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Influence of ionic strength on drug adsorption onto and release from a poly(acrylic acid) grafted poly(vinylidene fluoride) membrane

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Abstract

Ion exchange resins have several applications in pharmacy for contolled or sustained release of drugs. In the present study, effects of the ionic strengths of adsorption medium and dissolution medium on drug adsorption onto and release from a acrylic acid grafted poly(vinylidene fluoride) (PAA–PVDF) were studied. Despite their porosity, PAA–PVDF membranes act reasonable well as cation exchange membranes. It was observed, that ionic strength of adsorption medium, degree of grafting and concentration of propranolol-HCl in adsorption medium affect propranolol-HCl adsorption onto the membrane. The fluxes of smaller molecules (MW < 500) across the membrane decreased with ionic strength of buffer solution, whereas the fluxes of the large molecules (FITC-dextran, MW 4400) increased with ionic strength. Release rate of adsorbed propranolol-HCl from the membrane into phosphate buffer was greatly affected by ionic strength of adsorption medium. These results can be explained by a cation exchange process between membrane and cations present in the buffer solution and swelling behavior of the grafted PAA chains.

Keywords: Ionic strength; Polyacrylic acid; Polymer membrane; Drug release; Drug flux; Propranolol-HCl

1. Introduction

Acrylic polymers are widely used excipients in pharmaceutical preparations due to their pH de-

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pendent swelling behavior. For example, acrylic polymers are used in sustained release of drugs in ocular, nasal, buccal, gastro-intestinal, epidermal and transdermal drug delivery (Dittgen et al., 1997). Iwata et al., (1988) and Ito et al., (1989) have studied glucose-sensitive porous poly(acrylic acid) grafted membrane for pulsatile release of insulin. The release of insulin is controlled by pH in the polymer, which in turn, depends on external glucose concentration. We have studied the suitability of a pH and ionic strength responsive poly(acrylic acid) grafted poly(vinylidene fluoride) membrane (PAA–PVDF) for controlled drug delivery (Åkerman et al., 1998; Järvinen et al., 1998). The results suggested that PAA–PVDF membranes might be capable of controlled release of macromolecules in response to the environmental pH.

In addition to environmental pH, interaction between anion exchange films (Eudragits) and acidic drugs affects drug release from ion exchangers (Jenquin et al., 1990; Jenquin and McGinity, 1994). Bodmeier et al., (1996) and Knop, (1996) have reported that the extent of ion exchange between anions of the polymer and the anions of the buffer solution affect drug release from beads and pellets coated with cationic polymers. Despite their porosity, PAA–PVDF membranes act reasonable well as cation exchange membranes (Hautojärvi et al., 1996; Åkerman et al., 1998). Compact conformation of PAA chains and higher convective permeability occur in response to an increase in ionic strength (Hautojärvi et al., 1996). Release of acidic and neutral drugs from the membrane bags prepared from PAA–PVDF membrane was not substantially affected by the ionic strength of dissolution medium, while release rate of cationic drugs decreased with increased ionic strength of dissolution medium (Järvinen et al., 1998).

The advance of charged polymers for sustained release is their ability to adsorb oppositely charged drug molecules. Since PAA binds monovalent and divalent cations (Charman et al., 1991; Kriwet and Kissel, 1996), controlled drug release could occur due to replacement of the drug by cations in the body. Therefore, drug-loaded PAA–PVDF membrane might be suitable, e.g. for topical ophthalmic use, since cations are present in the tearfluid. Consequently, the aim of the present study was to examine the effect of ionic strength on the drug adsorption onto and release from the PAA–PVDF membrane.

2. Materials and methods

2.1. Materials

FITC-dextran (MW 4400) and propranolol-HCl were purchased from Sigma (St. Louis, MO). Mannitol was from Merck (Darmstadt, Germany), [^{3}H]mannitol (specific activity 19.70 Ci/mmol) from Dupont (NEN Products, Boston, MA, USA). Timolol (free base) was a gift from Inter Research Corp. (Merck & Co., Lawrence, KS, USA).

2.2. Membrane preparation

Hydrophobic PVDF membranes, (Millipore) with pore sizes of 0.22 μm, and acrylic acid (AA), (Aldrich, Steinheim, Germany) stabilized with 200 ppm hydroquinone, were used as received. Ion-exchange water was used throughout.

Pre-irradiation grafting was accomplished by first irradiating the PVDF membranes under nitrogen atmosphere (< 200 ppm O_2) using Electrocurtain electron accelerator (Energy Sciences Inc.) operating at an acceleration voltage of 175 kV. The membranes were irradiated with 25 kGy. Immediately after irradiation the membranes were immersed at ambient temperature in a graft solution containing AA. This solution was continuously purged with nitrogen in order to remove oxygen. After grafting, the membranes were soxhlet extracted with water to remove the remaining monomer and dried in vacuo at 40°C overnight. The degree of grafting was determined gravimetrically according to:

$$G = ((m_1 - m_0/m_0)) \times 100 \text{ wt.}\%$$

where m_0 represents the mass of the original PVDF membrane and m_1 represents the mass of the grafted, extracted and dried PVDF membrane.

2.3. Effect of ionic strength on drug fluxes across the membrane

The effect of ionic strength on the flux of drug across the 48 wt.% grafted membrane was studied using 0.5 mM of mannitol (contained [^{3}H]mannitol 160 μCi/mmol), propranolol-HCl and timolol and 50 μM or 200 μM FITC-dextran (MW 4400) as model drugs. Studies were performed in glass side-by-side -diffusion cells (Crown Glass Co. Inc., Sommerville, NJ). The area of the membrane exposed was 0.64 cm^2. Blank buffer was placed in receiver compartments of the diffusion cells and drug solution in the donor compartment. Stirring was with magnetic bars. Both donor and receiver solutions were constantly circulating at a flow rate of 1 ml/h (Ismatech, MCP V5.10, Switzerland). Fractions of 1 ml were collected from the receiver compartment with an automated fraction collector.

FITC-dextran concentrations were determined fluorometrically (Luminescence Spectrophotometer LS 50B, Perkin Elmer Ltd., Buckingshamshire, England), excitation at 495 nm and emission at 515 nm. Mannitol concentrations were determined using liquid scintillation counting (Rackbeta 1218 liquid scintillation counter, LKB Wallac, Turku, Finland). A 4.5 ml of aqueous counting scintillant (Ultima Gold) was added to the samples of 500 μl. Counting was performed for 360 s. Propranolol-HCl and timolol concentrations were measured spectrophotometrically at 288 (propranolol-HCl) or 295 nm (timolol) (Hitachi 220, Tokyo, Japan).

At equilibrium, the flux (J) of the permeant was calculated using the equation:

$$J = V_a C_a / A$$

where V_a is the flow rate of the buffer in the receiver compartment, C_a is the steady state concentration of the permeant in the receiver com-

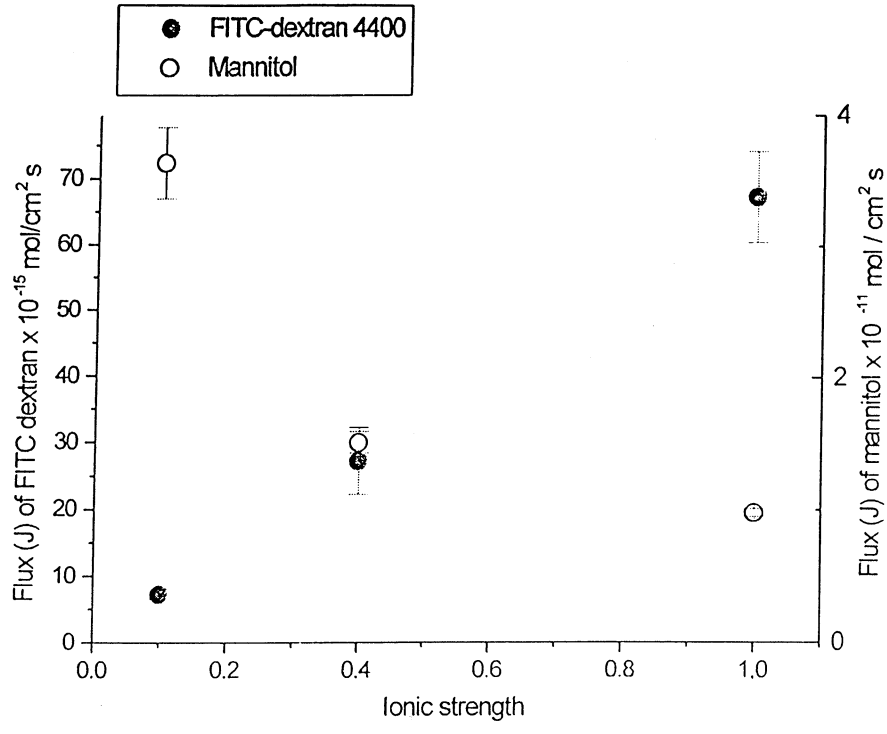

Fig. 1. Effect of ionic strength on the flux of mannitol (0.5 mM) and FITC-dextran (MW 4400) (200 μM) across the 48 wt.% PAA grafted PVDF membrane. Values are means (±S.D.) of three experiments.

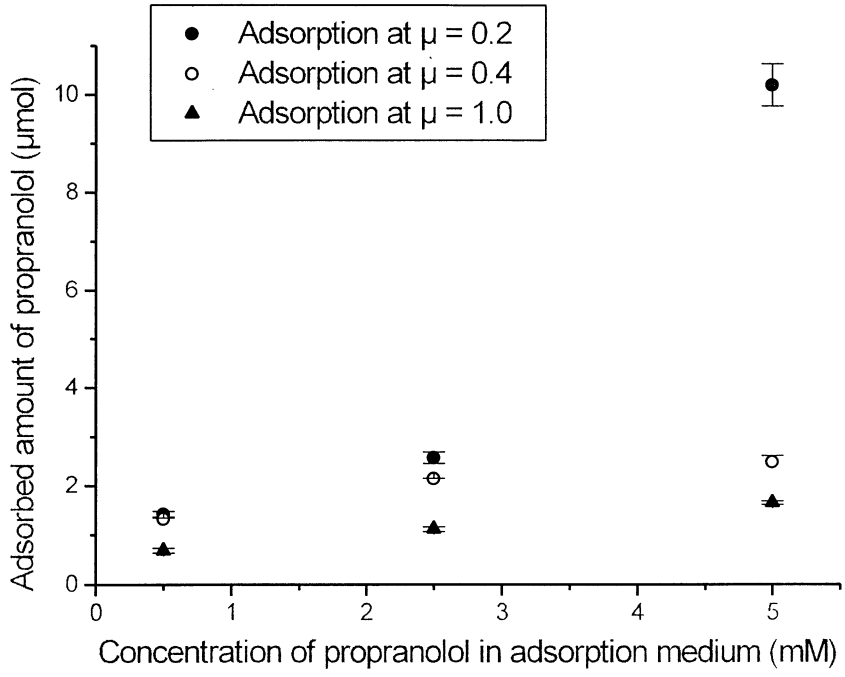

Fig. 2. Effect of ionic strength and drug concentration on the drug adsorption on the 54 wt.% PAA grafted PVDF membrane. Values are means (± S.D.) of three experiments.

partment, and A is the area of the membrane exposed.

2.4. Adsorption of drug onto the membrane

Adsorption of cationic propranolol-HCl onto the membrane was studied by soaking PVDF-PAA membranes (area 0.38 cm^2, weight varied between 4.5–6.0 mg) in 60 mM phosphate buffer solution (20 ml, pH 7.0) containing drug in concentrations of 0.5 mM, 2.5 mM, and 5.0 mM at room temperature overnight. The ionic strength of the phosphate buffer was adjusted with NaCl to 0.2, 0.4, and 1.0 M. The membranes were washed quickly with distilled water before the adsorbed drug was released from the membrane by soaking the membrane in 0.01 M HCl solution (ionic strength of 0.2 M with NaCl, pH 2.14) overnight. The adsorbed amounts of the drugs were measured spectrophotometrically as described earlier. The effect of the degree of grafting on the drug adsorption was studied as described above, using 5 mM propranolol-HCl solution in 60 mM phosphate buffer (pH 7.0, ionic strength 0.2 M) and membrane area of 0.79 cm^2.

Table 1
The effect of degree of grafting on the adsorption of propranolol-HCl onto the PAA grafted PVDF membrane at ionic strength 0.2 M. Mean ± S.D. (n = 3–6)

Degree of grafting (wt.%)	Adsorbed amount of propranolol (μmol)	Propranolol/acrylic acid (mol/mol)
7	24.5 ± 1.5	6.1:1
15	26.9 ± 2.4	3.1:1
58	37.3 ± 5.2	0.8:1
105	36.1 ± 7.5	0.4:1
162	39.4 ± 3.9	0.2:1

2.5. Propranolol-HCl release from the membrane

For studies of propranolol-HCl release, the

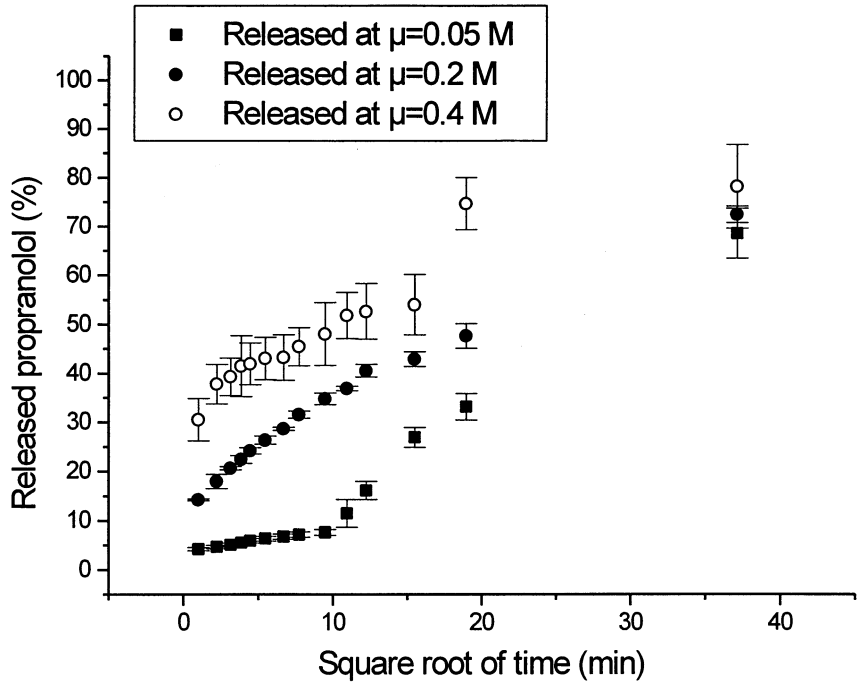

Fig. 3. The effect of ionic strength on propranolol-HCl release from 54 wt.% PAA grafted PVDF membrane, adsorption of propranolol-HCl onto membrane was performed at the ionic strength of 0.4 M. Values are means ($\pm$S.D.) of three experiments.

dry 54 wt.% grafted PVDF-PAA membranes were soaked in 0.5 mM propranolol-HCl solutions in 6 mM phosphate buffer (pH 7.0, $\mu =$ 0.05 M, 0.2 M or 0.4 M) overnight. The membranes were removed from the solution, washed in distilled water and dried in air. The blank membrane was soaked in phosphate buffer without the drug.

Release of propranolol-HCl from the dried membrane was studied by immersing the membrane in a beaker which contained 50 ml of phosphate buffer (pH 7.0) at various ionic strengths equipped with a magnet stirrer at room temperature. Samples of 5 ml were collected and replaced with fresh buffer. Concentrations of propranolol-HCl were measured with UV-spectrophotometer at 288 nm. After removing from the beaker, membranes were soaked in 0.01 M HCl as described above to measure the total amount of drug still bound to the membrane.

3. Results and discussion

3.1. Effect of ionic strength on drug flux

Fig. 1 shows the ionic strength sensitivity of the PAA–PVDF membrane with a grafting degree of 48 wt.%. The flux (J) of mannitol across the membrane decreased by 3.7-fold when the ionic strength of the buffer solution was increased from 0.1 M to 1.0 M. A similar trend was observed when propranolol ($J = (4.98 \pm 0.44) \times 10^{-11}$ mol/cm^{2}s at $\mu = 0.05$ M and $(2.10 \pm 0.27) \times 10^{-11}$ mol/cm^{2}s at $\mu = 0.4$ M), and timolol ($J = (7.07 \pm 0.18) \times 10^{-11}$ mol/cm^{2}s and $(2.08 \pm 0.50) \times 10^{-11}$ mol/cm^{2}s, respectively) were used as model drugs. In contrast to the model compounds with low molecular weight (MW), the flux of FITC-dextran (MW 4400) across the membrane was increased as the ionic strength was elevated. When 200 μM solution was used in the donor compartment, the flux across the membrane increased by 9.2 times

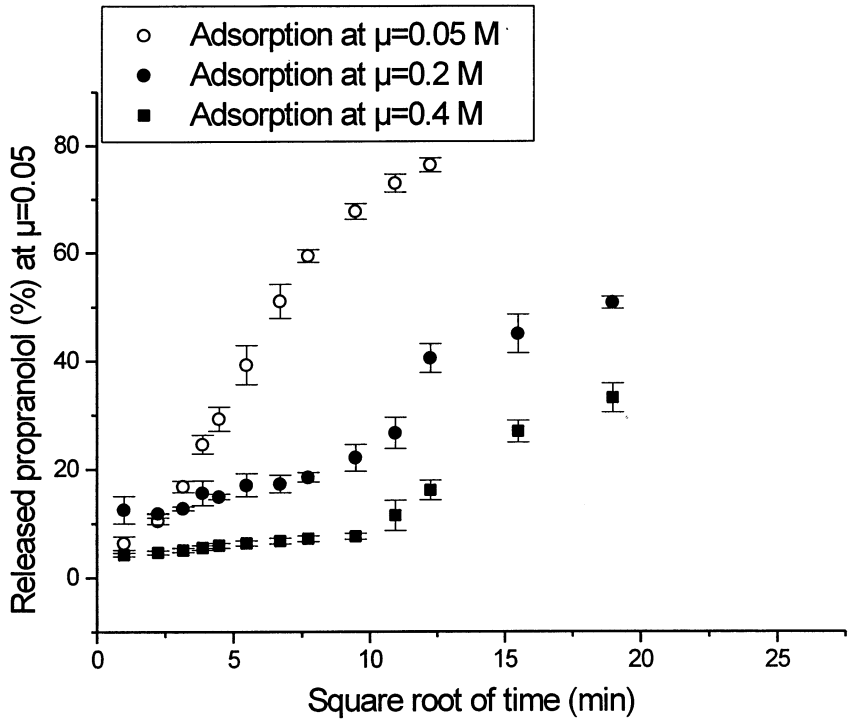

Fig. 4. The release of propranolol-HCl from 54 wt.% PAA grafted PVDF membrane at ionic strength 0.05 M, adsorption of propranolol-HCl onto membrane was performed at ionic strengths of 0.05 M, 0.2 M, and 0.4 M. Values are means (± S.D.) of three experiments.

when the ionic strength was increased from 0.1 to 1.0 M.

Hautojärvi et al., (1996) have reported that the permeability of 85 wt.% PAA grafted PVDF membrane increases by about four orders of magnitude when the ionic strength is increased from 10 mM to 1 M. This is due to the fact that that conformation of grafted PAA chains are more compact in 1 M KCl than in 0.01 M KCl. The compact conformation opens the pores and therefore the membrane becomes more permeable at increasing ionic strength. Similar conformational changes in the polymer have been observed as a function of pH. Our earlier studies have demonstrated that changing the pH from 7 (swollen state) to 2 (collapsed state), increases the flux of FITC-dextran (MW 4400) across the PAA–PVDF membrane by several orders of magnitude, while the flux of the mannitol (MW 182) across the membrane increases only by 1.8 times (Åkerman et al., 1998).

Table 2
Effect of ionic strength (μ) of medium on release of propranolol-HCl from 54 wt.% grafted PVDF–PAA -membrane[a]

Adsorption onto membrane (μ)	Release from membrane (μ)	$t_{50\%}$ (min)
0.4	0.4	105 ± 55
0.4	0.2	372 ± 16
0.4	0.05	852 ± 105
0.2	0.05	243 ± 22
0.05	0.05	44 ± 4
0.05	0.4	22 ± 1

[a] Mean ± S.D. ($n = 3$) are shown

The conformational changes of PAA induced by ionic strength had a more significant effect on the fluxes of larger molecules than smaller molecules. At low ionic strength, the swollen polymer hinders the diffusion of FITC-dextran (MW 4400) and an increase in the ionic strength alters PAA conformation allowing the flux of larger molecules. In the case of small molecules,

however, the effect of ionic strength on the fluxes is not straight forward. There are two reasons for the decreased fluxes of small cationic drug molecules with ionic strength, first the ionic exchange capacity is lowered, and secondly the lipophilicity of the PAA chains becomes greater. The decreased electrostatic association of the cationic drug with PAA leads lowered concentration gradient of the drugs in the membrane and subsequently decreased fluxes. Since the diffusivity of small drugs in the membrane is not affected significantly by the polymer, the above interactions with polymer determine the flux changes.

Although electrostatic binding plays an important role in drug adsorption onto ion exchange membranes, Okada et al., (1987) indicated that adsorption may occur also via non-electrostatic interactions by hydrogen bonding. Consequently, mannitol may bind to dissociated carboxyl groups of PAA since the hydroxyl groups of mannitol have partial polarity. This leads to a higher concentration gradient in the membrane and to increased flux in the membrane. The reduction in flux of mannitol at higher ionic strengths (Fig. 1) may be due to the decreased ability of hydroxyl groups of mannitol to form hydrogen bonds with undissociated carboxyl groups of polyacrylic acid. While FITC-dextran consist mainly glucose, it may also bind to the membrane by hydrogen bonding. However, due to the molecular size, the flux of FITC-dextran is mainly affected by conformation of grafted PAA chains and therefore, the possible hydrogen bonding does not determine the changes in flux.

3.2. Drug adsorption on the polymer

Fig. 2 depicts the adsorption of propranolol-HCl on the polymer as a function of ionic strength. When the concentration of propranolol-HCl was increased, the amount of propranolol-HCl adsorbed was elevated significantly only at a low ionic strength. The adsorbed amount of propranolol-HCl increased about 10-fold when the concentration of propranolol-HCl was increased from 0.5 to 5.0 mM at an ionic strength of 0.2 M. Adsorption of propranolol-HCl on the membrane tended to decrease with increased ionic strength at each studied propranolol HCl concentrations, but only at propranolol-HCl concentration of 5 mM ionic strength had substantial effect on adsorption. These results are in accordance with earlier studies of Okada et al., (1987), where adsorption of various cationic drugs onto the microcrystalline cellulose decreased with increased ionic strength. They suggested that increased ionic strength decreases drug adsorption mainly by inhibition of electrostatic binding of oppositely charged drugs. Since PAA has been reported to be more selective for cations with higher valence (Kriwet and Kissel, 1996; Ghimici et al., 1997), it can be expected that not only the ionic strength of surrounding solution but also the nature of counterion present in adsorption medium affect drug adsorption on the membrane.

When the adsorption capacity of the membrane was studied as a function of the grafting, a plateau in adsorption was observed with higher grafting rates of the membrane (Table 1). When the extent of grafting is measured by the gravimetric method, it is possible to calculate the molar amount of adsorbed propranolol-HCl per mole of PAA. As seen in Table 1, binding of propranolol-HCl per mole of PAA decreases at higher degrees of grafting. This result indicates that increasing the grafting does not linearly increase the accessible adsorption sites in the membrane. These results suggest that a highly grafted polymer forms a compact structure and the reduced electrostatic repulsion of the charged carboxyl groups also prevents drug adsorption to the inner part of membrane.

In conclusions, in the case of grafted, porous cation exchange membrane, there exists a number of factors that affect amount of adsorbed drug. These factors include the composition of adsorption medium, degree of grafting, conformation of grafted polymer chains as well as concentration and physicochemical properties of drug.

3.3. Effect of ionic strength on propranolol-HCl release

Release of propranolol-HCl from the membrane was dependent on the ionic strength of the adsorption medium as well as on the ionic

strength of the dissolution medium (Figs. 3 and 4, Table 2). When propranolol-HCl was adsorbed at $\mu = 0.4$ M and it was released at $\mu = 0.05$ M, a long lag time (90 min) with slow drug release observed (Fig. 3). When propranolol-HCl was released at $\mu = 0.2$ M or 0.4 M, no lag time was observed (Fig. 3). Increasing the ionic strength at adsorption medium decreased the release rate of propranolol-HCl at ionic strength 0.05 M (Fig. 4).

There are many factors that influence drug release from the membrane. Chang and Bodmeier, (1997) reported that ionic strength of the dissolution medium has only a minor effect on propranolol release from non-ionic, amphiphilic monoglyceride matrices. In the case of cation exchange membrane, the fact that drug release is dependent on ionic strength could be due to a cation exchange process. When the drug is adsorbed on the membrane at a high sodium ion concentration, the ion exchange capacity of the membrane is more saturated with sodium ions. Subsequently the cation exchange process releases propranolol-HCl slowly at low sodium ion concentrations (Fig. 3). If it has been adsorbed onto the membane at low ionic strength, propranolol is released more efficiently at high ionic strengths due to the exchange of sodium ions (Table 2).

In addition to the cation exchange process, also the conformation of PAA chains is affected by ionic strength. Increasing the ionic strength of the adsorption or dissolution medium changes the conformation of the polymer chains to a more compact form (Hautojärvi et al., 1996). Therefore, when the dissolution study is performed at a higher ionic strength than that used for drug adsorption, the polymer chains collapse, inducing rapid drug release. When the drug adsorption was performed at a high ionic strength, the membrane is in its collapsed state and swells when it is changed to a dissolution medium of low ionic strength. The conformational change of the PAA chains seems to occur more slowly from collapsed to swollen state, which is observed as a long lag-time in the release of propranolol-HCl (Table 2, Fig. 3). Swelling dependent propranolol-HCl release was observed also from non-ionic, amphiphilic monoglyseride matrices (Chang and Bodmeier, 1997). In conclusion, our results show that in the case of cation exchange polymer membrane, both ion exchange capacity of the membrane and swelling of PAA chains affect drug release from the PAA–PVDF membrane.

4. Conclusion

Ionic strength affect behavior of ion exchange membranes by several mechanisms. Our results suggest that changes in the flux of the large model compound (FITC-dextran 4400) across the PAA–PVDF membrane as a function of ionic strength were determined by conformational changes of the grafted PAA chains. In contrast, ionic strength induced changes in the fluxes of the small cationic molecules were likely determined by electrostatic forces and lipophilicity of the PAA chains while flux of neutral mannitol might be controlled by hydrogen bond formation. Propranolol-HCl adsorption onto the PAA–PVDF membrane was affected by several factors, such as ionic strength and propranolol-HCl concentration of adsorption medium and grafting rate of the membrane. Ionic strength of adsorption medium affected substantially release rate of propranolol-HCl from the membrane probably due to a cation exchange process and swelling behavior of grafted PAA chains.

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