determined at intervals of from 5 to 20 min. during periods up to 120 min.

As can be seen in Fig. 8, the addition of DMSO to solutions of 3.3×10^{-5} *M* benzalkonium chloride in saline slows the rate of hemolysis, with 15% concentrations of DMSO being more effective than 5% concentrations in this effort. Thus, whereas earlier data seemed to indicate that 15% DMSO actually had the ability to reduce or even prevent preservative-induced hemolysis, the present results show that it is a time-related phenomenon. The same pattern of data was obtained in experiments using DMSO–phenol and DMSO–chlorhexidine diacetate systems. This would seem to reinforce the premise that DMSO exerts a cellular effect on the erythrocyte which results in a reduction in the rate of preservative-induced hemolysis.

Work soon to be reported from this laboratory shows that erythrocytes take up DMSO from solution and resist attempts to remove it by washing. Gerhards and Gibian (5) found that in human blood about 30% of injected DMSO is bound to plasma protein and 25% to the formed elements of the blood, the remainder remaining free. Thus, it is not unlikely that the attachment of DMSO to the erythrocyte in some manner affects the vulnerability of the cell toward the preservative agents or alters the permeability barriers of the cell affecting the permeation of the preservative agents into the cell or the exit of hemoglobin from the cell.

Spectral Studies—Preliminary studies of the UV absorption spectra of three preservatives, benzalkonium chloride, chlorhexidine diacetate, and *m*-cresol, alone and in combination with DMSO, were performed to indicate whether or not there is a likelihood of a chemical interaction between DMSO and the preservative agents. The preservatives and DMSO were studied at concentration combinations found to be most inhibitory on preservative-induced hemolysis during the present work. Preliminary data suggest that complexes were not formed. However, more complete studies to rule out complex formation need yet to be made.

In conclusion, the evidence collected more strongly suggests that DMSO interferes with the hemolytic activity of antimicrobial preservatives through a direct action on the erythrocyte or by alteration of its permeability barriers rather than by chemical interaction with the various preservative agents. Further, the degree of this interference is dependent upon the concentrations of both the preservative and DMSO and also upon the length of exposure to these agents.

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Interaction of Amine Drugs with a Polycarboxylic Acid Ion-Exchange Resin

SAUL BORODKIN and MARTIN H. YUNKER

Abstract □ The interaction of polacrilin potassium, the salt of a polycarboxylic acid ion-exchange resin, with 11 amine drugs was studied. All drugs showed maximum interaction at pH 4.5–5.5. Tertiary amines exhibited a much greater affinity for the resin than primary, secondary, and quaternary amines. Selectivity coefficients were used to express the degree of interaction, with experiments showing that these values remain constant over wide variations in resin, drug, and alkali metal concentrations. Rate studies demonstrated that both adsorption of drug onto the resin and elution from the resin are very rapid. The rapid elution rates, along with decreasing resin affinity for amine drugs above pH 6.0, indicate that the presence of polacrilin potassium in a dosage form should not affect total drug availability in the gastrointestinal tract.

Keyphrases □ Polacrilin potassium—interaction, amine drugs □ Amine drugs—interaction, polycarboxylic acid ion-exchange resin □ Ion-exchange chromatography—separation □ UV spectrophotometry—analysis

The use of synthetic polycarboxylic ion-exchange resins in pharmacy and medicine has been quite extensive. Their use in congestive heart failure and edema (1), isolation and purification of streptomycin and other drugs (2), and analysis of drugs (3) is well documented. Adsorbates of amine drugs with carboxylic ion-exchange resins for sustained release (4–7) and taste coverage (8) have been prepared, although to a lesser extent than complexes with sulfonic acid resins.

Because of their unusually large swelling capacities, polymethacrylic carboxylic acid ion-exchange resins have found usage in pharmacy as tablet disintegrants. Van Abbe and Rees (9) reported on the effectiveness of polacrilin potassium[1] as a disintegrating agent, while a later patent (10) describes the use of a similar resin in the acidic form for the same purpose. Being cation exchangers, however, these insoluble polymers have the capability of adsorbing amine drugs, thus possibly interfering with drug availability and assay. This potential incompatibility may have limited the use of these resins as tablet disintegrants to some extent.

The present investigation was undertaken to study the interaction between amine drugs and polacrilin potassium. Eleven commonly used drugs were selected to include primary, secondary, tertiary, and quaternary

[1] Amberlite IRP-88, Rohm and Haas Co., Philadelphia, Pa. Previously sold as Amberlite XE-88.

Table I—Drugs Used in Study

Drug	pKa[a]	$\lambda_{max.}$ (0.08 *N* HCl), mμ
Phenylpropanolamine hydrochloride	9.4	257
Ephedrine base	9.5	257
Pseudoephedrine hydrochloride	9.7	257
Desoxyephedrine hydrochloride	9.5	257
Carbinoxamine maleate	8.1	262
Quinidine sulfate	8.8	280
Methapyrilene hydrochloride	8.8	312
Chromonar hydrochloride	8.3	320
Dextromethorphan hydrobromide	8.3	278
Thiamine mononitrate	—[b]	245
Neostigmine bromide	—[b]	260

[a] The pKa's for carbinoximine and chromonar were determined in this laboratory by potentiometric titration while the others were obtained from the literature. Only the pKa for the most basic amine group in the molecule is listed. [b] Thiamine and neostigmine are quaternary amines.

amines. Although the primary goal of this study was to assess the extent of the potential incompatability in regard to the use of carboxylic acid resins as disintegrating agents, it was believed that the approach taken and information generated might also be useful for other ion-exchange resin applications.

EXPERIMENTAL

Resin—Polacrilin potassium is the potassium salt of a weakly acidic cation-exchange resin with a polymethacrylic acid–divinylbenzene matrix having a particle size range of 100–500 mesh. A single lot was used in all experiments. Assays showed a potassium content of 5.38 meq./g., a total exchange capacity of 6.97 meq./g., and a water content of 18.0% (Karl Fischer).

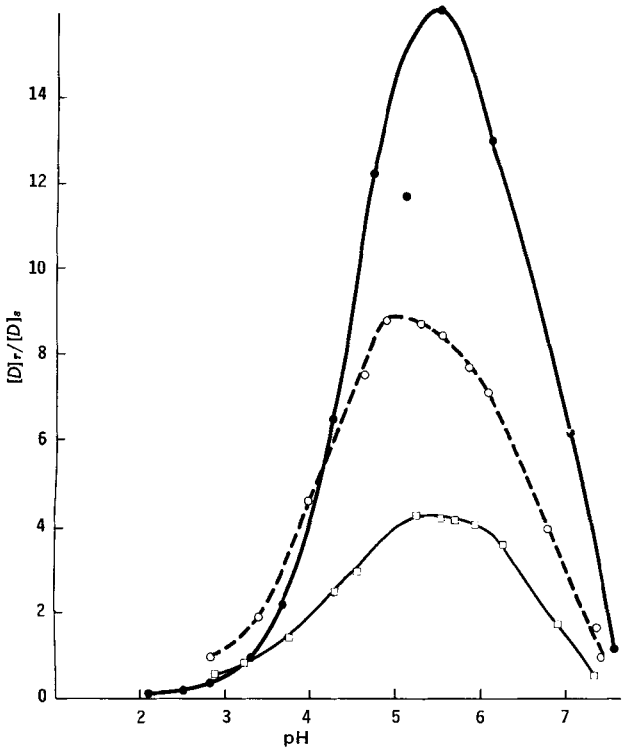

Figure 1—*Effect of pH on drug distribution ratio. Key: ●, quinidine sulfate (1 mg./ml.) + polacrilin K (10 mg./ml.); ○, dextromethorphan HBr (1 mg./ml.) + polacrilin K (10 mg./ml.); and □, dextromethorphan HBr (1 mg./ml.) + polacrilin K (5 mg./ml.).*

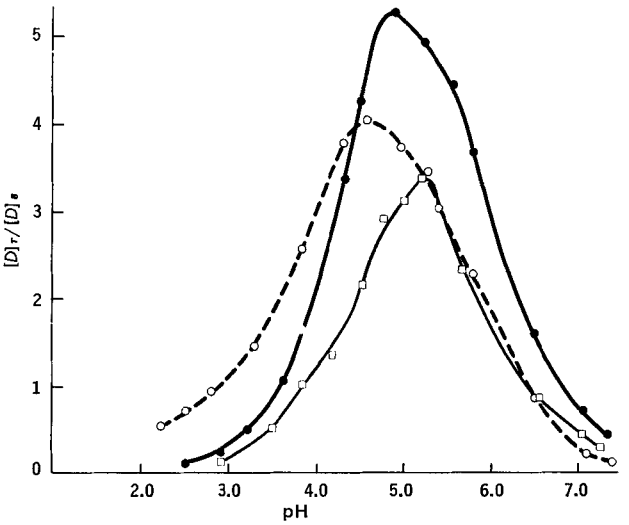

Figure 2—*Effect of pH on drug distribution ratio. Key: ●, methapyrilene HCl (1 mg./ml.) + polacrilin K (10 mg./ml.); ○, chromonar HCl (1 mg./ml.) + polacrilin K (10 mg./ml.); and □, carbinoxamine maleate (0.25 mg./ml.) + polacrilin K (2.5 mg./ml.).*

Drugs—Table I lists the drugs used in this study. Other salt forms would be expected to behave similarly. The UV absorbance maxima used in their analysis and the pKa's are included.

Equilibrium Studies—To establish the relationship between interaction of a drug and pH, a series of 12–14 solutions was prepared to contain 200 mg. drug (except for carbinoxamine maleate where 50 mg. was used), 1.8 g. of sodium chloride (isotonic saline concentration), and various predetermined amounts of hydrochloric acid in 200 ml. of solution. Each solution was added to a 300-ml. bottle along with constant amount (0.5–5.0 g. depending on the drug) of polacrilin potassium, and the bottles were rolled at 24–25°. To improve accuracy, the resin–drug ratios in these experiments were much higher than would normally be used in tablets. After 24 hr. the pH was determined, the resin was separated by filtration, and the drug concentration in the filtrate was determined by UV absorbance using a Beckman DU spectrophotometer after the required dilution with 0.08 *N* HCl. In the case of chromonar, the samples were drawn after 4 hr. as a precaution because of the drug's reported instability. Rate studies with other drugs indicated that adsorption should be close to equilibrium after that time period.

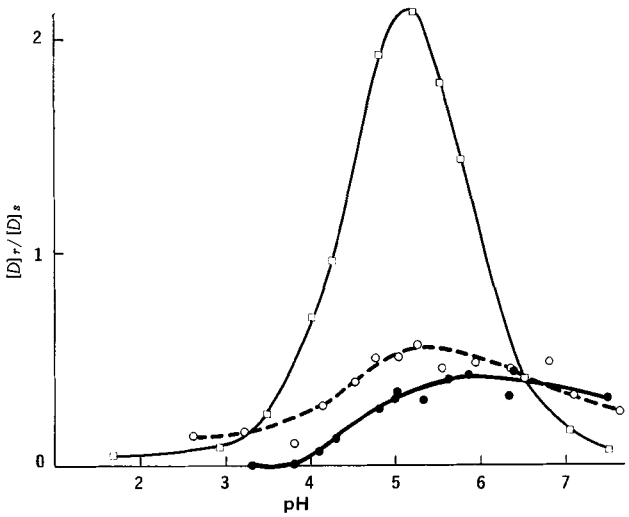

Figure 3—*Effect of pH on drug distribution ratio. Key: ●, phenylpropanolamine HCl (1 mg./ml.) + polacrilin K (25 mg./ml.); ○, ephedrine (1 mg./ml.) + polacrilin K (25 mg./ml.); and □, thiamine mononitrate (1 mg./ml.) + polacrilin K (10 mg./ml.).*

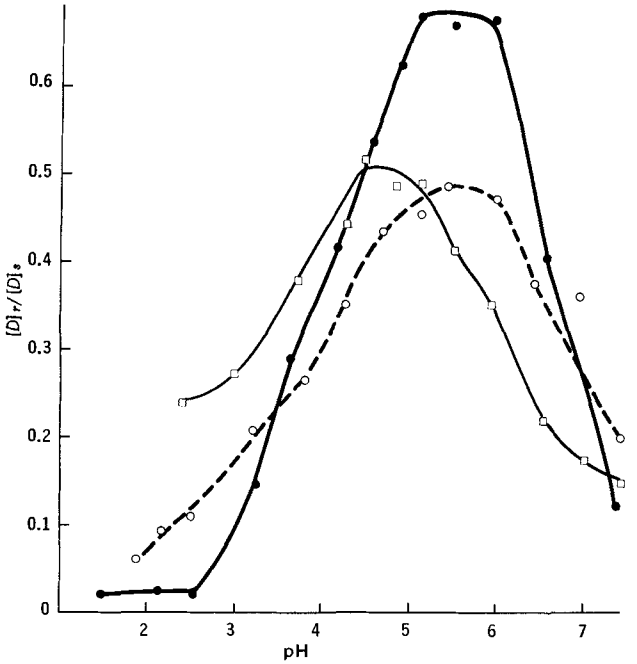

Figure 4—*Effect of pH on drug distribution ratio. Key:* ●, *desoxyephedrine HCl (1 mg./ml.) + polacrilin K (25 mg./ml.);* ○, *pseudoephedrine HCl (1 mg./ml.) + polacrilin K (25 mg./ml.); and* □, *neostigmine bromide (1 mg./ml.) + polacrilin K (10 mg./ml.).*

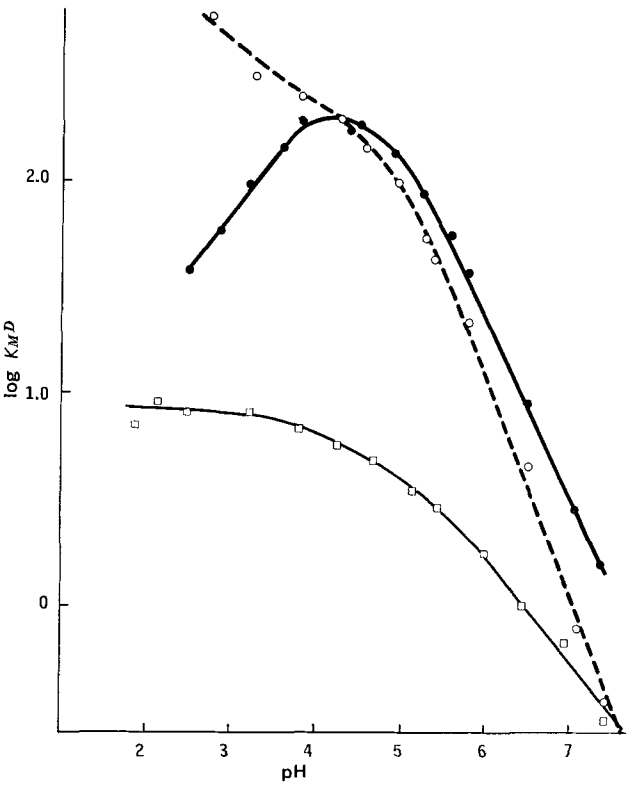

Figure 6—*Effect of pH on the selectivity coefficient. Key:* ●, *methapyrilene;* ○, *chromonar; and* □, *pseudoephedrine.*

The procedures used to determine the effects of alkali metal, resin, and drug concentrations were identical to the above except for varying concentrations of the component being studied. To ensure the constant pH required in each series, fine adjustments were made with HCl after 4 and 6 hr.

In the temperature study experiments, the equilibrations were run in flasks equipped with mechanical stirrers and submerged in constant-temperature baths.

Relationship between Degree of Resin Dissociation, α, and pH (Fig. 5)—A series of 13 solutions was prepared to contain 1.8 g. of sodium chloride and various predetermined amounts of HCl (for an equilibrium pH range of 2.5–7.5) in 200 ml. of solution. Each solution was added to a 300-ml. bottle along with 2.0 g. of polacrilin potassium and the bottles were rolled at 24–25° as in the equilibrium studies. After 24 hr., the pH of each mixture was determined and the resin was separated from the solution phase by filtration. The resin was then reslurried in 200 ml. of 1 *N* HCl for 2 hr. to elute the cations that had remained in the resin phase. Aliquot samples (20 ml.) were pipeted from both the equilibrium and acid elution solutions and evaporated to constant weight under an IR lamp. Since the solids were a mixture of sodium and potassium chlorides in the molar ratio 154 to 54, the weight concentrations were converted to equivalents per liter by dividing by the weighted average molecular weight (62.63). The concentrations in the equilibrium and elution solutions were equal to $[M]_s$ and $[M]_r$, respectively. Their sum varied from 205–209 meq./l. (theoretical 208) at the 13 different pH's. The fraction of resin in the dissociated form, α, was obtained by dividing $[M]_r$ by the total exchange capacity of the polacrilin (69.7 meq./l.).

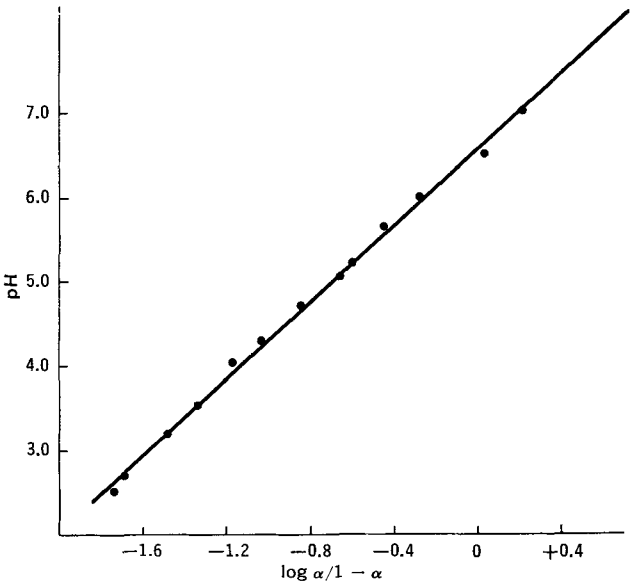

Figure 5—*Relationship between pH and polacrilin K dissociation in 0.154* M *NaCl* (n = *2.28, pKa = 6.60*).

Rate Studies—In the adsorption rate studies, 500 ml. of buffer containing 0.154 eq. of sodium was prepared by dissolving 1.94 g. of dibasic sodium phosphate and 19.2 g. of monobasic sodium phosphate in water. Ten grams of polacrilin potassium was added and the pH of the slurry was adjusted to 5.50–5.60 with HCl over a 4-hr. period. One gram of drug was dissolved in 500 ml. of water and the solution was added to initiate adsorption. The slurry was

Table II—Selectivity Coefficients (K_M^D) at Various pH's

Drug	pH 4.5	pH 5.0	pH 5.5	pH 6.0
Phenylpropanolamine	2.48	2.67	2.13	1.45
Desoxyephedrine	7.44	5.81	3.80	2.38
Ephedrine	5.37	4.49	2.77	1.72
Pseudoephedrine	5.55	3.87	2.61	1.64
Carbinoxamine	267	236	131	49.2
Chromonar	151	77.7	17.1	15.4
Quinidine	353	308	208	116
Methapyrilene	179	122	61.9	24.4
Dextromethorphan	276	196	112	68.6
Thiamine	52.5	44.3	23.7	9.03
Neostigmine	6.42	4.22	2.22	1.14

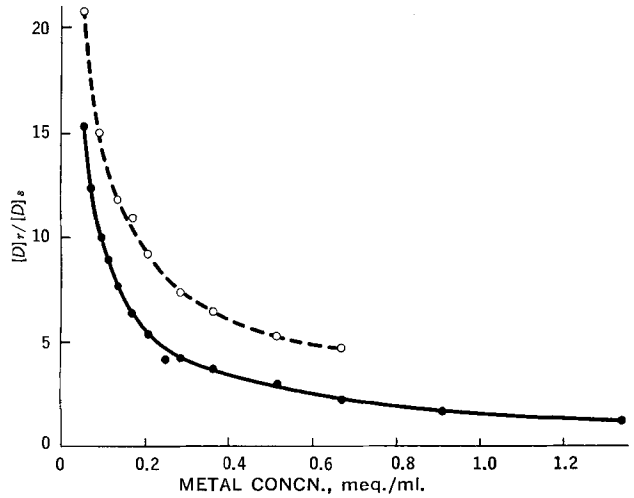

Figure 7—*Effect of alkali metal concentration on drug distribution ratio. Key:* ●, *methapyrilene HCl (1 mg./ml.), polacrilin K (10 mg./ml.), NaCl (0–1.283 meq./ml.), pH 5.3; and* ○, *dextromethorphan HBr (1 mg./ml.), polacrilin K (10 mg./ml.), NaCl (0–0.616 meq./ml.), pH 5.1.*

stirred at 25° for 4 days with methapyrilene and dextromethorphan and for 2 weeks in the case of carbinoxamine and quinidine. Ten-milliliter samples were removed at 2, 5, 10, and 30 min.; at 1, 4, and 24 hr.; and at the end of the run. The solution phase was filtered from the resin and assayed for drug by UV spectroscopy.

In the elution rate studies, 1 g. of methapyrilene hydrochloride, 1.94 g. of dibasic sodium phosphate, and 19.2 g. of monobasic sodium phosphate were dissolved in enough water to make 1 l. Ten grams of polacrilin potassium was added, the pH was adjusted to 5.5 with HCl, and the slurry was stirred for 24 hr. at 25°. The resin, containing approximately 82.0% of the drug, was filtered from the solution and added to 1 l. of fresh buffer solution containing 0.154 meq./ml. of sodium. The pH 6.8 elution-rate run used a buffer containing 18.8 g. of dibasic and 1.86 g. of monobasic sodium phosphate. The buffer in the pH 5.4 study contained 1.94 g. of dibasic and 19.2 g. of monobasic sodium phosphate. Stirring was continued at 25° for 24 hr. with samples being removed after 2, 5, 10, and 30 min. and after 1, 3, and 24 hr. The solution phase was filtered from the resin and assayed for drug by UV spectroscopy.

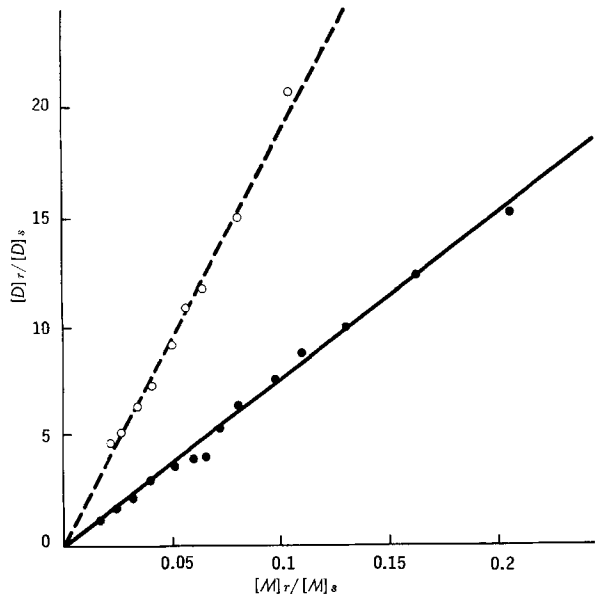

Figure 8—*Relationship of alkali metal distribution ratio to drug distribution ratio. Key:* ●, *methapyrilene at pH 5.3* (K_M^D = *77.2); and* ○, *dextromethorphan at pH 5.1* (K_M^D = *195).*

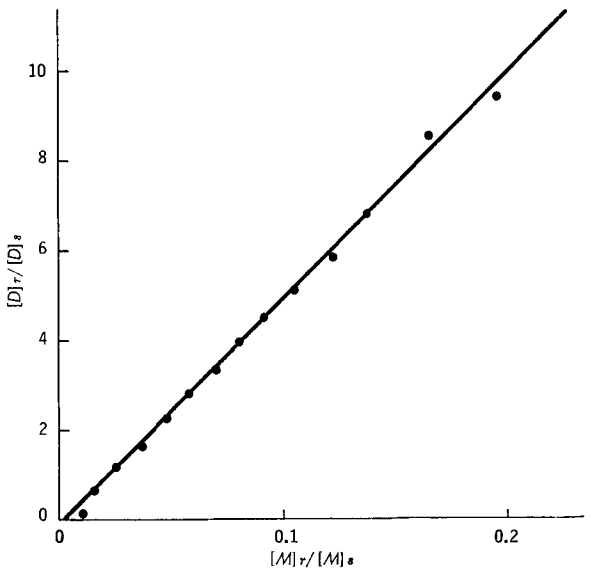

Figure 9—*Effect of polacrilin potassium concentration on drug distribution ratio, methapyrilene HCl (1 mg./ml.), KCl (0.154 meq./ml.), polacrilin K (1.25–30.0 mg./ml.), pH 5.4,* K_M^D = *50.4.*

RESULTS AND DISCUSSION

Effect of pH—Figures 1–4 show the effect of pH on the interaction at equilibrium between polacrilin potassium and the eleven drugs tested. Drug interaction is expressed as a distribution ratio, drug in resin phase, $[D]_r$, divided by drug in solution phase, $[D]_s$, both expressed as meq./ml. of solution. Although the extent of interaction varied considerably with the drug, in all cases the ratio showed a maximum at pH 4.5–5.5. The sharp decrease in complexation below pH 4.5 is apparently caused by the diminishing number of anionic sites on the resin due to its low dissociation constant. The decreasing interaction above pH 5.5, despite the greater ionization of the resin, can be attributed to a decreasing affinity of the polacrilin for amine drugs relative to alkali metal cations. The increasing portion of drug in the unionized form may contribute to this.

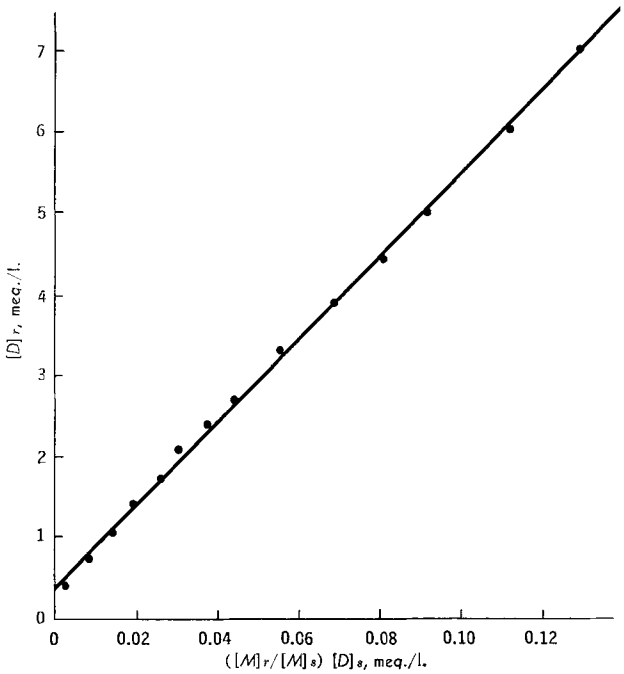

Figure 10—*Effect of drug concentration on interaction, methapyrilene HCl (0.42–10.08 meq./l.), polacrilin K (10 mg./ml.), NaCl (0.154 meq./ml.), pH = 5.4,* K_M^D = *50.9.*

Table III—Rates of Equilibration at 25°

Drug	Process	pH	% Drug in Resin Phase after— 2 min.	1 hr.[a]	4 hr.	24 hr.	Final
Methapyrilene	Adsorption	5.5	71.7	79.8	80.7	82.0	82.3[b]
Dextromethorphan	Adsorption	5.6	64.5	75.9	77.1	79.2	79.2[b]
Carbinoxamine	Adsorption	5.5	86.9	93.2	95.1	95.1	94.8[c]
Quinidine	Adsorption	5.5	80.3	86.0	87.9	89.7	89.6[c]
Methapyriline	Elution	6.8	68.7	64.9	62.1[d]	63.4	—
Methapyrilene	Elution	5.4	90.5	89.5	89.1[d]	89.0	—

[a] Results of samples at 5, 10, and 30 min. were all intermediate between the 2-min. and 1-hr. percentages. [b] Sampled after 4 days. [c] Sampled after 3 weeks. [d] Sampled at 3 hr.

Although the drug distribution ratio is a convenient term for expressing drug interaction, it will vary with drug, resin, and sodium ion concentrations, as well as with pH. This is demonstrated in Fig. 1 where two different resin concentrations were used with dextromethorphan. Samuelson (3) suggests the use of a selectivity coefficient to express the relative affinities of resins for different cations. In this study the selectivity coefficient, $K_M{}^D$, would be defined by the following equation:

$$K_M{}^D = \frac{[D]_r\,[M]_s}{[D]_s\,[M]_r} \qquad \text{(Eq. 1)}$$

where $[M]_s$ and $[M]_r$ represent the concentrations, in meq./ml., of alkali metal in the solution and resin phases, respectively. The alkali metal concentration includes both the sodium from added sodium chloride and potassium contributed by the polacrilin potassium, with the sodium ion predominating. The selectivity coefficients would be expected to remain constant with variations in drug, resin, and metal concentrations, although it does change with pH.

Calculations of selectivity coefficients from the distribution ratios found in Figs. 1–4 require accurate estimations of $[M]_r$ ($[M]_s$ can be obtained by difference once $[M]_r$ is known). Since the meq. of alkali metal in the resin phase is approximately equal to the meq. of ionized sites on the resin, less those occupied by drug cations, the following equation may be written:

$$[M]_r = \alpha[Re] - [D]_r \qquad \text{(Eq. 2)}$$

where α is the fraction of total resin equivalents in the dissociated form while $[Re]$ is the resin concentration expressed in meq. total exchange capacity per ml. of solution. Gustafson (11) has demonstrated that polymethacrylic carboxylic ion-exchange resins follow the empirical relationship:

$$\text{pH} = \text{pKa} + n \log \frac{\alpha}{1-\alpha} \qquad \text{(Eq. 3)}$$

where pKa is an apparent dissociation constant which changes with ionic strength, while n is a second constant specific for the resin and independent of ionic strength. The linear relationship obtained between pH and log $\alpha/1-\alpha$ (Fig. 5) shows that polacrilin potassium follows Eq. 3. The values from this experiment allow calculation of selectivity coefficients from the drug distribution ratios shown in Figs. 1–4 using Eqs. 1–3.

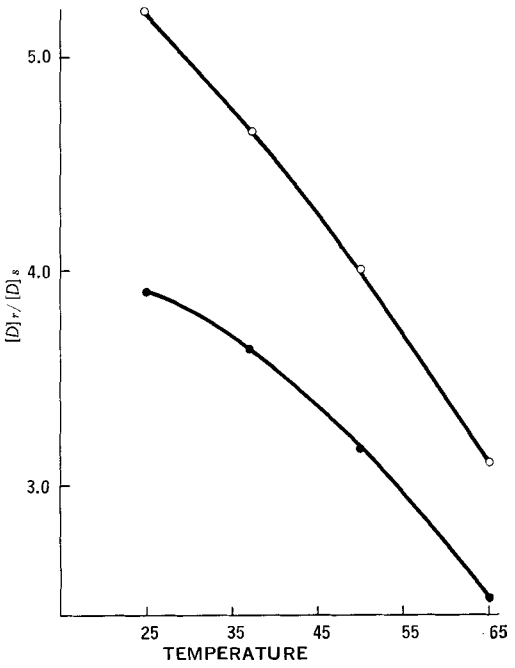

Figure 11—*Effect of temperature on the drug distribution ratio, methapyrilene HCl (1 mg./ml.), polacrilin K (10 mg./ml.), NaCl (0.154 meq./ml.). Key: ● pH 4.6, and ○, pH 5.3.*

The relationship between the selectivity coefficients and hydrogen ion concentration was obtained by plotting log $K_M{}^D$ *versus* pH for each drug. Figure 6 shows some typical results. In all cases the relationship appeared linear between pH 5.5 and 7.5 with slopes of 0.5–1.0. This linearity indicates that the selectivity coefficient is proportional to a power (equal to the slope) of the hydrogen ion concentration. Results below pH 5.5 were inconsistent in that maxima, levelings, and nonlinear increases were observed in the graphs.

Comparison of Drugs—Table II shows the selectivity coefficients obtained for each drug at pH 4.5, 5.0, 5.5, and 6.0. Since all drugs should be essentially in the cationic form at the pH's used, the considerable variations in selectivity coefficients between drugs cannot be attributed to their dissociation constants. The differences are more likely related to steric and resonance effects within the drug cation. Nevertheless the magnitude of the selectivity coefficients can be related to the degree of nitrogen substitution. The five tertiary amine drugs (dextromethorphan, methapyrilene, quinidine, carbinoxamine, and chromonar) showed substantially greater interaction than the other six drugs. At pH 5.0, the average selectivity coefficient for the tertiary amines was approximately 40 times greater than the average for the three secondary amine drugs (ephedrine, pseudoephedrine, and desoxyephedrine). Phenylpropanolamine, the only primary amine studied, showed the smallest interaction. The two quaternary amine drugs varied somewhat in their behavior. Neostigmine gave a selectivity coefficient similar to the secondary amine drugs while the value for thiamine was intermediate between secondary and tertiary amines.

Effects of Alkali Metal, Resin, and Drug Concentrations—The relationship between the drug distribution ratio and the sodium ion concentration is shown in Fig. 7 for methapyrilene and dextromethorphan. Similar curves were obtained with the other drugs tested. To show that these results are consistent with the selectivity coefficient relationship (Eq. 1), the drug distribution ratios were plotted against the calculated alkali metal ratios (Fig. 8). Since Eq. 1 may be rearranged to

$$\frac{[D]_r}{[D]_s} = K_M{}^D \frac{[M]_r}{[M]_s} \qquad \text{(Eq. 4)}$$

the linearity obtained demonstrates that the selectivity coefficients remain constant over a wide alkali metal concentration range. $[M]_r$ and $[M]_s$ were calculated from Eqs. 2 and 3, with the variability of pKa with ionic strength being estimated from Gustafson's relationship (11).

Experiments in which the potassium ion concentration was varied gave similar results to those obtained with sodium ion variation. Potassium gave approximately the same selectivity coefficients. The similarity indicates that small changes in the potassium–sodium

ratio within a system should have negligible effect on drug distribution ratios.

Figure 9 shows the effect of polacrilin potassium concentration on the methapyrilene distribution ratio. The distribution ratio was plotted against the calculated $[M]_r/[M]_s$ to attain the linearity predicted by Eq. 4. The results show that the selectivity coefficient also remains constant over a wide range of resin concentration.

In evaluating the effect of drug concentration, a plot of the methapyrilene distribution ratio *versus* $[M]_r/[M]_s$ showed deviation from linearity at low drug concentration. However a straight line was obtained when the concentration of resin-adsorbed drug, $[D]_r$, was plotted against $[D]_s[M]_r/[M]_s$ (Fig. 10). Although the linearity is consistent with Eq. 1, the intercept is not. Apparently the total drug adsorbed is the sum of that adsorbed according to the selectivity coefficient relationship plus a constant:

$$[D]_r = K_M{}^D \frac{[M]_r}{[M]_s}[D]_s + \text{constant} \qquad \text{(Eq. 5)}$$

This constant, which becomes significant only at very low drug–resin ratios, can be attributed to a small quantity of drug bound to the resin by forces other than ionic bonding.

Effect of Temperature—The effect of temperature on the methapyrilene distribution ratio at two different pH's is shown in Fig. 11. The decrease in drug–resin interaction with rising temperature is in agreement with Samuelson's generalization (3) that an increase in temperature results in a decrease in ion selectivity.

Rate of Equilibration—Although the large size of the drug cations might be expected to affect exchange kinetics, the rate of equilibration was found to be quite rapid, both for adsorption and elution. Table III summarizes the results of rate studies at 25°. The lack of significant change after 24 hr. in the adsorption runs emphasizes the fact that equilibrium is attained in that time.

The rapid exchange rates are consistent with the results reported by Kunin (12) for carboxylic ion-exchange resins. He noted that, although the exchange rate in going from acid to metal cycle is slow and may require weeks for completion, attainment of equilibrium in going from one metal cycle to another occurs in minutes or hours. Since the latter process most closely resembles both adsorption onto polacrilin potassium (potassium to drug cycle) and elution from the resin (drug to sodium cycle) the rapid rates are not surprising. Further, the fine particle size of polacrilin potassium might contribute significantly to acceleration of the exchange rates.

The rapid exchange rates along with the selectivity coefficient results indicate that the presence of polacrilin potassium in a dosage form should have insignificant effect on the total drug availability. Although appreciable resin adsorption of drug may occur in the gastrointestinal tract during pH 4.5–6.0 exposure, rapid desorption should result as the adsorbate passes into the higher pH of the small intestine. The decreased selectivity coefficients at higher pH along with the rapid elution rates ensure drug availability. Even in the pH 4.5–6.0 range, continuous absorption of drug into the blood would result in elution from the resin. The higher temperatures that would be encountered in the body compared with the 24–25° data obtained in this study would promote greater drug availability, both through lower selectivity coefficients and faster exchange rates.

SUMMARY AND CONCLUSIONS

1. The interaction between amine drugs and polacrilin potassium follows the selectivity coefficient relationship. It would be expected that other carboxylic acid ion-exchange resins would behave similarly.

2. Tertiary amines show a greater affinity for polacrilin potassium than other amine drugs. In all cases, maximum interaction occurs at pH 4.5–5.5.

3. The rapid elution rates, along with decreasing interaction above pH 6.0, indicate that the presence of polacrilin potassium in a dosage form should not affect total *in vivo* availability. It is questionable whether any significant delay in absorption would occur.

4. The high selectivity coefficients obtained with some drugs indicate that precautions must be taken in assaying for amine drugs in the presence of polacrilin potassium. Buffers above pH 7.0 or below pH 3.0 or solutions with high cation concentrations may be used to effect complete drug elution.

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