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Research Article

Kinetics of Drug Loading onto Cation-exchange Resins and Effect of Concurrent Counter-ions

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ABSTRACT: The patterns of chlorpheniramine loading onto cation-exchange resins with and without concurrent counter-ions were investigated. All of them were found to give the best fit with the model according to film diffusion-controlled process. The existence of concurrent counter-ions has a varying degree of influence on drug loading onto the resins depending on the ionic size and the concentration of concurrent counter-ions. The smaller concurrent counter-ions competed the charged drug more effectively than the larger ions. The competition dramatically increased with an increase in the concentration of concurrent counter-ions. However, at low concentrations of drug solution, the pattern of chlorpheniramine loading and the equilibrium of the exchange process were not changed.

KEY WORDS: cation-exchange resin, kinetic, drug loading, concurrent counter-ions

INTRODUCTION

The passage of a charged drug, as well as an ion, through an ion-exchange resin involves the exchange process between the ion attached on the resin and that presented in the surrounding solution. Ions having electrical charge opposite to the fixed charge of the ion-exchange resin are generally called counter-ions. On the other hand, ions processing the same charge as the fixed charge of the ion exchange resin are called co-ions which are normally not involved in the ion-exchange process (1, 2). The mechanisms of drug loading onto and drug release from the ion-exchange resins are attributed to one of the three distinct kinetic processes; chemical reaction-controlled process, film diffusion-controlled process and particle diffusion-controlled process (3, 4, 5). However, all the exchange kinetics which have appeared in the literature to date, none have been shown to be controlled by the chemical process (1). Boyd et al were the first to derive precise expressions for both the film diffusion-controlled process and the particle diffusion-controlled process (3). Consequently, Reichenberg et al had modified Boyd's model of particle diffusion-controlled process to the more simple approximate expressions (7). Bhaskar et al proposed another directly simple and elegant expression to test for particle diffusion-controlled process and to determine the diffusibility value (6). Several reports have shown successful results from employing these approaches to determine the pattern of drug release from the ion-exchange resin but none of them have been applied to study the pattern of drug loading onto the resins (5, 8-15).

There were several reports which studied the factors influencing the rate of drug passing through an ion-exchange resin and the amount of drug loading, i.e., the degree of crosslinking and particle size of an ion-exchange resin (8, 10), valency, molecular structure and the concentration of charged drug (8, 11) or competitive ion (16, 17), temperature, stirring speed and pH of the surrounding solution (10, 12). There is lack of report which explained the influence of concurrent counter-ions despite the fact that they are commonly present in some situations such as in the gastrointestinal tract and in a mixture of sample for drug analysis and purification. Therefore, the purposes of this investigation were to employ the above approaches to determine the pattern of drug loading onto ion-exchange resin and also to study the influence of concurrent counter-ions on drug loading. In this study, chlorpheniramine maleate was used as a model drug because of its avialability and ease of analysis. The rate of drug loading, as repre-

sented by the diffusion or permeability coefficient, and the amount of drug loading, as represented by the percent of drug exchange at equilibrium, were determined and discussed.

MATERIALS AND METHODS

Materials

Cation-exchange resins (particle size 100-200 mesh) having 2% crosslinking (Dowex® 50W×2), and 8% crosslinking (Dowex® 50W×8) were from Sigma Chemical Company. Chlorpheniramine meleate (Pharmaceutical Trader), Sodium chloride (Farmitalia Carlo Erba), Calcium choride (Merck), Magnesium chloride (Merck), Aluminum chlrohydrate 50% w/v (P.C. Drug Center) were used as received.

Methods

Purification of cation-exchange resins

Prior to use, five grams of the cation-exchange resins were washed three times with 100 ml of purified water. Then, they were collected by filtration with filter paper and were kept in desiccator until investigation.

Determination of particle size

The particle size of cation-exchange resins was determined by microscopy. About five hundred particles were measured at magnification 10×40 and were later calculated for the average particle size.

Determination of moisture content

The moisture content of the washed resins were investigated by automatic thermo control infrared dryer (Sartorius YTC 01L). Briefly, one gram of resins spread on an aluminum dish was constantly heated at temperature of 160 °C until the ratio of loss of moisture over time (50 sec.) was less than 0.1% w/w. Then, the relative moisture content was automatically calculated and displayed.

Investigation of chlorpheniramine loading onto cation-exchange resins

Apparatus setting

The apparatus used for investigation of chlorpheniramine loading onto the resins consisted of a continuous flow cell UV spectrophotometer (Perkin Elmer Lamda-2) connecting to a peristaltic pump, with Teflon tubing of diameter 2.0 mm. Both ends of the tubing were immersed in the exchange chamber, a 150 ml of covered beaker, which was placed on a magnetic stirrer.

Effect of concurrent counter-ions

One hundred milliliters of chlorpheniramine maleate solution (0.5 meq/L) containing different concurrent counter-ions were prepared in the exchange chamber. The concentrations of concurrent counter-ions are shown in Table 1. Then, 250 mg of cation-exchange resins were accurately weighed and added in the solution. The mixture was constantly agitated by a magnetic bar and was left to exchange at room temperature. At the moment, the supernatant was circulated through prefilter and the absorbance was continuously measured at wavelength of 261 nm. The content of chlorpheniramine loaded onto the resins was investigated by extrapolating the absorbances from the calibration curve of chlorpheniramine standard solution. All preparations were studied in duplicate.

Table 1 The type and the concentration of concurrent counter-ions contain in each preparation

No	Type of resin	Concurrent counter-ions (meq/L)			
		Na^+	Mg^{2+}	Ca^{2+}	Al^{3+}
1	Dowex® 50W×2	–	–	–	–
2	Dowex® 50W×2	0.5	–	–	–
3	Dowex® 50W×2	–	0.5	–	–
4	Dowex® 50W×2	–	–	0.5	–
5	Dowex® 50W×2	–	–	–	0.5
6	Dowex® 50W×8	–	–	–	–
7	Dowex® 50W×8	0.5	–	–	–
8	Dowex® 50W×8	–	0.5	–	–
9	Dowex® 50W×8	–	–	0.5	–
10	Dowex® 50W×8	–	–	2.5	–
11	Dowex® 50W×8	–	–	–	0.5

RESULTS AND DISCUSSION

Characteristic of cation-exchange resins

In this study, Dowex® 50W×2 and Dowex® 50W×8 were representative of low crosslinking resins (2%) and high crosslinking resins (8%), respectively. Both resins are hydrogen-form sulfonated copolymers of styrene and divinylbenzene. They are spherical particles and their re-

spective arithmetic mean diameters measured microscopically are 113.88 μm and 180.51 μm. After being dried overnight at 50 °C in hot air oven, their moisture contents were close to each other (17.56% and 18.55%).

Kinetics of chlorpheniramine loading onto cation-exchange resins

All the kinetic studies of drug release from the resins have been published in the literature but none have been published with respected to the approach according to the chemical-reaction controlled process. In practice, therefore, it is appropriate to confine this discussion to the drug release controlled only by the particle diffusion and the film diffusion processes.

Approaches according to the particle diffusion-controlled process

The expression of the particle diffusion-controlled process employed for fitting the pattern of drug release from cation-exchange resin had originally been presented by Boyd et al (3).

$$F = 1 - \frac{Q_t}{Q_o} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \exp(-n^2 Bt) \quad \text{Eq. 1}$$

$$B = 4\pi^2 \frac{D}{(d_p)^2} \quad \text{Eq. 2}$$

Eq. 1 was applicable for complete drug release. In case of uncompleted drug release or the system being at equilibrium, Eq. 1 was modified as in the following:

$$F = \frac{Q_0 - Q_t}{Q_0 - Q_{eq}} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \exp(-n^2 Bt) \quad \text{Eq. 3}$$

Where the variables in Eq. 1 and Eq. 2 are intermediate variables (B, min^{-1}), inital drug content of resin (Q_0, g/g), drug content of resin at any time (Q_t, g/g), drug content of resin at the last time or drug content of resin at equilibrium (Q_{eq}, g/g) fraction of dissolution value (F), diameter of resin (d_p, mm), diffusion coefficient (D, mm^2/min) and time (t, min).

Reichenberg et al simplified Eq. 1 to obtain two following approximations (7).

$$Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi \left(1 - \frac{\pi F}{3}\right)^{\frac{1}{2}} \quad \text{For } F \le 0.85 \quad \text{Eq. 4}$$

$$Bt = -\log_e \frac{\pi^2}{6}(1 - F) \quad \text{For } F > 0.85 \quad \text{Eq. 5}$$

By substituting F (from dissolution studies) at different times in either Eq. 4 or Eq. 5, depending on the magnitude of F, produced corresponding Bt. A plot of the time against the corresponding values of Bt provides a linear plot if the pattern of drug release from the ion-exchange resins follows the particle diffusion-controlled process (7). Then, the slope of the plot is B and the diffusion coefficient may be calculated from Eq. 2.

Supposing that the particle diffusion-controlled process is responsible for both the kinetics of drug loading onto and the drug release from the resins (1, 4), Reichenberg et al's expressions could be used to determine the pattern of drug loading onto the resins. The reaction of the exchange process has reached the equilibrium so Eq. 3 should be applied to the investigation. However, the direction of the drug loading was opposed to the drug release, the definition of variables in the above equations had to be slightly modified as in the followings; Q_o, Q_t, Q_{eq} and F were replaced by; Q^*_o, Q^*_t, Q^*_{eq} and F_{in}, respectively. Where Q^*_o is the initial drug content in the loading solution, Q^*_t is the drug content in loading solution at any time, Q^*_{eq} is the drug content in loading solution at equilibrium and F_{in} is the fraction of drug loading in the resins at any time. Therefore, to determine the pattern of drug loading, Eq. 3-5 have to be modified as in the followings:

$$F = \frac{Q^*_0 - Q^*_t}{Q^*_0 - Q^*_{eq}} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \exp(-n^2 Bt) \quad \text{Eq. 6}$$

$$Bt = 2\pi - \frac{\pi^2 F_{in}}{3} - 2\pi \left(1 - \frac{\pi F_{in}}{3}\right)^{\frac{1}{2}} \quad \text{For } F_{in} \le 0.85 \quad \text{Eq. 7}$$

$$Bt = -\log_e \frac{\pi^2}{6}(1 - F_{in}) \quad \text{For } F_{in} > 0.85 \quad \text{Eq. 8}$$

Substituting Q^*_o, Q^*_t, and Q^*_{eq} at different times in Eq. 6 produced a series of F_{in} values which were further substituted in either Eq. 7 or Eq. 8, depending upon the magnitude of F_{in}, provided the corresponding values of Bt at different times. The values of Bt were plotted against t and

the slopes were calculated for Reichenberg et al's diffusion coefficient (D_R) as shown in Figure 1 and Figure 2, Table 2 and Table 3, respectively.

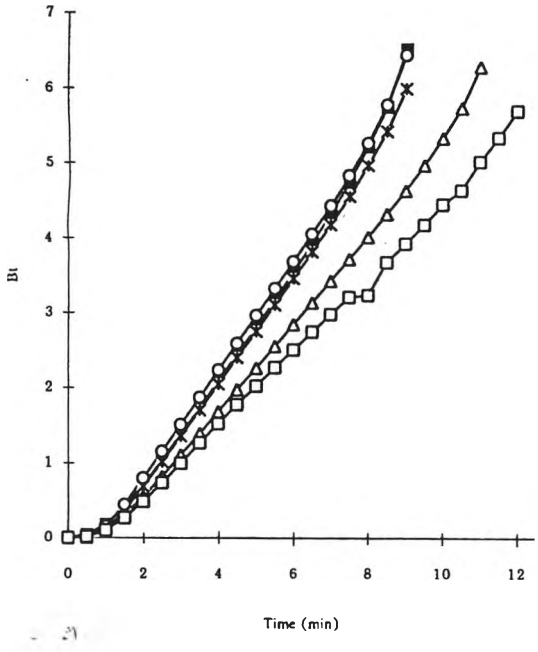

Figure 1 The relationships between Bt and t of chlorpheniramine loading onto the low crosslinking resins (2%) with and without concurrent counterions; None (■), Na^+ (✳), Ca^{2+} (O), Mg^{2+} (Δ), and Al^{3+} (□).

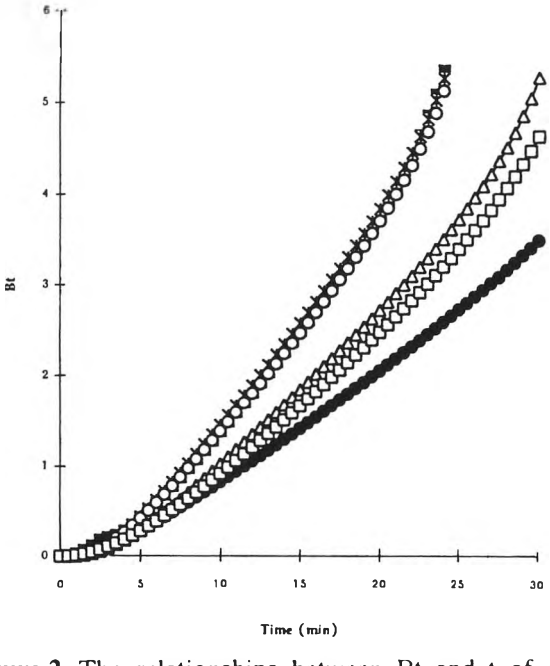

Figure 2 The relationships between Bt and t of chlorpheniramine loading onto the high crosslinking resins (8%) with and without concurrent counterions; None (■), Na^+ (✳), 0.5 meq/L of Ca^{2+} (●), Mg^{2+} (Δ), and Al^{3+} (□).

Bhaskar et al had proposed another approach to test the drug release controlled by particle diffusion process (6). The original expression had been presented in his work so it did not need to be displayed in this study. To determine the pattern of drug loading onto the resins, the expression has to be slightly modified as described above and the final expression is:

$$-\ln(1-F_{in}) = -\ln \frac{Q^{\bullet}_0 - Q^{\bullet}_t}{Q^{\bullet}_0 - Q^{\bullet}_{eq}} = 1.59\left(\frac{6}{d_p}\right)^{1.3} D_B^{0.65}\, t^{0.65} \quad \text{Eq. 9}$$

It was suggested that particle diffusion-controlled process can be sufficiently tested by simply testing for linearity between $-\ln(1-F_{in})$ and $t^{0.65}$. The slope of the resulting straight line is related to the Bhaskar et al's diffusion coefficient (D_B) according to.

$$D_B = \frac{d_p^2}{36}\left(\frac{\text{slope}}{1.59}\right)^{\frac{1}{0.65}} \quad \text{Eq. 10}$$

Substituting $Q^{\bullet}_0$, $Q^{\bullet}_t$, and $Q^{\bullet}_{eq}$ at different times in Eq. 9 produced a series of F_{in} values which were further calculated for $-\ln(1-F_{in})$. The values of $-\ln(1-F_{in})$ were plotted against $t^{0.65}$ and the slopes were calculated for Bhaskar et al's diffusion coefficient (D_B) as shown in Figure 3 and Figure 4, Table 2 and Table 3, respectively.

Approach according to the film diffusion-controlled process

Boyd et al (3) derived the equation for an exchange rate controlled by film diffusion process (diffusion through a bounding liquid film). The equation for drug loading onto the resins and the system being at equilibrium may be written as in the following.

$$-\ln(1-F_{in}) = -\ln\left(\frac{Q^{\bullet}_0 - Q^{\bullet}_t}{Q^{\bullet}_0 - Q^{\bullet}_{eq}}\right) = \frac{3Dt}{d_p \Delta dK} \quad \text{Eq. 11}$$

Where Δd is the thickness of bounding liquid film and K is the distribution coefficient. Assuming that Δd and K are constant in each resin and defining the constant P by $\frac{D}{\Delta dK}$, Eq. 11 changes to be

$$-\ln(1-F_{in}) = -\ln\left(\frac{Q^{\bullet}_0 - Q^{\bullet}_t}{Q^{\bullet}_0 - Q^{\bullet}_{eq}}\right) = \frac{3Pt}{d_p} \quad \text{Eq. 12}$$

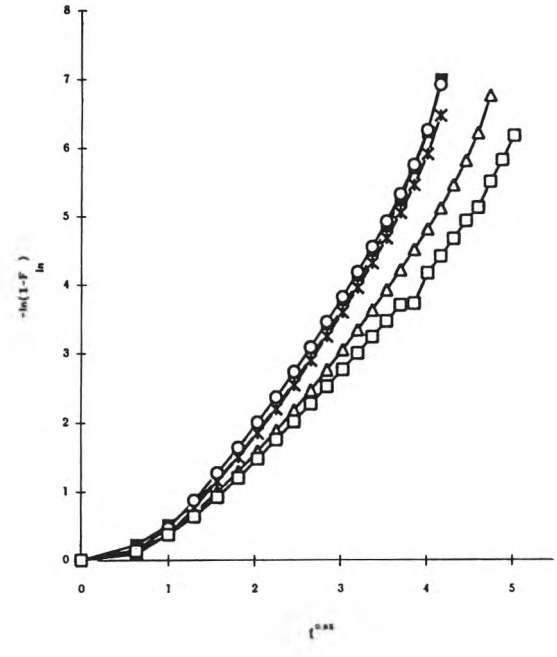

Figure 3 The relationships between $-\ln(1-F_{in})$ and $t^{0.65}$ of chlorpheniramine loading onto the low crosslinking resins (2%) with and without concurrent counter-ions; None (■), Na^+ (✳), Ca^{2+} (O), Mg^{2+} (Δ), and Al^{3+} (□).

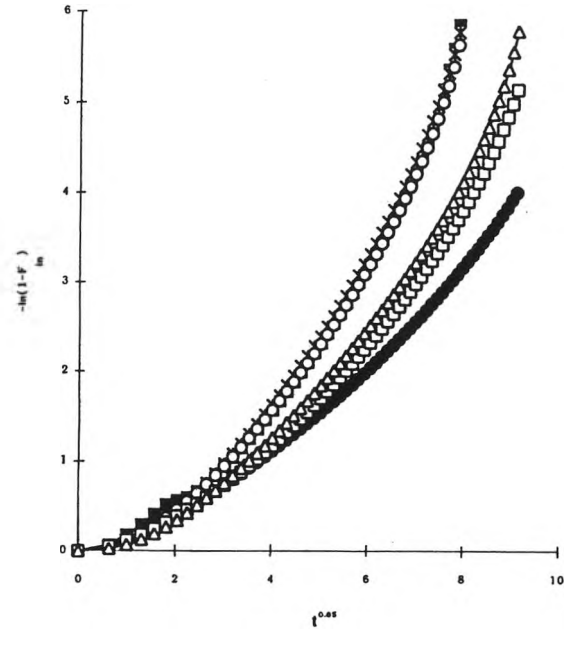

Figure 4 The relationships between $-\ln(1-F_{in})$ and $t^{0.65}$ of chlorpheniramine loading onto the high crosslinking resins (8%) with and without concurrent counter-ions; None (■), Na^+ (✳), 0.5 meq/L of Ca^{2+} (O), Mg^{2+} (Δ), and Al^{3+} (□).

P is known as permeability. The plot of $-\ln(1-F_{in})$ and the time will provide a linear line with a constant slope if the pattern of drug loading onto the resins was controlled by film diffusion process. The permeability is determined from the slope by Eq. 13.

$$P = \frac{(\text{Slope})d_p}{3} \qquad \text{Eq. 13}$$

Substituting Q^*_o, Q^*_t, and Q^*_{eq} at differnt times in Eq. 12 produced a series of F_{in} values which were further calculated for $-\ln(1-F_{in})$. The values of $-\ln(1-F_{in})$ were plotted against t and the slops were calculated for permeability (P) as shown in Figure 5 and Figure 6, Table 2 and Table 3, respectively.

The fractions (F_{in}) of chlorpheniramine loading onto the resins at different times were attempted to fit with all approaches. The linearity of each fit as represented by coefficient of determination (R^2) was calculated by regression analysis and was compared. The results revealed that the patterns of chlorpheniramine loading onto the resins, with and without concurrent counter-ions, gave the best fit to the approach of Boyd et al according to the film diffusion-controlled process. Also, they had satisfactory fits with Reichenberg et al's approach for particle-diffusion-controlled process. However, with another approach for particle diffusion-controlled process (Bhaskar et al's model), they showed unsatisfactory relationships. It may be concluded that the patterns of chlorpheniramine loading onto the resins were predominantly controlled by the film diffusion process.

Effect of degree of crosslinking

The rate of drug loading onto the resin with low degree of crosslinking was greater than with high degree of crosslinking while the percent of drug exchange was similar as shown in Table 2 and Table 3. It has been recognized that the rate of drug release from a resin decreases with an increasing degree of resin crosslinking (5, 8, 10). Because the resin with higher degree of crosslinking has a tighter pore structure, this should lead to greater resistance for drug release. Also, the explanation could be accounted for the effect of degree of crosslinking on the rate of drug loading. The amount of drug exchange obatined from low crosslinking resin was close to that from high crosslinking which was not complied with the previous studies (8-10). Regardless of procedure for determining drug exchange/

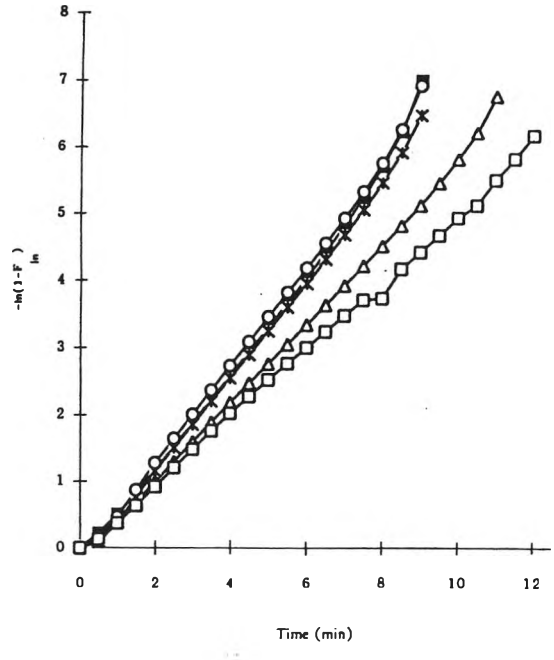

Figure 5 The relationships between $-\ln(1-F_{in})$ and t of chlorpheniramine loading onto the low crosslinking resins (2%) with and without concurrent counter-ions; None (■), Na^+ (✳), Ca^{2+} (O), Mg^{2+} (Δ), and Al^{3+} (□).

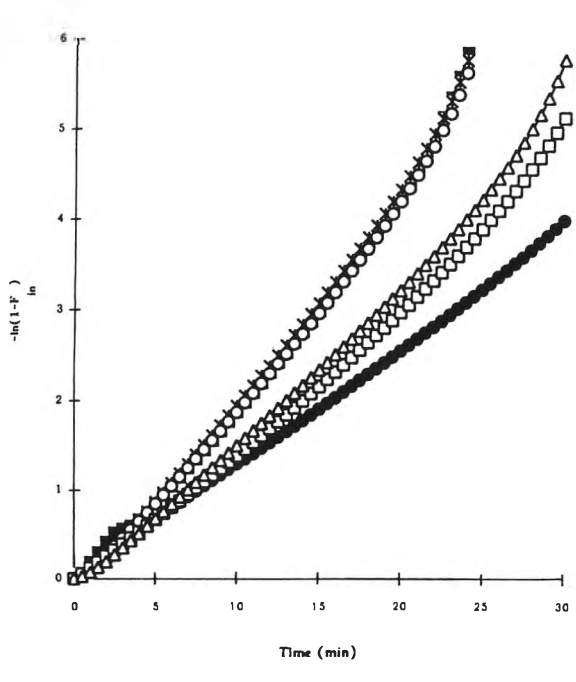

Figure 6 The relationships between $-\ln(1-F_{in})$ and t of chlorpheniramine loading onto the high crosslinking resins (8%) with and without concurrent counter-ions; None (■), Na^+ (✳), 0.5 meq/L of Ca^{2+} (O), 2.5 meq/L of Ca^{2+} (●) Mg^{2+} (Δ), and Al^{3+} (□).

content, the amount of drug exchange generally tended to decrease with an increasing degree of resin crosslinking. However, the proportion of the charged drug solution employed in this study to the total exchange capacity of the cation-exchange resin was much lower than the earlier studies. A this condition, the exchange reaction of any exchange system is very effective (1). Therefore, the effect of crosslinking was negligible and the results were similar between the two resin systems.

Effect of concurrent counter-ions

The amount of chlorpheniramine exchange in surrounding solution with and without different concurrent counter-ions were presented in Table 2 and Table 3. The results indicated that the amount of drug loading was not affected by the existence of any concurrent counter-ions. The possible explanation may be that the concentration of charged chlorpheniramine solution compared to the total maximum capacity of the cation-exchange resin was extremely low. At this condition, in spite of competition from concurrent counter-ions, there are excess of exchange sites on the cation-exchange resin for binding or exchange with the charged drug. Then, the equilibrium of the exchange reaction is likely to remain constant.

The patterns of chlorpheniramine loading onto the resin with and without concurrent counter-ions were fitted best with the approach according to the film diffusion-controlled process. Therefore, the permeability was employed as an indicator to study the effect of concurrent counter-ions. The permeability of each preparation was calculated and was presented in Table 2 and Table 3. Although the co-ions automatically existed in the exchange system, it had no significant impact (1). Since the influence of the concurrent counter-ions on both the lowly and the highly crosslinked resins was similar, they will be simultaneously discussed. By comparing with the system without concurrent counter-ions, the existence of Ca^{2+} as well as Na^+ has no significant effect on the rate of drug loading, while that of Ma^{2+} and Al^{3+} could considerably reduce the permeability. However, the rate of drug loading dramatically reduced with an increase in the concentration of Ca^{2+}. This indicates that the existence of the counter-ions has a varying degree of influence on the rate of drug loading onto the resins depending on the type and the concentration of the concurrent counter-ions. The rate of drug loading, represented by permeability, tended to decrease in the presence of different concurrent counter-ions as in the following order; Ca^{2+} ~

Table 2 Effect of concurrent counter-ions on the drug exchange at equilibrium and the rate of drug loading onto the low crosslinking cation-exchange resins (Dowex® 50W×2)

Process	The drug exchange at equilibrium (% w/w)	Particle diffusion-controlled processes						Film diffusion-controlled process		
Models		Reichenberg et al' model			Bhaskar et al' model			Boyd et al' model		
Type of concurrent counter ions (meq/L)		Slope	R^2	D_R (mm^2/sec) $\times 10^{-4}$	Slope	R^2	D_B (mm^2/sec) $\times 10^{-4}$	Slope	R^2	P (mm/sec) $\times 10^{-2}$
None	90.16	0.6383	0.9562	2.0952	1.3634	0.8774	2.8436	0.7139	0.9836	2.7100
Na^+ (0.5)	98.68	0.6149	0.9664	2.0183	1.3368	0.8906	2.7587	0.6868	0.9896	2.6071
Ca^{2+} (0.5)	89.83	0.6361	0.9703	2.0857	1.3459	0.9004	2.7876	0.7168	0.9927	2.7210
Mg^{2+} (0.5)	89.63	0.5221	0.9651	1.7137	1.1952	0.8913	2.3221	0.5849	0.9882	2.2203
Al^{3+} (0.5)	89.72	0.4513	0.9741	1.4813	1.0834	0.9074	1.9965	0.5073	0.9911	1.9257

Table 3 Effect of concurrent counter-ions on the drug exchange at equilibrium and the rate of drug loading onto the high crosslinking cation-exchange resins (Dowex® 50W×8)

Process	The drug exchange at equilibrium (% w/w)	Particle diffusion-controlled processes						Film diffusion-controlled process		
Models		Reichenberg et al' model			Bhaskar et al' model			Boyd et al' model		
Type of concurrent counter ions (meq/L)		Slope	R^2	D_R (mm^2/sec) $\times 10^{-4}$	Slope	R^2	D_B (mm^2/sec) $\times 10^{-4}$	Slope	R^2	P (mm/sec) $\times 10^{-2}$
None	90.04	0.1891	0.9262	1.5595	0.5801	0.8489	1.9187	0.2182	0.9682	1.3129
Na^+ (0.5)	98.50	0.1902	0.9395	1.5686	0.5833	0.8630	1.9349	0.2192	0.9779	1.3189
Ca^{2+} (0.5)	91.22	0.1871	0.9285	1.5430	0.5771	0.8508	1.9034	0.2156	0.9697	1.2973
Ca^{2+} (2.5)	91.46	0.1214	0.9308	1.0012	0.4362	0.8590	1.2375	0.1402	0.9668	0.8436
Mg^{2+} (0.5)	92.45	0.1510	0.9270	1.2453	0.5016	0.8499	1.5342	0.1741	0.9676	1.0476
Al^{3+} (0.5)	91.70	0.1407	0.9239	1.1604	0.4769	0.8481	1.4195	0.1628	0.9659	0.9796

$Na^+ > Mg^{2+} > Al^{3+}$. Because of the similar charge, the concurrent counter-ions may be able to compete with the charged drug during loading onto the resin. The ionic radius determined by X-ray measurement of Ca^{2+}, Na^+, Mg^{2+}, Al^{3+} were 0.99, 0.95, 0.65 and 0.55 Å, respectively (19, 20). At equivalent normal concentration, comparision between the decrease in the permeability and the decrease in ionic radius (or size) of the concurrent counter-ions suggests that the concurrent counter-ions with smaller ionic size may relatively compete with the charged drug in loading onto the resins more effectively than the larger ones. Although the effect of the concentration of the concurrent counter-ions on the rate of chlorpheniramine loading was not extensively studied, permeability data of the system containing different concentrations of Ca^{2+} (0.5 and 2.5 meq/L) suggests that the competition dramatically increased with increasing concentration.

CONCLUSION

The slightly modified approaches to determine drug release from the resin can be employed to determine the pattern of drug loading. The patterns of chlorpheniramine loading onto the resin with and without concurrent counter-ions were predominantly controlled by the film diffusion process. At low concentrations of chlorpheniramine maleate solution, the existence of concurrent counter-ions has a varying degree of influence on the rate of drug loading onto the resin depending on the type and the concentration of concurrent counter-ions but it did not affect on the pattern of drug loading and the quilibrium of the exchange process.

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