Transport Properties of Ionic Drugs in the Ammonio Methacrylate Copolymer Membranes

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Purpose. Ammonio methacrylate copolymer is a pharmaceutical excipient widely used as a coating material for encapsulation of pellet and tablet dosage forms. Because of the charged ammonio function groups within the polymer, ionic drugs may interact with the coating film while transporting through it. The kinetic swelling and drug permeation properties of the ammonio methacrylate copolymer membranes were studied to delineate the effect of ionic interaction between the ionic drugs and the membranes.

Methods. The pH and ionic strength of the solutions and the charged properties of drugs were varied to study the effects on the transport properties through the membranes. Ambroxol was chosen as a model cationic drug and aspirin as a model anionic drug.

Results. The degree of membrane swelling in the drug-free solution decreases as the ionic strength increases but it is irrelevant to the pH. With the presence of ionic drugs, the degree of membrane swelling is affected by the drug species as well as the pH of the solutions in addition to the effect of ionic strength. The degree of swelling for a membrane in a solution containing aspirin is higher at a lower pH and ambroxol is lower at a lower pH. Aspirin experiences a three-stage permeation and ambroxol a two-stage one. The ion-exchange reaction between the anionic carboxylic groups in aspirin and the cationic ammonio groups in the membranes results in a slow permeation stage during the transient state. The pseudo steady-state permeability for each drug follows the trend as the degree of membrane swelling in the drug media at various pH and ionic strengths. However, it is much higher for aspirin than ambroxol although the degree of membrane swelling is higher in an ambroxol solution than that in an aspirin solution. The permeability of ambroxol through the membrane is largely reduced because of the Donnan exclusion effect.

Conclusions. The interaction between ionic drugs with the cationic groups in the membranes affects the ionic strength of the solutions and results in a pH-dependent degree of swelling. The ionic interaction also determines the drug permeation rates as well as the transient permeation behaviors.

KEY WORDS: swelling; permeation; Eudragit RS/RL; ionic strength; ion-exchange.

INTRODUCTION

Acrylate polymers and their derivatives are used widely in the pharmaceutical industry as dosage excipients or coating materials, which have been commercially available by the trade name of Eudragit (Röhm Phama, Germany) for many years (1). Formulation with this kind of polymers has been applied to dosage form for controlled release in oral drug delivery as well as in transdermal therapeutic system (2,3). Many copolymers of acrylic and methacrylic acid or ester with various function groups have been developed to fulfill various formulation requirements. Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) [poly(EA-MMA-TAMCl)] is one such polymer with the introduction of hydrophilic quaternary ammonio groups (TAMCl) to modify the permeability of the acrylic and methacrylic ester copolymer. The copolymers are produced by bulk polymerization and available as solid granules or as milled powder with composition of EA:MMA:TAMCl = 1:2:0.2 (Eudragit RL-100) and 1:2:0.1 (Eudragit RS-100). Pseudo-latex solutions of 30% solid content (Eudragit RL 30D and RS 30D, respectively) are obtained by directly dispersing the micronized polymer particles in water containing sorbic acid as a preservative at elevated temperatures without the use of an emulsifier.

Membranes or coatings prepared from the ammonio methacrylate copolymers or their pseudo-latex solutions are insoluble in the aqueous media over the physiological pH range; however, the membranes are swellable and permeable to drugs because of the ionizable quaternary ammonio groups. Because of the difference in the content of the TAMCl group in the polymer, Eudragit RL is more hydrophilic than Eudragit RS, and the drug or water vapor permeability is higher through the membrane made by the former material than the later (4–7). The permeability of urea through the Eudragit RL could be as high as 500-fold of that through Eudragit RS (8). Blending those two copolymers, as well as other acrylate polymers, has been suggested to adjust the drug permeability in controlled release application (2,3).

The ionization of the quaternary ammonio groups can significantly alter the swelling behavior of the polymer. The effects of pH, buffer species, buffer strength, and ionic strength on the drug release from the drug beads coated with the cationic polymers have been investigated (9–13). It was reported that the buffer species rather than the pH had a significant effect on the hydration and hence on the drug release from the coated beads. Increasing the ionic strength of the dissolution medium could reduce the drug release rate from the beads (13). However, the kinetic behaviors of membrane swelling and permeation in the presence of ionic drugs in the system have seldom been discussed.

It is the aim of the study to investigate the membrane swelling and permeation of ionic drugs through the membranes in the mediums with various pH and ionic strengths. The interaction among the quaternary ammonio ions within the membrane, buffer species, and the ionic drugs was examined to identify the transport mechanism of the ionic drugs through the cationic polymer membranes.

EXPERIMENTAL

Materials

Ammonio methacrylate copolymers (Eudragit RL and RS) were obtained from Röhm Pharma (Germany). Metha-

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nol and acetone of reagent grade were obtained from Merck. Talc was obtained from Showa Chemicals (Japan) and dibutyl phthalate was obtained from Nippon Shiyaku (Japan). Ambroxol and aspirin were kindly provided by Standard Chem. and Pharm. Co. (Tainan, Taiwan).

Membrane Preparation

Polymer granules of predetermined ratio of Eudragit RL/RS 100 were dissolved in methanol/acetone (80/20, v/v) solution. Talc (0.5% of the polymer) was added as an anti-sticking agent and dibutyl phthalate (20% of the polymer) was added as a plasticizer. The solution was thoroughly mixed and degassed before pouring onto a fluoro-treated polyester film supported by a 16 × 16 cm rimmed glass plate. The casting solution was allowed to evaporate freely in a hood for 3 hours at room temperature and then at 40°C for 1 hour. The dry membrane, as well as the polyester film, was taken off from the glass plate and was stored in a polyethylene sample bag at room temperature before use. The membranes were tested within 1 week after being prepared.

Swelling Study

The effects of pH and ionic strength of the buffer solution and ionic drugs themselves on the degree of swelling and swelling kinetics of the cationic polymer membranes have been studied. Buffer solutions were prepared by mixing disodium hydrogen phosphate, hydrogen chloride, and sodium chloride of adequate amounts in deionized water in order to adjust to a particular pH or ionic strength for experiments. In all the solutions with drug, the drug concentration was kept the same as 5 mg/ml. The membranes were cut into adequate sizes and vacuum dried until a constant weight was obtained. The dry weight of the membrane sample was recorded as W_d. The membrane was dipped into the buffer solutions of selected pH and ionic strength with or without drugs in the flask. The flask was placed in a reciprocating shaker bath at 37°C and 50 rpm. The membrane sample removed from the solution and weighed at predetermined interval until equilibrium swelling was achieved. The surface of the membrane was wiped dry with tissue paper before each weighing. The weight of the swollen membrane was recorded as W_s and the weight of the swollen membrane containing the drug was recorded as W_{sd}. The drug-impregnated membranes after vacuum drying for 24 hours were weighed and recorded as W_{dd}. The degree of swelling (SW), the degree of swelling in drug solution (SWD), and the drug loading (DL) were determined as

$$SW = \frac{W_s - W_d}{W_d} \qquad SWD = \frac{W_{sd} - W_{dd}}{W_d} \qquad DL = \frac{W_{dd} - W_d}{W_d}$$

Permeation Study

A two-compartment side-by-side permeation cell was used to characterize the permeation properties of ionic drugs through the membranes. The detailed apparatus and procedure are available elsewhere (14). The membranes had been swollen in the drug-free medium before being placed into the cell. The nominal thickness of dry membranes was kept around 315 μm. The initial drug concentration in the buffer solution of the donor side was 5 mg/ml. The receptor side was filled with the same buffer solution but without drug. The concentration of the permeated drug in the receptor side (C_2) was monitored by an UV/Vis spectrophotometer through an auto-sampling system. The permeability of a drug was determined from the pseudo steady-state permeation rates as follows:

$$P = \frac{V}{A}\frac{l}{(C_1 - C_2)}\frac{dC_2}{dt} \approx \frac{l}{AC_1}\frac{dQ}{dt} \text{ as } C_1 >> C_2 \approx 0$$

where V is the receptor volume, A is the membrane area (4.91 cm^2), l is the membrane thickness (dry thickness was used here to make comparison among membranes with different degrees of swelling), C_1 and C_2 are the donor and receptor concentration of drug, respectively, Q ($=C_2V$) is the total permeated amount of drug through the membrane. The mass transfer boundary layer resistance near the membrane surface was estimated to be negligible (15,16).

RESULTS AND DISCUSSION

Effect of pH on the Membrane Swelling

The swelling kinetics for the ammonio methacrylate copolymer membranes immersed in buffered solution of various ionic strengths at pH from 1.2 to 6.7 are shown in Figure 1. It is found that the swelling kinetics as well as the equilibrium swelling is almost the same for membranes in different pH buffered solutions with the same ionic strength. Because the degree of swelling is highly related to the permeability of solutes through membranes (17), the results correlate well with the drug release properties reported in the literature. It has been reported that the release of the drug from the polymer coated beads or tablets were independent of the pH *in vitro* as well as *in vivo* (2,18). In addition, the permeability of Eudragit RL/RS was claimed to be "independent of pH" as suggested in the manufacture's product data sheet (19). It should be noted that our results were obtained when the pH of the buffer solution was adjusted by the same series of salts. However, the outcomes could be altered if different organic

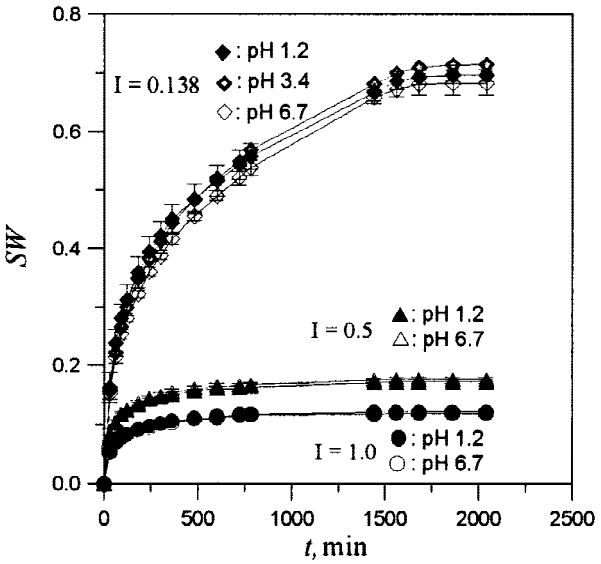

Fig. 1. The swelling kinetics for membranes in buffered drug-free solutions at various ionic strengths and pH. (Eudragit RL/RS = 50/50 v/v%, Talc = 0.5%, DBP = 20%, and n = 4).

acids were used to adjust the pH (9,13). The interaction of the quaternary ammonio groups in the polymer with different buffer species may be different, and the degree of ionization of the functional groups is affected so that the degree of membrane swelling and the drug release rate became pH-dependent. Later we will see that the degree of swelling becomes "pH-dependent" when ionic drug is present in the same buffered solutions.

Effect of Ionic Strength on the Membrane Swelling

The equilibrium degree of swelling was significantly affected by the ionic strength as shown in Figure 1. The increase of ionic strength would result in a decrease of the equilibrium degree of swelling. The increase of ionic strength was adjusted by increasing the ionized salt concentration so that the osmotic pressure in the solution increases. The swelling of the membrane can be restricted due to the increase of osmotic pressure in the solution (10,13). The situation is similar to the so-called "salting-out" effect, as the solubility of the hydrophobic portion of the polymer in the buffered solution decreases because of increasing of the salt concentration. In addition, the common ion effect due to the presence of chlorine ion in solution limits the ionization of the quaternary ammonio groups (TAMCl) so that the degree of swelling is reduced.

Effect of Ionic Drugs on the Membrane Swelling

The presence of ionic drugs in the media could significantly affect the degree of membrane swelling (Fig. 2 and Table I). The degree of membrane swelling in a buffered ambroxol solution is similar (pH 6.7) to or just 20 % lower (pH 1.2) than that in the buffered solution free of drug. However, the degree of swelling for a membrane in a buffered aspirin solution is largely reduced (48 to 65% lower than that in the buffered drug-free solution). The dissociated cationic ammonio groups in membranes may precipitate when they interact with the carboxylic groups in aspirin so that the degree of membrane swelling is reduced.

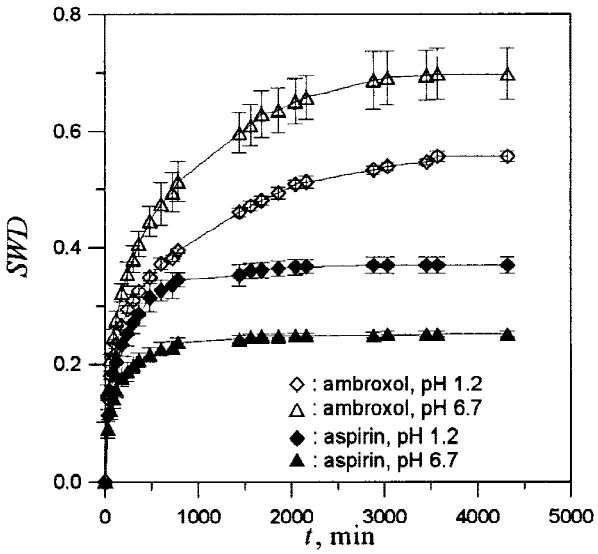

Fig. 2. The swelling kinetics for membranes in buffered drug solutions at pH = 1.2 and 6.7. (Eudragit RL/RS = 50/50 v/v%, Talc = 0.5%, DBP = 20%, I = 0.138, drug concentration = 5 mg/ml, and n = 4).

Table I. Degree of Swelling and Drug Loading for Membranes Equilibrated with Drug Solutions[a]

	Aspirin		Ambroxol	
	(pH 1.2)	(pH 6.7)	(pH 1.2)	(pH 6.7)
SWD	0.37 ± 0.02	0.252 ± 0.004	0.557 ± 0.009	0.70 ± 0.04
DL	0.17 ± 0.02	0.067 ± 0.005	0.146 ± 0.003	0.154 ± 0.01

[a] Eudragit RL/RS = 50/50 w/v%, Talc = 0.5%, DBP = 20%, I = 0.138, drug concentration = 5 mg/ml, and n = 4.

It is found that the degree of swelling for a membrane in a solution containing aspirin is higher at a lower pH and ambroxol is lower at a lower pH (Fig. 2). Because aspirin is a weak acid drug, the dissociation of aspirin is limited at a lower pH. The ionic strength for the aspirin solution is lower at a lower pH as a result. Because of the same reason proposed above, the degree of swelling for the membrane in an aspirin solution is higher at a lower pH than that at a higher pH. On the other hand, ambroxol is a weak base drug so that it may dissociate better in a solution of lower pH. The ionic strength for the ambroxol solution is higher at a lower pH. The degree of swelling for the membrane in an ambroxol solution is lower at a lower pH than that at a higher pH. The ionic strength affected by the degree of dissociation of the drug at different pH levels plays a key role in determining the degree of membrane swelling. The degree of swelling of the ammonio methacrylate copolymer behaves "pH-dependent" when ionic drugs are present in the solutions.

The drug loading in the membrane also depends on the pH of the solution. As shown in Table I, the higher degree of swelling would result in higher drug loading. When the membrane is better swollen, the space between polymer chains dilates more for drug molecules entering the membrane. It has been reported that the drug loading in Eudragit RS microspheres also relates to the degree of drug dissociation in solutions of various pH. When drug dissociates poorly, molecular drug can be absorbed better in the interstitial space between polymer chains and the drug loading is higher (20). The same arguments can also be applied to explain the drug loading data in this study.

Swelling Rate and the Equilibrium Degree of Swelling

It is of interest to note that the rate of swelling depends on the equilibrium degree of swelling. The more membranes swell the longer time they may take to reach their equilibrium as shown in Figures 1 and 2. It is reasonable to consider that swelling kinetics is related to the viscoelastic relaxation (or creep) of the polymer chains in response to the swelling stress. However, swelling is different from mechanical stress relaxation or creep because the swelling agent may interact with the polymer and results in change of the relaxation rate constant. The phenomena can be semi-quantitatively explained if water sorption in the membrane is modeled as simultaneous diffusion and a rapid and reversible immobilization reaction (21,22). Only unbound water can diffuse freely so that the apparent water diffusion coefficient is reduced to be $D/(1+K)$, where D is the true diffusion coefficient of free water and K is the equilibrium constant in the reversible water immobili-

zation reaction. The higher equilibrium degree of swelling results in larger K and thus lower apparent water diffusion coefficient. The swelling may take longer time to reach equilibrium and have smaller relaxation rate constant. Nevertheless, sorption of water is not the sole reason to account for the swelling kinetics, and the swelling may include the transport of buffer species and drugs and the interaction among all the components in the systems. The proposed mechanism is considered because water is the main swelling agent responsible for the membrane swelling process.

Drug Permeation Properties

Drug permeation profiles through the ammonio methacrylate polymer membranes at various ionic strengths are shown in Figures 3 and 4 for aspirin and ambroxol, respectively. It is interesting to note that anionic and cationic drugs behave differently in transient permeation through the membranes. For all the cases studied, there is an initial fast permeation (Stage I) and then followed with a slow-down period (Stage II). It is speculated that such a fast initial permeation is due to non-interactive solute diffusion through the swollen region within the membranes. Averaged initial permeabilities with comparable values ($1.5–3.5 \times 10^{-7}$ cm^2/min) are obtained for all cases no matter the drug species, pH, or ionic strength (Fig. 5). Aspirin may have a slightly higher permeability than ambroxol, but the difference is not significant. At this stage, the membranes are at a non-equilibrium state. The pendent function groups in the polymer main chains as well as the main chains are relaxing from the equilibrated state established before encountering drug molecules. The permeation rate varies with time until Stage II. Such transition generally takes time in the order of several hundred minutes similar to the time needed for the swelling kinetics to reach equilibrium. This may be a time characteristic of the polymer membrane in response to external stimulus, and it is related to the viscoelastic properties of the ammonio methacrylate polymer used to fabricate the membrane as well as the slowly developed interaction among all the species present in the system.

After the initial non-interactive permeation, the interaction between the ionic drugs and the quaternary ammonio groups becomes significant. The electric repulsion or attraction occurs thereafter and tends to slow down the permeation rate for both anionic and cationic drugs. Ambroxol tends to reach a slow pseudo-steady state (Stage II) because of the build-up of repulsive force between the cationic moieties of the drug and in the membranes. The effect is known as Donnan exclusion (23,24). A two-stage permeation is observed for ambroxol (Fig. 4). Aspirin also has a slow permeation period (Stage II) after the initial fast permeation but the reason is different from that for ambroxol. The anionic carboxylic moieties in aspirin can interact with the cationic ammonio groups in the membrane and an ion-exchange reaction occurs to immobilize aspirin molecules (25). The permeation rate is reduced because less aspirin molecules free from immobilization are available for permeation. When all the cationic sites in the membrane are saturated with the anionic moieties of aspirin, the permeation tends to achieve a pseudo-steady state (Stage III) at a rate comparable to the magnitude of the initial fast permeation rate. A three-stage permeation is resulted for aspirin (Fig. 3). Except the permeation rate, the two-stage (ambroxol) or three-stage (aspirin) permeation behaviors are similar in a medium of different ionic strength (Fig. 3 and 4).

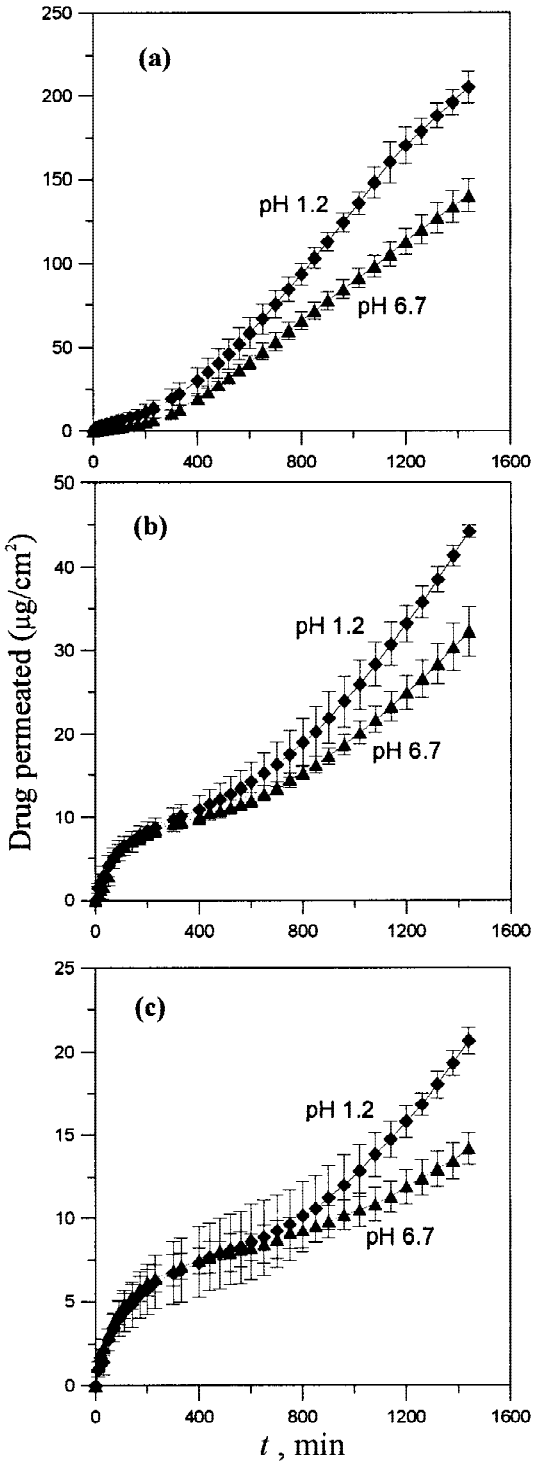

Fig. 3. Accumulated aspirin permeated amount per membrane area ($= Q/A$) as a function of time for (a) I = 0.138, (b) I = 0.5, and (c) I = 1.0. (Eudragit RL/RS = 50/50 v/v%, Talc = 0.5%, DBP = 20%, donor concentration = 5 mg/ml, and $n = 4$).

Unlike the initial permeability, the pseudo steady state (Stage II for ambroxol and Stage III for aspirin) permeability for each drug highly depends on the ionic strength and pH of the medium (Fig. 6). The pseudo steady-state permeability decreases significantly as the ionic strength of the medium increases. The permeability of aspirin is higher at pH 1.2 than

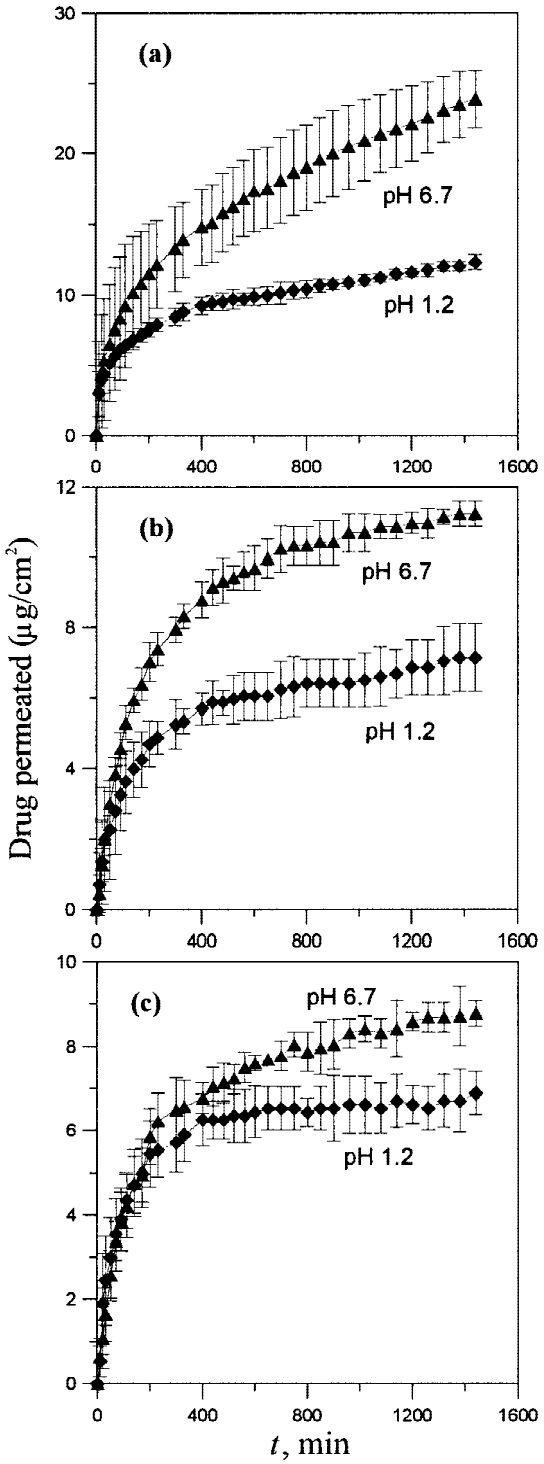

Fig. 4. Accumulated ambroxol permeated amount per membrane area (= Q/A) as a function of time for (a) I = 0.138, (b) I = 0.5, and (c) I = 1.0. (Eudragit RL/RS = 50/50 v/v%, Talc = 0.5%, DBP = 20%, donor concentration = 5 mg/ml, and n = 4).

that at pH 6.7, and that of ambroxol is lower at pH 1.2 than that at pH 6.8. The trends are the same as those of the degrees of membrane swelling in the buffered drug solutions (Fig. 2). It seems that the degree of swelling plays an important role in drug permeation. According to Yasuda's free volume theory, the higher degree of swelling of membrane would result in

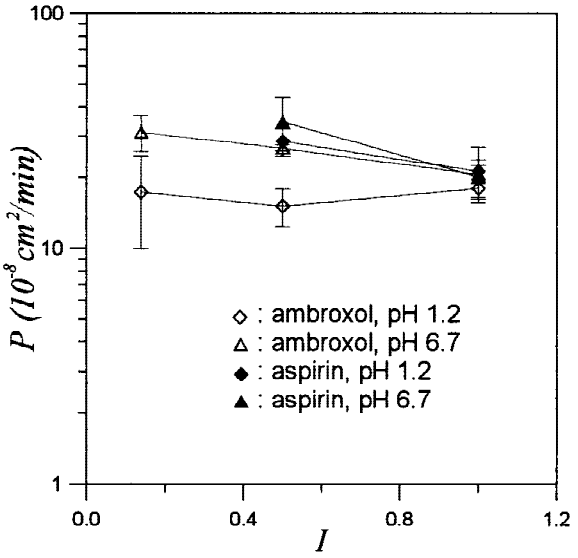

Fig. 5. Initial drug permeability through the membranes as a function of ionic strength at pH = 1.2 and 6.7. (Eudragit RL/RS = 50/50 v/v%, Talc = 0.5%, DBP = 20%, drug concentration = 5 mg/ml, and n = 4).

larger free volume available for diffusion of water-soluble drug and thus higher permeability is obtained in a consequence (17).

The pseudo steady-state permeability also depends on the drug species. Ambroxol has much lower pseudo steady-state permeabilities than aspirin in media of the same ionic strength and pH (Fig. 6), although the membrane encountering ambroxol experiences higher degree of swelling than that encountering aspirin. The large difference in permeabilities cannot be solely correlated by their relative molecular sizes. Donnan exclusion of the membrane to its co-ion (ions with charge of the same sign) is responsible for the much lower permeability of ambroxol. In addition to the effect of the

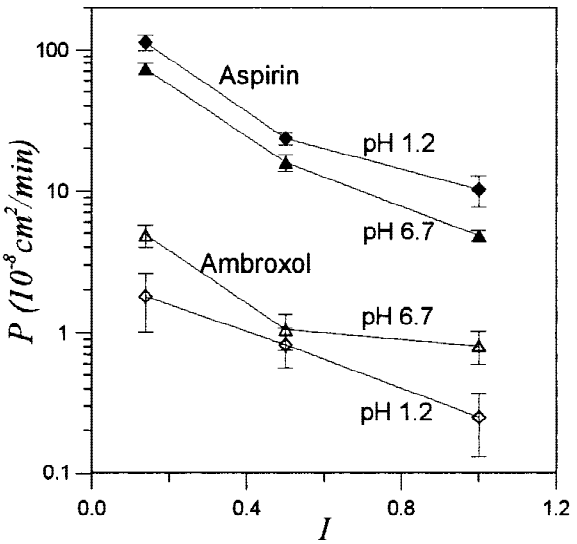

Fig. 6. Pseudo steady-state drug permeability through the membranes as a function of ionic strength at pH = 1.2 and 6.7. (Eudragit RL/RS = 50/50 v/v%, Talc = 0.5%, DBP = 20%, drug concentration = 5 mg/ml, and n = 4).

degree of swelling, the interaction of the ionic drug species with the membranes strongly determines the permeation rates as well as the permeation behaviors of the drug transport through the membranes.

CONCLUSIONS

In the drug-free buffered solutions, the degree of swelling for the ammonio methacrylate membranes is independent of pH but depends on the ionic strength of the solutions. With the presence of ionic drugs, the degree of membrane swelling is related to the drug species as well as the pH of the solutions in addition to the effect of ionic strength. The degree of membrane swelling in a buffered ambroxol solution is similar (pH 6.7) to or 20% lower (pH 1.2) than that of a buffered drug-free solution. On the other hand, the degree of membrane swelling in an aspirin solution is largely reduced (48 and 65% lower than that in a drug-free solution) because of the ionic interaction between the cationic ammonio groups in the membranes and the carboxylic groups in aspirin. The degree of swelling for membranes in the solution containing aspirin is higher at lower pH and ambroxol is lower at lower pH. The degree of the dissociation of ionic drugs may vary due to the change of pH in the solutions so that the ionic strength of the solutions varies accordingly. It is the ionic strength of the solution that dominates the membrane swelling instead of the solution pH itself.

The permeation of ionic drugs is strongly affected by the ionic interaction between the drug species and the quaternary ammonio groups in the membranes. In a transient permeation, there is an initial fast permeation for both model drugs possibly because of a non-interactive transport mechanism. Ambroxol may have a cationic repulsive interaction with the membranes so that it attains a slow pseudo-steady state permeation after the initial fast permeation and performs a two-stage behavior. Anionic carboxylic groups in aspirin can interact with the cationic ammonio groups in the membranes and an ion-exchange reaction occurs. The permeation rate is reduced because of the ion-exchange reaction and results in the slow down after the initial fast permeation. When all the cationic sites are saturated with the anionic permeates, the permeation tends to achieve a pseudo-steady state at a higher rate comparable to the magnitude of the initial fast permeation rate. Aspirin experiences a three-stage permeation. The pseudo steady-state permeability for each drug depends on the ionic strength and pH of the solution as it can be qualitatively explained by the Yasuda's free volume theory according to their relative values of the degree of membrane swelling data. However, it is much higher for aspirin than ambroxol although the degree of membrane swelling is higher in ambroxol solution than that in aspirin solution. The pseudo-steady state permeability of the ambroxol is largely reduced resulting from the Donnan exclusion effect. It has been demonstrated that the interaction between the ionic drug species with the cationic groups in the membranes highly determines the drug permeation rates as well as the permeation transient behaviors.

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REFERENCES

1. A. J. Shukla. Polymethacrylates. In A. Wade and P. J. Weller, (eds.), *Handbook of Pharmaceutical Excipients,* American Pharmaceutical Association, Washington DC, 1994 pp. 362–366.
2. K. O. R. Lehmann. Chemistry and application properties of polymethacrylate coating system. In J. W. McGinity (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Dosage Form,* Chap. 4., Marcel Dekker, New York, 1994 pp. 101–176.
3. I. Ghebre–Sellassie, R. U. Nesbitt, and J. Wang. Eudragit aqueous dispersions as pharmaceutical controlled release coatings. In J. W. McGinity, (ed.), *Aqueous Polymeric Coatings for Pharmaceutical Dosage Form,* Chap. 7, Marcel Dekker, New York, 1997 pp. 267–286.
4. K. O. R. Lehmann. Acrylic latices from redispersible powders for oral and transdermal drug formulations. *Drug Dev. Ind. Pharm.* **12**:265–287 (1986).
5. P. J. Watts, M. C. Davies, and C. D. Melia. Encapsulation of 5-aminosalicylic acid into Eudragit RS microspheres and modulation of their release characteristics by use of surfactants. *J. Control. Release* **16**:311–318 (1991).
6. T. Baykara and A. Karatas. Preparation of acetaminophen microcapsules by coaservation-phase separation method. *Drug Dev. Int. Pharm.* **19**:587–601 (1993).
7. T. Kristmundsdóttir, Ó. S. Gudmundsson, and K. Ingvarsdóttir. Release of diltiazem from Eudragit microparticles prepared by spray-drying. *Int. J. Pharm.* **137**:159–165 (1996).
8. R. S. Okor. Effect of polymer cation content on certain film properties. *J. Pharm. Pharmacol.* **34**:83–86 (1981).
9. X. D. Guo, R. Sarabia, P. Skultety, and R. Bodmeier. The effect of buffer species on hydration and mechanical properties of polymeric films prepared from aqueous colloidal cationic polymer dispersions. *Polym. Preprints* **34**:633–634 (1993).
10. B. A. Firestone and R. A. Siegel. pH, salt, and buffer dependent swelling in ionizable copolymer gel: Test of the ideal Donnan equilibrium theory. *J. Biomater. Sci., Polym. Ed.* **5**:433–450 (1994).
11. H. Yoshino, S. Narisawa, M. Nagata, Y. Hirakawa, C. Danyoshi, K. Murata, and K. Noda. An organic acid-induced sigmoidal release system for oral controlled-release preparations. *Pharm. Res.* **11**:111–116 (1994).
12. H. Yoshino, S. Narisawa, M. Nagata, Y. Hirakawa, and M. Kobayashi. An organic acid-induced sigmoidal release system for oral controlled-release preparations. III Elucidation of the anomalous drug release behavior through osmotic pumping mechanism. *Int. J. Pharm.* **148**:85–91 (1997).
13. R. Bodmeier, X. Guo, R. E. Sarabia, and P. F. Skultety. The influence of buffer species and strength on diltiazem HCl release from beads coated with the aqueous cationic polymer dispersions, Eudragit RS, RL 30 D. *Pharm. Res.* **13**:52–56 (1996).
14. Y.-M. Sun, Huang, W.-F., and C.-C. Chang. Spray-coated and solution-cast ethylcellulose pseudolatex membranes. *J. Membr. Sci.* **157**:159–170 (1999)
15. K. A. Smith, C. K. Colton, E. W. Merrill, and L. B. Evans. Convective transport in a batch dialyzer: Determination of true membrane permeability from a single measurement. *Chem. Eng. Prog. Symp. Ser.* **64**:45–58 (1968).
16. Y.-M. Sun and J. N. Chang. Solute transport in poly(2-hydroxyethyl methacrylate) hydrogel membranes. *J. Polym. Res.* **2**:71–82 (1995).
17. H. Yasuda, A. Peterlin, C. K. Colton, K. A. Smith, and E. W. Merrill. Permeability of solutes through hydrated polymer membranes. *Die Makro. Chem.* **126**:177–186 (1969)
18. S. Narisawa, M. Nagata, T. Ito, H. Yoshino, Y. Hirakawa, and K. Noda. Drug release behavior in gastrointestinal tract of beagle dogs from multiple unit type rate-controlled or time controlled release preparations coated with insoluble polymer-based film. *J. Control. Release* **33**:253–260 (1995).
19. Eudragit® RL/RS, *Technical Application Pamphlet* (info RL/RS 12/e), Röhm Phama, Darmstadt, Germany.

20. J. Akbuga and N. Bergisadi. Effect of drug properties on physical and release characteristics of Eudragit microspheres prepared by spherical crystallization technique. *Drug Dev. Int. Pharm.* **23**:407–411 (1997).
21. E. L. Cussler. *Diffusion: Mass Transfer in Fluid Systems* (2nd Ed.), Cambridge University Press, Cambridge, 1997 pp. 32–34.
22. Y.-M. Sun. Sorption/desorption properties of water vapor in poly(2-hydroxyethyl methacrylate): II. Two-stage sorption models. *Polymer* **37**:3921–3928 (1996).
23. M. Mulder. *Basic Principles of Membrane Technology,* Kluwer, Dordrecht, 1991 pp. 192–196.
24. S.-T. Hwang and K. Kammermeyer. *Membranes in Separations,* Wiley, New York, 1975 pp. 136–138.
25. S. Narisawa, M. Nagata, Y. Hirakawa, M. Kobaayashi, and H. Yoshino. An organic acid-induced sigmoidal release system for oral controlled-release preparations. 2. Permeability enhancement of Eudragit RS coating led by the physicochemical interaction with organic acid. *J. Pharm. Sci.* **85**:184–188 (1996).