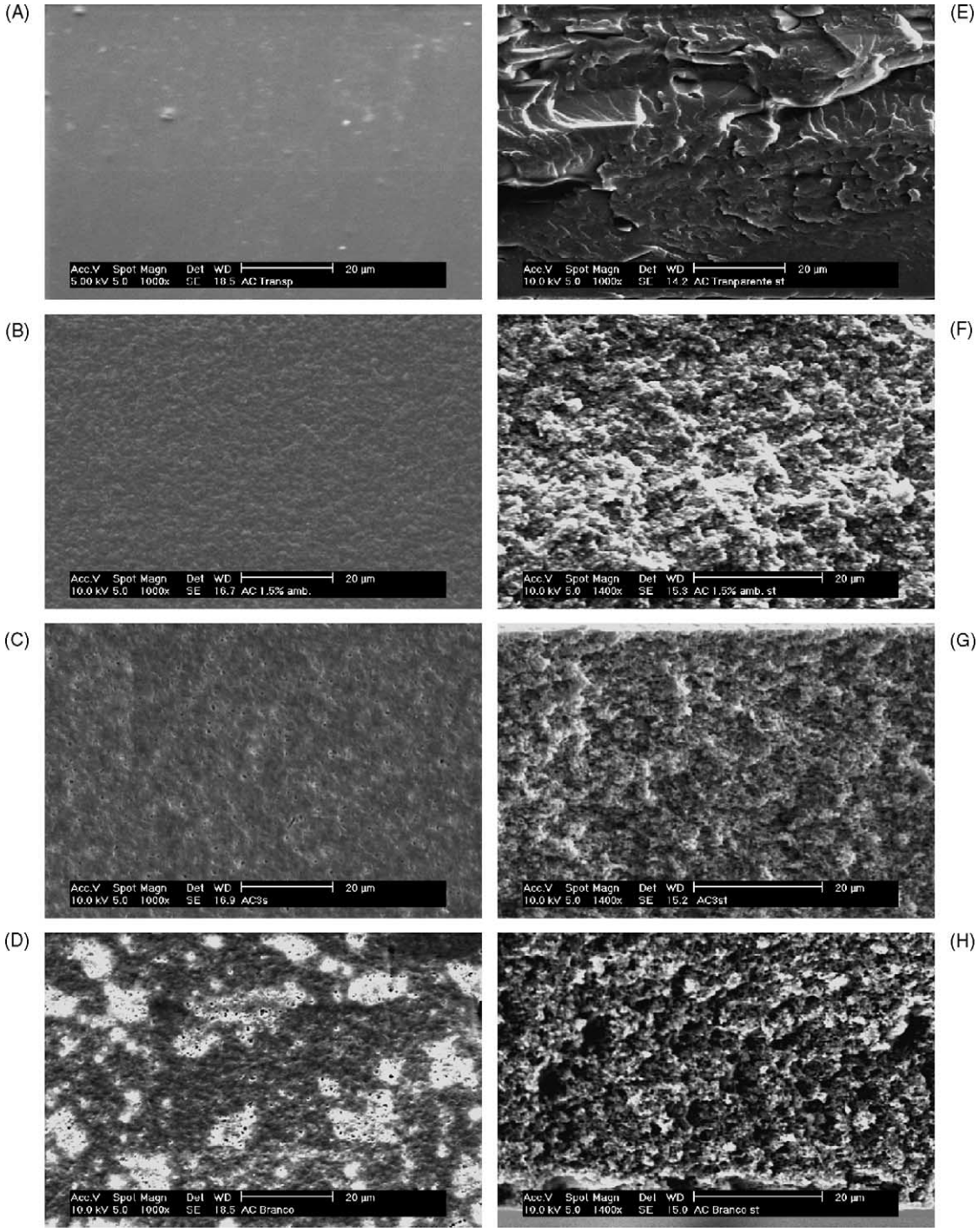

Fig. 2. SEM micrographs of the surfaces (A–D) and cross-sections (E–H) of CA membranes prepared with 0 wt.% (A, E), 1.5 wt.% (B, F), 3.0 wt.% (C, G) and 4.0 wt.% (D, H) of water in the casting solution.

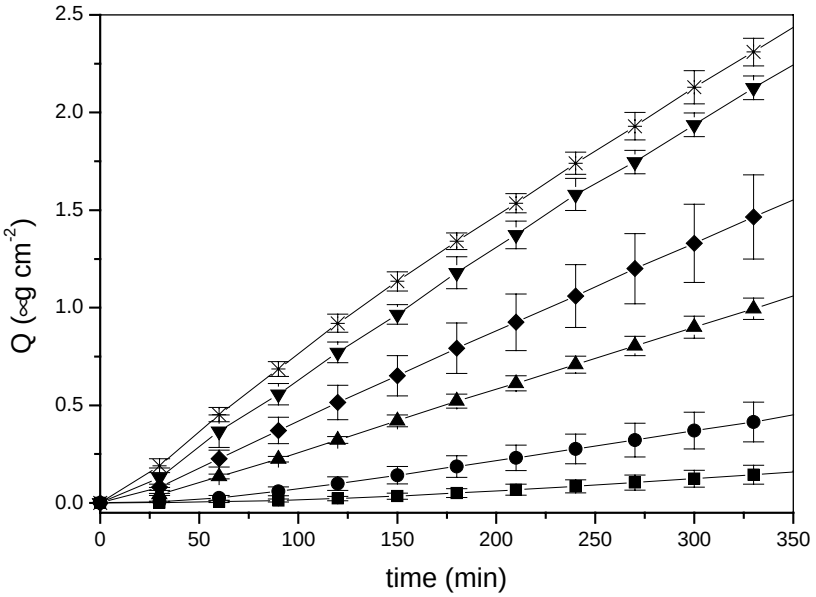

Fig. 3. Profiles of paracetamol permeation through CA/PCL-T membranes prepared with different amounts of PCL-T: (■) 0 wt.%; (●) 10 wt.%; (▲) 20 wt.%; (◆) 30 wt.%; (▼) 40 wt.% and (✳) 50 wt.%. The error bars represent the standard deviation.

decrease crystallinity. However, the permeation coefficient did not increase proportionally with the decrease in melting enthalpy. This behavior suggests that the CA crystallinity did not significantly affect the paracetamol permeation through the membranes. The CA membrane without PCL-T had a low degree of crystallinity (ca. 30%), suggesting that most of the polymer molecules are in the amorphous state. The decrease in crystallinity of CA resulting from the addition of PCL-T, does not therefore entirely explain the observed increase in the permeation coefficient of paracetamol.

The free volume theory of diffusion postulates that the diffusion of the molecule occurs by localized activated jumps from one pre-existing cavity to another (Fan and Singh, 1989). When the diffusion species is larger than a pre-existing cavity, a certain number of monomer segments must first be rearranged to allow the molecules to diffuse. The mobility of the polymer chains are therefore an important factor and could

Table 1
Results for the analysis of CA/PCL-T membranes prepared in the absence of water (dense) and with 1.5 wt.% water

CA/PCL-T composition	Dense membrane			Porous membrane[a] (1.5 wt.% water)
	Permeation coefficient P (±S.D.) ($\times 10^{-6}$ cm s^{-1})	ΔH_m[b] (±S.D.) (cal g^{-1})	Weight loss[c] (±S.D.) (%)	Permeation coefficient P (±S.D.) ($\times 10^{-6}$ cm s^{-1})
100/0	0.27 (±0.03)	1.94 (±0.44)	0.7 (±0.3)	1.66 (±0.06)
90/10	1.00 (±0.05)	0.56 (±0.21)	5.2 (±0.6)	5.77 (±0.04)
80/20	2.58 (±0.01)	0.36 (±0.12)	14.2 (±0.4)	14.70 (±0.01)
70/30	3.86 (±0.02)	0.24 (±0.12)	21.8 (±0.8)	36.10 (±0.08)
60/40	5.32 (±0.05)	0.28 (±0.19)	30.7 (±0.6)	56.50 (±0.21)
50/50	5.85 (±0.10)	0.29 (±0.05)	37.5 (±1.0)	–

[a] Membrane prepared with 1.5 wt.% water in the casting solution.
[b] CA melting enthalpy obtained through DSC measurements.
[c] After 12 h in phosphate buffer (pH 7.4) at 37 °C.

be modified by the presence of a plasticizer agent (Siepmann et al., 1999).

Table 1 suggests that PCL-T content is an important factor which influences the paracetamol-permeation coefficient. However, it seems that the CA/PCL-T membrane weight loss, associated with the partial dissolution of PCL-T during the permeation experiments has some relationship with the increase in *P*-values. The SEM analysis of the membranes after the permeation experiments (not shown) suggested the presence of pores and channels in the membranes.

Even in the pure CA membrane without PCL-T, small pores were observed on the SEM micrographs (not shown) after the permeation experiments which could be associated with the swelling of the matrix in aqueous medium. The experimental determination of the CA swelling indicates that 13.4 wt.% water was absorbed by the CA membrane after immersion for 24 h in water.

Based on these observations, it is possible to conclude that the amount of PCL-T is a decisive factor in modulating the paracetamol permeation through the CA membranes due to the association of two aspects: (i) the decrease in polymer–polymer interactions with the addition of PCL-T and (ii) the formation of small pores and channels generated by PCL-T dissolution. In addition, the CA swelling process during the permeation experiments could also be an important factor affecting the paracetamol-permeation profile.

3.3. The influence of water and PCL-T on the properties of CA membranes

In this section, two variables are combined: the presence of water as a pore forming agent and the presence of PCL-T as a plasticizer agent.

Three compositions of water in the CA/PCL-T casting solution were studied: 1.5, 3.0 and 4.0 wt.%. In Fig. 4A and B the profiles for the paracetamol permeation through the series of membranes prepared with 1.5 and 4 wt.% of water, respectively, are shown. The profiles for the paracetamol permeation through the CA/PCL-T membranes prepared with 3 wt.% of water (data not shown) were very similar to the membranes prepared with 4 wt.% of water.

Some general features can be recognized from Fig. 4. A lesser amount of drug permeates through the series of CA/PCL-T membranes prepared with 1.5 wt.% of water (CA/PCL-T/1.5w) when compared with the membranes prepared with 4 wt.% of water (CA/PCL-T/4w). The amount of PCL-T exerted greater influence on the permeation profile in the case of the CA/PCL-T/1.5w membranes. The amount of permeated paracetamol increased with the amount of plasticizer. However, this behavior was not observed in the CA/PCL-T/4w membranes.

In order to evaluate the influence of water content on the morphology of the CA/PCL-T membranes, in Fig. 5 the SEM micrographs of the surfaces and cross-section of CA/PCL-T membranes prepared with 1.5 and 4.0 wt.% of water (Fig. 5A–C and D–F, respectively) are compared.

In Fig. 5A and B, there is no evidence of pores on the surface of the CA/PCL-T/1.5w membranes. In contrast, the CA/PCL-T/4w membranes had many pores on the surface (Fig. 5D and E) which facilitate the percolation of higher amounts of paracetamol, in agreement with the paracetamol-permeation profiles discussed above (Fig. 4). The cross-section of the CA/PCL-T 90/10 membranes shows that the membrane prepared with 4 wt.% of (Fig. 5F) water is more porous than that prepared with 1.5 wt.% of water (Fig. 5C).

The amount of water used to prepare the CA/PCL-T/1.5w membranes was not enough to generate pores or channels that are connected with the membrane surfaces. This observation and the argument that paracetamol can percolate through the inner pores of the membranes, led to the hypothesis that in the CA/PCL-T/1.5w membranes the drug permeates partially by diffusion through the dense polymer matrix and partially by percolation through the pore network. This hypothesis is sustained by two observations: (i) the amount of PCL-T influenced the drug permeation in the CA/PCL-T/1.5w membranes and; (ii) more drug is permeated through the CA/PCL-T/1.5w membranes (Fig. 4A) when compared with the equivalent dense membranes prepared in the absence of water (Fig. 3).

Based on this hypothesis, we suggest that in the CA/PCL-T/4w membranes the percolation through the inner pores and interconnecting channels is a decisive factor in paracetamol permeation. In this system the amount of PCL-T has only a small effect on paracetamol permeation, as seen in the permeation profile presented in Fig. 4B.

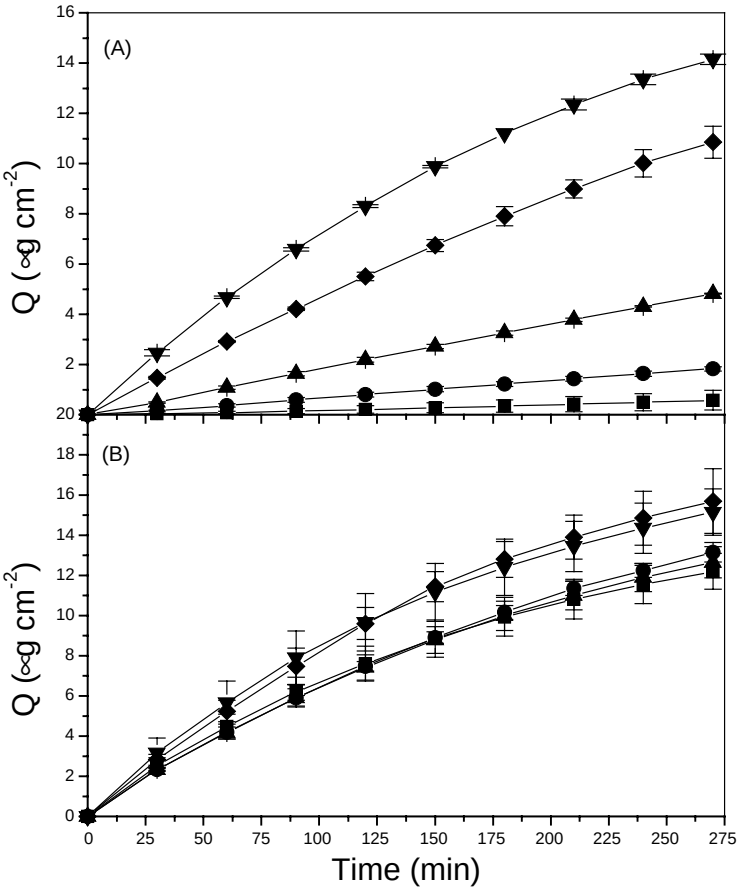

Fig. 4. Permeation profiles for paracetamol permeation through CA/PCL-T membranes prepared with different amounts of PCL-T: (■) 0 wt.%; (●) 10 wt.%; (▲) 20 wt.%; (◆) 30 wt.%; (▼) 40 wt.% in the presence of (A) 1.5 wt.% of water and (B) 4.0 wt.% of water in the polymer casting solution. The error bars represent the standard deviation.

Due to the high permeability of the CA/PCL-T/4w membranes, the sink conditions were not obeyed after 90 min of the permeation experiment and the permeation coefficient could not be determined.

In Table 1 the paracetamol-permeation coefficients for the CA/PCL-T/1.5w membranes are shown. When the *P*-values of the CA/PCL-T/1.5w membranes are compared with those of dense membranes (Table 1), it is possible to observe the strong influence of pore structure generated by the water molecules during membrane casting. In addition, both series of membranes presented a positive relationship between PCL-T amount and *P*-values.

The above observations suggest that the application of a non-solvent during the membrane casting process is a simple and effective way to change membrane porosity and consequently the degree of drug permeation. When small quantities of non-solvent are used to obtain low porosity, the presence of a plasticizer agent can be used to better modulate drug permeation. Combining the amount of PCL-T and the membrane porosity it was possible to obtain CA membranes with *P*-values in the range of ca. 10^{-7} to 10^{-5} cm s^{-1}.

3.4. Quantitative relationship between the permeation coefficient values and amount of PCL-T in the CA membranes

To develop a new controlled drug release system containing a plasticizer agent, it is very important to

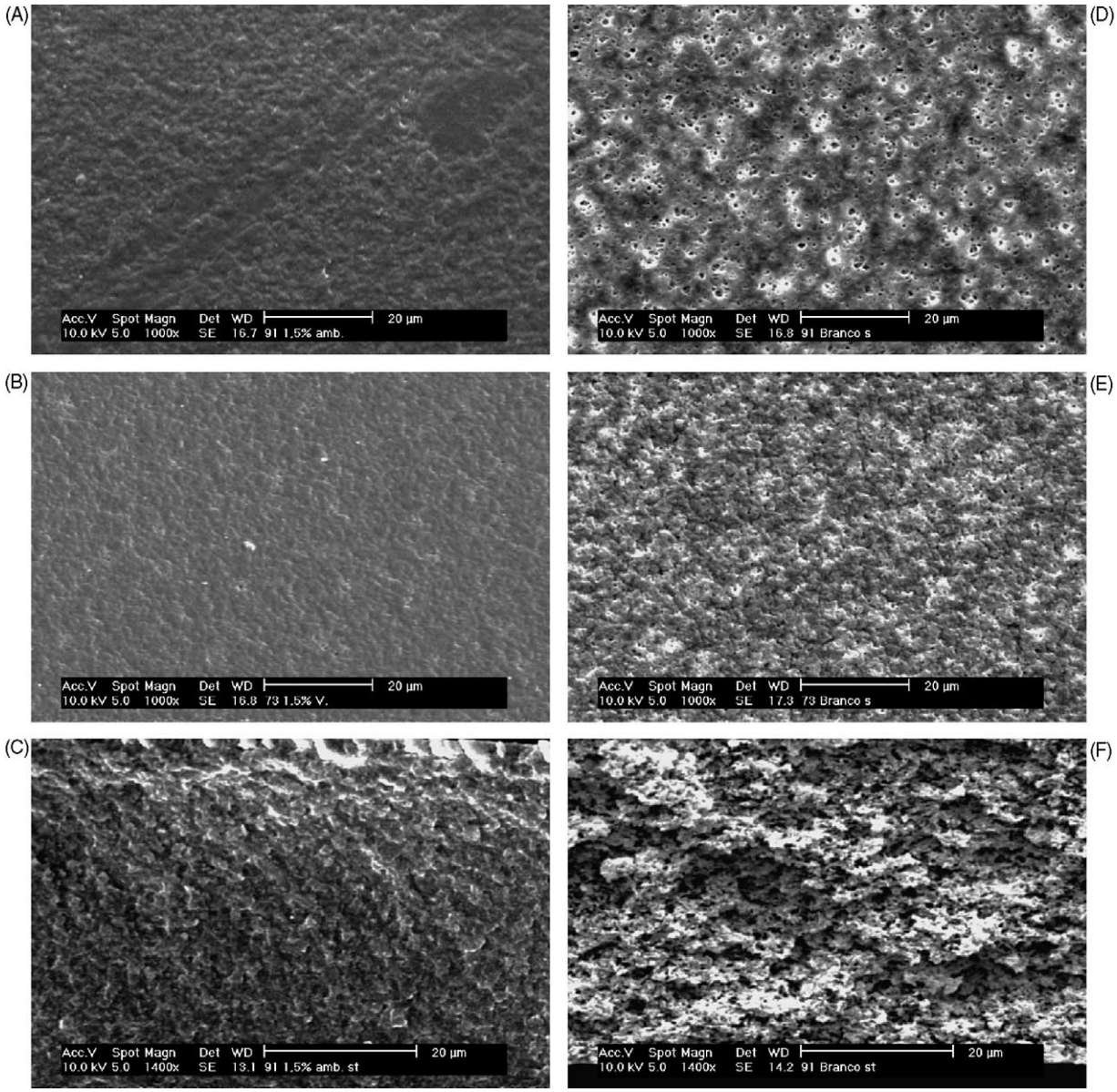

Fig. 5. SEM micrographs of CA/PCL-T membranes: surface—90/10 (A, D); surface—70/30 (B, E) and cross-section—90/10 (C, F). The membranes were prepared in the presence of 1.5 wt.% of water (A, B, C) and 4.0 wt.% of water (D, E, F).

know the relationship between the amount of plasticizer used and the drug-permeation coefficient. This relationship can be determined in a series of experiments, as described above, or can be predicted using a quantitative relationship between permeation coefficient (P) and amount of plasticizer. Siepmann et al. (1999) obtained exponential equations which described the relationship between the plasticizer level and the diffusion coefficient of theophylline through ethyl cellulose and Eudragit® RS-100 films with different plasticizer agents. In a similar way, the relationship between the paracetamol-permeation coefficient and the amount of PCL-T in the CA membranes was determined in this study.

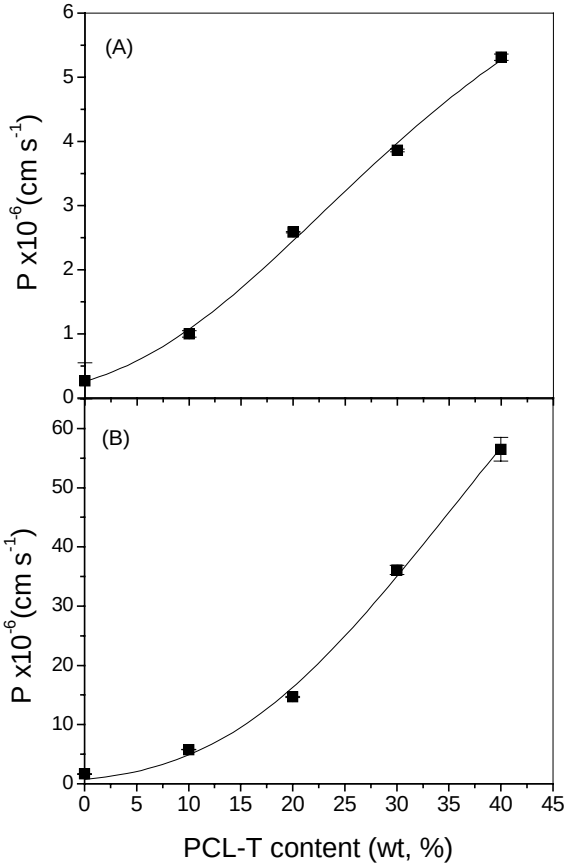

Fig. 6. Influence of the plasticizer content on the permeation coefficient of paracetamol for CA/PCL-T membranes prepared in the absence of water (A) and 1.5 wt.% of water in casting solution (B). Symbols and solid lines represent experimental and fitted data ($R = 0.999$), respectively.

Fig. 6A and B show the variation in the permeation coefficient (P) of paracetamol through the CA membranes plasticized with different amounts of PCL-T. The solid lines represent the respective fit obtained with the following equations:

$$P = 7.83 \exp^{-a},$$

$$a = \exp(-0.0537(\text{PCL-T (wt.\%)} - 22.7))$$

for dense CA/PCL-T membranes;

$$P = 131.1 \exp^{-b},$$

$$b = \exp(-0.0456(\text{PCL-T (wt.\%)} - 36.1))$$

for CA/PCL-T/1.5w membranes.

With the above quantitative relationships it is not necessary to conduct permeation experiments for all the amounts of plasticizer, because the respective amount of PCL-T can be theoretically calculated in order to obtain a desired permeation coefficient.

4. Conclusions

This study demonstrated the possibility to obtain CA membranes for drug controlled permeation combining two strategies: water as a pore forming agent and PCL-T as a plasticizer. It was observed that the membranes with interconnecting pores or dead-end pores could be obtained by controlling the amount of water in the casting solution, which consequently affected the drug-permeation profile of the membranes. The drug permeation increased with the amount of plasticizer in the dense membranes.

The application of a non-solvent during the membrane casting process is a simple and effective way to change the membrane porosity and consequently the drug permeation. When small quantities of non-solvent are used to obtain low porosity, the presence of a plasticizer agent can be used to better modulate drug permeation. Combining the amount of PCL-T and the membrane porosity it was possible to obtain CA membranes with *P*-values in the range of ca. 10^{-7} to 10^{-5} cm s^{-1}.

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