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Research paper

Poly(ethylene-co-methyl acrylate) membranes as rate-controlling barriers for drug delivery systems: characterization, mechanical properties and permeability

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Abstract

Poly(ethylene-co-methyl acrylate) (EMA) membranes with different amounts of methyl acrylate (MA) content were studied in terms of the thermal and mechanical properties, swelling and drug permeation. The increase in MA content in the copolymer significantly increased the percentage of elongation and decreased the tensile strength and modulus of elasticity of the membranes. The degree of swelling of the EMA membranes increased with the ethanol composition and MA content. The contact angle of a sessile drop (10 μL of ethanol/water solution) decreased with an increase in the ethanol fraction suggesting that the membrane wettibility increased with the ethanol content. The flux of diltiazem hydrochloride increased from 0.012 to 0.018 mg cm^{-2} h^{-1} with an increase in the MA content from 16.5 to 29.0%. By increasing the ethanol fraction from 0.4 to 1.0, the flux of diltiazem hydrochloride into the membranes with 29.0% MA, increased from 2.56 ($\pm$0.09)$\times 10^{-3}$ to 18.38 ($\pm$0.62)$\times 10^{-3}$ mg cm^{-2} h^{-1}. The permeability coefficient increased from 5.85×10^{-6} to 3.53×10^{-4} cm h^{-1} with an increase in the ethanol fraction. The flux can also be correlated with the drug solubility in the membrane and ethanol. For example, the solubilities of diltiazem hydrochloride, paracetamol and ibuprofen were 0.64, 6.68 and 504.48 mg cm^{-3} in the membrane, respectively. Under the same conditions, the flux for the above mentioned drugs was 0.08 ($\pm$0.01), 0.53 ($\pm$0.01) and 45.11 ($\pm$2.00) mg cm^{-2} h^{-1}.

Keywords: Poly(ethylene-co-methyl acrylate); Membranes; Diltiazem hydrochloride; Ibuprofen; Paracetamol; Permeability coefficient

1. Introduction

Polymeric membranes have been used to control the drug release rate in, for example, transdermal delivery systems [1–8]. Commonly, a reservoir-type transdermal system is used in which the delivery of solvent and drug is controlled by the membrane [9,10]. Polystyrene, polypropylene, cellulose and acrylate derivatives, and poly(ethylene-co-vinyl-acetate) are some examples of polymers used to obtain membranes [3,4,11,12]. The release rate can be controlled by changing the polymeric material [3] and by factors such as membrane composition [13], cross-linking [5], plasticizer agents [14–16], film porosity [14,17–19] and solvent composition [10,20]. One of the most frequently used membranes is the ethylene–vinyl acetate (EVA) copolymer [21,22]. Properties such as easy processability through heating, flexibility and the low cost, are some important aspects of this material [22]. On the other hand, a similar copolymer, the ethylene-co-methyl acrylate (EMA), which is an elastomer composed of ethylene and methyl acrylate units, has not been extensively used as a rate-controlling barrier membrane for drug release. In the EMA copolymer, ethylene and methyl acrylate are crystalline and amorphous units, respectively [21]. Considering that the release of the solvent and the drug occurred preferentially in the amorphous phase, the release rate can be controlled by varying the methyl acrylate content in the copolymer.

In this study, membranes of poly(ethylene-co-methyl acrylate) (EMA) with different methyl acrylate (MA)

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content, were prepared and analyzed in terms of mechanical properties and drug permeability. Firstly, parameters such as, tensile strength, elongation, elasticity modulus and swelling in ethanol/water solution, were evaluated. The membrane was then analyzed in terms of the permeability to paracetamol, ibuprofen and diltiazem hydrochloride, which were chosen as 'model drugs' in this study. Specifically, the following were evaluated: (i) the effect of acrylate content on the permeability of diltiazem hydrochloride, and (ii) the permeability of paracetamol, ibuprofen and diltiazem hydrochloride in EMA membranes with 29.0% MA content. The above mentioned drugs were used as 'models' in the present study due to their different solubilities in ethanol which may affect their partitioning in the membrane and, in consequence, their permeation. Although these drugs have not extensively used in transdermal delivery systems, some related applications have been discussed in the literature [12,14,15,23–32]. Considering that EMA is a hydrophobic membrane, the principal aim was to evaluate the potential of controlling the drug release in ethanol/water solutions. Transdermal drug delivery have been evaluated in several polymeric membranes using different solvent, such as, ethanol, acetone and methanol [15,20,23,33,34]. Ethanol has been specifically recommended as a solvent in transdermal therapeutic systems such as estradiol [35] and nitroglycerin [9].

2. Experimental

2.1. Materials

Poly(ethylene-co-methyl acrylate) (EMA) copolymers with 16.5, 21.5 and 29.0% methyl acrylate (MA) contents were obtained from Aldrich Chem. Co. (St Louis, USA). Ethanol (99.5%) and chloroform were purchased from Vetec S.A. (Rio de Janeiro, Brazil). Both polymers, ethanol and chloroform were used without further purification. Pharmaceutical grade paracetamol, ibuprofen and diltiazem hydrochloride were obtained from Galena S.A. (São Paulo, Brazil) and also used without further purification.

2.2. Preparation of EMA copolymer membranes

Amounts of 0.1–0.2 g of EMA copolymer beads with 16.5, 21.5 and 29.0% MA were dissolved in 10 mL of chloroform. The polymer solutions were poured onto a teflon-coated plate (petri dish) for the solvent evaporation at room temperature. The membrane was removed from the plate, dried for 24 h at room temperature and stored in a desiccator under vacuum until analysis. The average thickness values of the membranes were determined after measurements at different points in the film using a micrometer (Mytotoyo, Japan).

2.3. Tensile strength and percentage of elongation

Ten centimeter length membrane samples with thickness in the range 0.05–0.08 mm were cut from the as-cast films. Tensile tests were performed at 25 °C using an EMIC DL 2000 analyzer (EMIC, Brazil), according to the ASTM D882-95a for thin films. The membranes were kept under vacuum conditions before analysis. Modulus of elasticity, tensile strength at rupture and elongation were calculated from the stress–strain curves considering at least six analyses of each sample.

2.4. Differential scanning calorimetry (DSC)

DSC thermograms were obtained on a differential scanning calorimeter (DSC 50, Shimadzu, Japan) by heating the samples from −100 to 200 °C at a heating rate of 10 °C min^{-1}. For all measurements, the samples were heated at 120 °C and then slowly cooled (to eliminate the thermal history), after which a second scan was performed and used to determine the transition values. The average sample size was 4 mg and the nitrogen flow-rate was 50 cm^3 min^{-1}. Indium (156.6 °C) and zinc (419.5 °C) standards were used for calibration.

2.5. Contact angle measurements

The surface wettibility of the membranes was evaluated by contact angle measurements [36–38]. The sessile drop experiment [38,39] consists of placing a known volume of a probe liquid (in this study, 10 μL of ethanol/water solution were employed) on the polymer surface. The drop spreads until it attains an equilibrium state, in which a three-phase system is formed [39]. Under these conditions, a finite contact angle (static angle, θ_s) formed by the static drop with the surface can be determined. With respect to the solid phase, the liquid may be either wetting ($\theta_s = 0°$), non-wetting ($\theta_s = 180°$) or partially wetting ($0 < \theta_s < 180°$) [37].

Three measurements were made on each sample and the data are presented as a mean with a standard deviation. Image data were captured with a video micrometer (Javelin model JV 600 T, Syosset, NY, USA) and Computer Eyes 5.12 software. Image analysis was performed with the Image Tool 1.28 software.

2.6. Determination of drug solubility in ethanol

An excess of paracetamol, ibuprofen and diltiazem hydrochloride was equilibrated with 10 mL of ethanol or ethanol/water solution at 37 °C (constant stirring) for 24 h. The saturated drug solution was then filtered through a membrane filter (0.45 μm). The concentration was determined after proper dilution by UV–vis spectrophotometry (HITACHI 2010, Japan) at wave numbers of 244 nm for paracetamol and 265 nm for diltiazem hydrochloride and ibuprofen.

2.7. Drug solubility in the polymer

One centimeter squared membranes were poured into saturated drug solutions at 37 °C under constant stirring. After 24 h, they were rinsed with ethanol, wiped dry with tissue paper and totally dissolved in chloroform (15 mL). The drug concentrations in the polymer were determined using a UV–vis spectrophotometer (HITACHI 2010, Japan) at wave numbers of 244 nm for paracetamol and 265 nm for diltiazem hydrochloride and ibuprofen.

2.8. Swelling measurements

Membrane swelling was measured as a function of ethanol/water composition. The weight of a dry sample (2 cm^2 and thickness of 0.6 mm) (W_d) was first determined. After equilibrating with ethanol or the ethanol/water solution, the fully swollen sample was wiped dry with tissue paper and weighed. The swelling was determined using Eq. (1)

$$\%\text{Swelling} = \frac{(W_s - W_o)}{W_o} \times 100 \quad (1)$$

where W_s and W_o are the weight of the swollen and dry film, respectively.

2.9. Membrane permeation

Permeation experiments were performed using a horizontal side-by-side diffusion cell at 37.0±0.5 °C. The membranes were clamped between two compartments (donor and receptor) of equal volumes (6 mL, diffusion area 2.25 cm^2). The donor side contained the ethanol/water solution saturated with the drug (ethanol varying from 0 to 100%) and the receptor side only the ethanol/water solution. The cell was shaken horizontally at a rate of 120 rpm to minimize the boundary effect. Every 60 min, the total volume of the receptor solution was removed from the cell and replaced with fresh solution. The drug concentration of the receptor side was determined by spectrophotometry as described above. All experiments were performed at least in triplicate.

The cumulative amount of drug which permeated through the membrane at a unit surface area (Q) can be expressed mathematically by Eq. (2), where P is the coefficient of permeability, C_D and C_R are the drug concentrations in the donor (D) and receptor (R)

$$Q = P(C_D - C_R)t \quad (2)$$

solutions, respectively, and t is time. When the drug concentration in the donor solution (C_D) is maintained at a level greater than the equilibrium solubility ($C_D > C_E$) and the drug concentration in the receptor solution (C_R) is maintained under sink conditions ($C_R \ll C_E$), Eq. (2) can be simplified to:

$$Q = PC_E t \quad (3)$$

The permeability of the membrane (P) is determined from the slope of the linear region of the plot Q versus t (permeation profile) [40,41].

2.10. Statistical analysis

Statistical evaluations were performed by one-way analysis of variance (ANOVA) using a statistical package OriginPro 7.0. In all cases the significance level was taken as $P < 0.01$.

3. Results and discussion

3.1. Characterization of poly(ethylene-co-methyl acrylate) membranes

Poly(ethylene-co-methyl acrylate) (EMA) can be classified as a rubbery-crystalline polymer at room temperature. In the EMA structure, ethylene is the nonpolar and highly crystalline unit while methyl acrylate (MA) is the polar and amorphous unit. The transition temperatures of the membranes (melting and glass transitions) are shown in Fig. 1. The glass transition temperatures, which are associated with the EMA amorphous phase [42], were −29.8, −31.0 and −35.6 °C for the copolymers with 16.5, 21.5 and 29.0% MA, respectively. Despite the slight change in the T_g, the melting temperature decreased from 90.9 (16.5% MA) to 63.3 °C (29.0% MA). From the literature it is known that polyethylene crystallizes with the chains in the fully extended planar zig-zag conformation [43]. The increase in MA groups which are randomly distributed along the copolymer chain, can reduce the inter-chain interaction affecting the crystallization of the chains, changing in consequence, the melting temperature. At the same time,

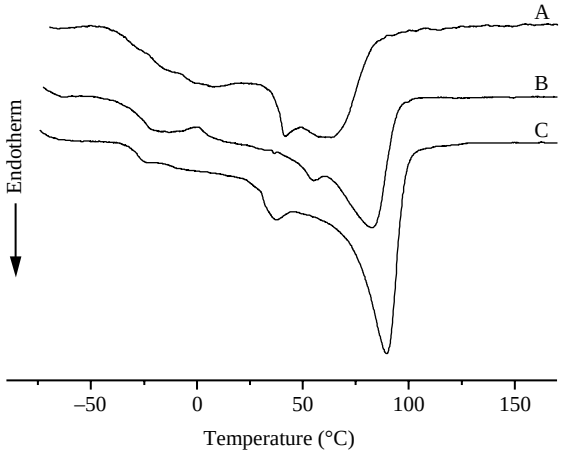

Fig. 1. DSC curves for EMA membranes with: (A) 29.0; (B) 21.5 and (C) 16.5% MA content.

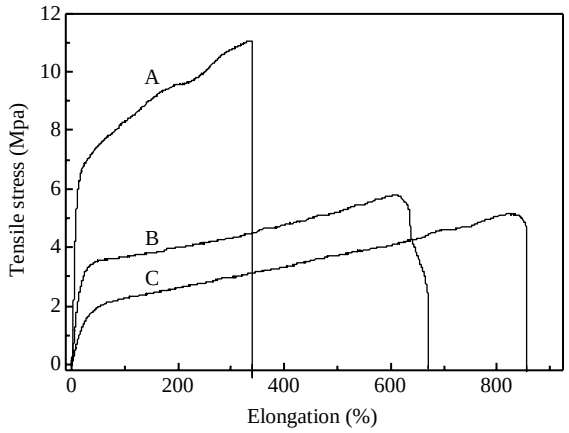

Fig. 2. Tensile stress versus elongation for EMA films with: (A) 16.5; (B) 21.5 and (C) 29.9% MA contents.

changes in the structural order can affect the mechanical and permeation properties of the membranes.

3.2. Mechanical properties

The final use of polymeric membranes strongly depends on their mechanical properties at room temperature. For example, for applications in transdermal therapeutic systems, polymeric membranes with high elasticity are generally needed. The tensile testing gives an indication of the strength and elasticity of the membrane, reflected by parameters such as tensile strength, modulus of elasticity and elongation at break. The curves corresponding to tensile stress versus elongation for EMA membranes with different MA contents, are shown in Fig. 2 and the associated mechanical parameters in Table 1.

The behaviour of the stress–strain curves for EMA membranes was consistent with elastomeric polymers. Significant differences were observed in all the parameters evaluated for the polymer films (Table 1). The increase in MA content in the copolymer membranes significantly reduced ($P<0.01$) the tensile strength and modulus of elasticity but significantly increased ($P<0.01$) the elongation, indicating that the copolymer membranes with 29.0% MA content were weaker, more elastic, more flexible and softer. The elongation, for example, increased 120% when the MA content in the copolymer changed from 16.5 to 29.0%. A similar trend was observed for the decreased in the tensile strength. Therefore, the modulus of elasticity showed a significant decreased for the copolymer membranes with the same variation in the MA content. These results showed that the elasticity of EMA strongly depends on the amorphous phase fraction in the copolymer.

Table 1
Mechanical parameters of EMA membranes composed of different MA contents

Copolymer (EMA)	Elongation (%)	Tensile strength (MPa)	Modulus of elasticity (MPa)
16.5% MA	382±62	10.79±1.25	80.77±17.0
21.5% MA	638±76	6.38±0.39	22.73±2.21
29.0% MA	847±101	4.95±0.33	6.47±0.71

Mean±SD of six experiments ($n=6$) ($P<0.01$).

3.3. Swelling studies

The solvent permeability in polymeric membranes is related to the swelling capacity. In general, a good barrier to the permeation of any substrate occurs when the polymer chains are closely packed. For the permeation, the substrate spaces between the chains have to dilate for the polymer to pass through. As a swollen membrane has much larger spaces between the polymer chains, the substrate can penetrate more easily [44]. The degree of swelling of the EMA membranes with different MA contents as a function of the ethanol/water composition, is shown in Fig. 3. As observed, the EMA does not swell in water and the degree of swelling significantly increased ($P<0.01$) with the ethanol composition for both membranes. It is well known that polyethylene is hydrophobic and almost impermeable to water. The presence of MA units in the polymeric chain (copolymer) did not change this behaviour but with the increase in ethanol composition a swelling increase occurred. The increase in the swelling with MA content can be explained by the solubility parameters. For ethanol the solubility parameter is 12.9, for polyethylene 7.9 and poly(methyl acrylate) 9.5. With the presence of MA in the copolymer chain the solubility parameter becomes close to that for ethanol, promoting an increase in the swelling degree of the EMA membranes.

The hydrophilic character (wettibility) of the polymer membrane surface, considering the copolymers with different MA contents, was analyzed by contact angle measurements. The contact angle is defined as the angle between the tangent of the solid–vapor and the line of the solid–liquid

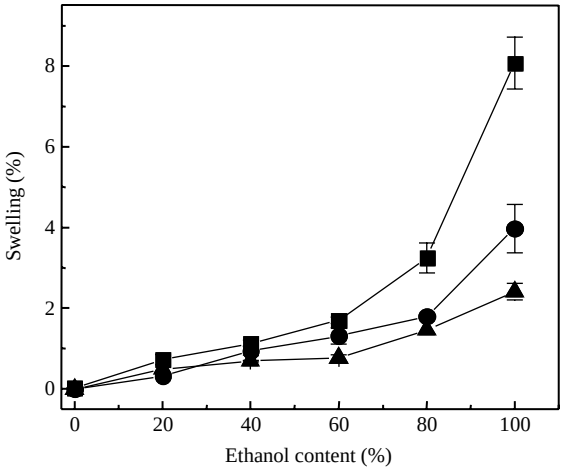

Fig. 3. Percentage of swelling as a function of the ethanol fraction for EMA membranes with different MA contents: (▲) 16.5; (●) 21.5 and (■) 29.0%. ($n=5$).

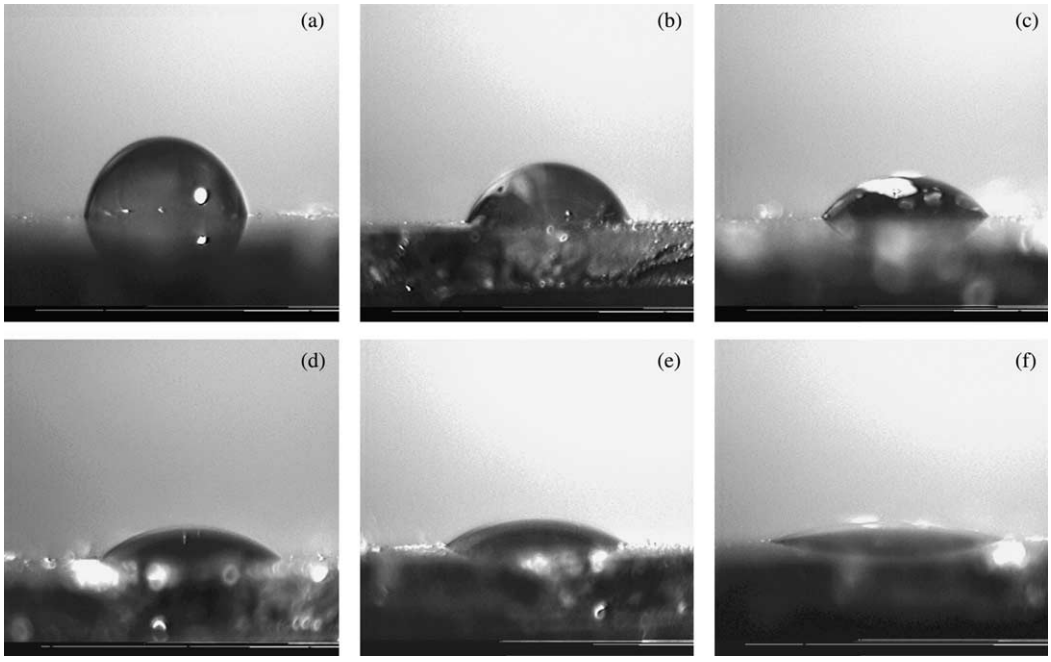

Fig. 4. Profile of a water or ethanol/water drop (10 μL) on EMA membranes with 16.5% MA content. Ethanol/water fraction: (a) 0/100; (b) 20/80; (c) 40/60; (d) 60/40; (e) 80/20 and (f) 100/0.

interface. The condition for complete wetting of a solid surface is when the contact angle is zero. This condition is fulfilled when the forces of attraction between the liquid and solid are equal or greater than those between a liquid/liquid interface [11]. In Fig. 4, the changes in the contact angle of ethanol or ethanol–water drops in the EMA membranes (16.5% MA content), are shown. The increase in ethanol content promoted a reduction in the contact angle with the EMA membrane surface. The contact angle for ethanol in the EMA with 29.0% MA content showed a value close to zero, which is the condition for complete wettibility. As observed in Table 2, the contact angle decreased with an increase in both the ethanol percentage and the MA content, suggesting that both conditions are important for controlling the drug permeation through the EMA membranes.

3.4. Permeation studies

First, the effects of MA content and ethanol fraction on the permeation of diltiazem hydrochloride in the EMA membranes, were analyzed. Due to the lower solubility in ethanol of diltiazem hydrochloride in comparison to paracetamol and ibuprofen, it was considered more appropriate for partitioning and permeation studies. As observed in Fig. 5, the permeation of diltiazem hydrochloride in ethanol increased with the percentage of MA in the copolymer. The flux of diltiazem hydrochloride increased from 0.012 to 0.018 mg cm^{-2} h^{-1} with the increase in MA content from 16.5 to 29.0%. This slight increase in permeation is apparently related with the decrease in the copolymer crystallinity, as observed by Shim and Byun [40] for membranes of EVA. As observed by DSC, in the EMA system, with the increase in MA comonomer content, the copolymer crystallinity decreased and the diffusivity of

Table 2
Values for contact angles calculated for EMA membranes ($n=3$)

Ethanol/water (%)	Contact angle		
	16.5% MA	21.5% MA	29.0% MA
0/100	85.2±2.9	80.8±1.8	63.8±1.4
20/80	70.0±2.3	66.5±2.2	56.7±2.0
40/60	55.9±1.7	48.0±2.5	44.9±2.3
60/40	46.9±2.3	38.7±2.1	28.1±3.3
80/20	31.3±1.4	31.5±2.8	19.9±5.3
100/0	11.6±3.4	13.0±4.4	–

Mean±SD of three experiments ($n=3$) ($P<0.01$).

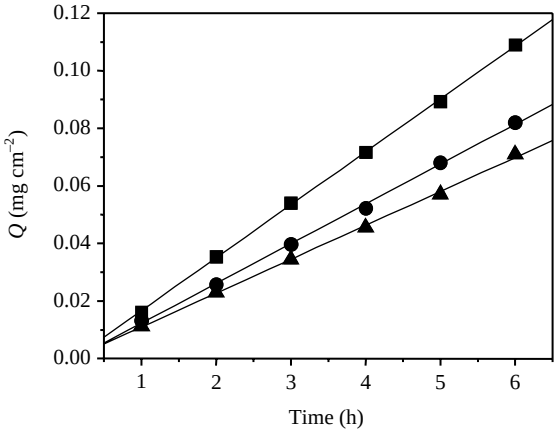

Fig. 5. Effect of MA content on the flux of diltiazem hydrochloride through the surface EMA membranes in ethanol: (▲) 16.5; (●) 21.5 and (■) 29.0% MA.

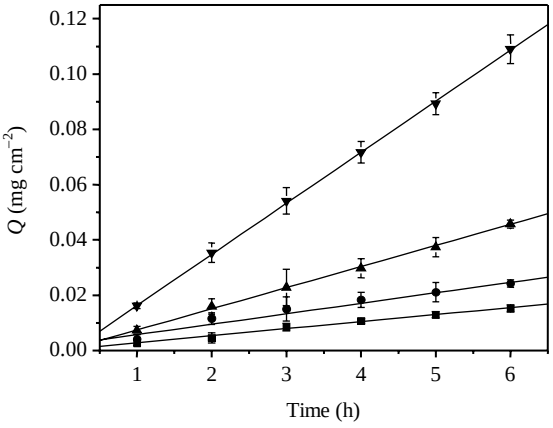

Fig. 6. Permeation profiles of diltiazem hydrochloride through EMA membranes (29.0% MA) in ethanol/water fraction: (■) 40/60; (●) 60/40; (▲) 80/20 and (▼) 100/0.

Table 3
Flux and permeability coefficients of diltiazem hydrochloride through EMA membranes (29.0% MA) at different ethanol fractions

Ethanol fraction	Flux (mg cm^{-2} h^{-1})$\times 10^3$	Swelling (%)	P (cm h^{-1})
0.4	2.56±0.09	1.12	5.85×10^{-6}
0.6	3.79±0.02	1.69	7.54×10^{-6}
0.8	7.54±0.10	3.25	1.44×10^{-5}
1.0	18.38±0.62	8.07	3.53×10^{-4}

Mean±SD of three experiments ($n=3$) ($P<0.01$).

the drug within the membrane, increasing, as a consequence. The diffusion of active agents in polymers occurs mainly through the amorphous regions of the polymer and is related to the mobility of the polymer chain and consequently, to the free volume of the system [11].

Another important factor that affects the flux is the ethanol fraction. The permeation profiles of diltiazem hydrochloride in EMA membranes (29.0% MA content) in solutions with different ethanol/water fractions, are shown in Fig. 6. Based on the swelling and contact angle data, the increase in the ethanol/water fraction, significantly increased the ethanol content in the polymer membrane. Apparently, this behavior promoted the partitioning of the drug within the EMA membrane, increasing the solute permeation. The permeation rates (Q/t) (flux), determined from the slope of Q versus t plots, and the permeability coefficient calculated using Eq. (3), are shown in Table 3. The increase in the ethanol fraction from 0.4 to 1.0 increased the rate of permeation through EMA membranes from 2.56×10^{-3} to 18.28×10^{-3} mg cm^{-2} h^{-1} and the permeability coefficient from 5.85×10^{-6} to 3.53×10^{-4} cm h^{-1}. The observed behavior can be directly correlated with the membrane swelling. Considering that a swollen membrane has a much larger space between the polymer chains, increases in both flux and permeability are to be expected. Similar results have been observed for EVA, where the chlorpheniramine maleate partition into EVA films increased for vehicles (solvents) with higher ethanol content [20].

Finally, the effect of drug partitioning on the flux and permeability coefficient, was analyzed (Table 4). The flux and permeability coefficient significantly increased ($P<0.01$) with the drug solubility in the polymer suggesting that ethanol acts as a co-solvent for the drugs, enhancing partitioning in the EMA membranes. The permeability of ibuprofen in relation to the EMA membrane is approximately a 100 times higher than diltiazem hydrochloride and 40 times higher than paracetamol. These values are totally consistent with the solubility of the drugs in the copolymer and ethanol and with the drug partitioning in the EMA membranes.

4. Conclusions

It was concluded from this study that the increase in MA content in the copolymer reduced the tensile strength and modulus of elasticity of the membranes, thus increasing the elongation at break. This behavior indicated that the copolymer membranes with 29.0% MA content were more elastic, more flexible and softer than the membranes with lower MA content.

An increase in the ethanol swelling and a decrease in the contact angle with the increase in ethanol percentage and MA content were observed. This behavior is consistent with the decrease in crystallinity observed by DSC for EMA with 29.0% MA content.

The permeation studies revealed that the flux and permeability coefficient of the diltiazem hydrochloride also increased with the MA content, suggesting that the membrane shows a lower resistance to the penetration of the drug molecules. The increase in ethanol fraction resulted in an increase in the flux through EMA membranes and also in

Table 4
Drug solubility in the copolymer and ethanol, flux and permeability in the EMA membranes (29.0% MA content) at 37 °C

Drugs	Solubility (mg cm^{-3})		Flux (mg cm^{-2} h^{-1})	P (cm h^{-1})
	Copolymer	Ethanol		
Diltiazem hydrochloride	0.64	231.42	0.08±0.01	3.46×10^{-4}
Paracetamol	6.68	503.55	0.53±0.01	1.05×10^{-3}
Ibuprofen	504.48	1139.70	45.11±2.00	3.96×10^{-2}

Mean±SD of three experiments ($n=3$) ($P<0.01$).

the permeability coefficient. The flux and permeability coefficient can be directly correlated with the membrane swelling and the drug solubility in the membrane and in ethanol.

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