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INVESTIGATION OF THE APPLICABILITY OF ION EXCHANGE RESINS AS A SUSTAINED RELEASE DRUG DELIVERY SYSTEM FOR PROPRANOLOL HYDROCHLORIDE

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ABSTRACT

The purpose of this study was to investigate the application of six strongly acidic cation exchange resins as a sustained release drug delivery system. Propranolol hydrochloride was chosen as the model drug to study the in vitro adsorption and desorption characteristics of the resins because of its chemical structure and pharmacokinetic properties which make it a good candidate for a sustained release formulation. The exchange rate constants and diffusion coefficients for the adsorption and desorption experiments were determined for each resin using the equations derived by Boyd, Adamson and Myers. Only one cation exchange resin showed potential as a sustained release drug delivery system for propranolol hydrochloride.

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INTRODUCTION

In 1935, Adams and Holmes (1) synthesized the first anionic and cationic exchange resins, citing potential uses in purification and removal of materials from solutions. During the 1940's and 1950's, investigations of the physical-chemical properties of ion exchange resins were conducted. The effects of crosslinkage (2), particle size (3), relative affinities (4), pKa (5), and capacity (6) of ion exchange resins were studied extensively. In addition to these properties, the kinetics of the ion exchange reaction were investigated by a limited number of researchers. Boyd, Adamson and Myers (7) conducted experiments to determine if the exchange was a chemical, film diffusion or particle diffusion process. They concluded that the exchange occured by particle diffusion or film diffusion. Other authors (6, 8, 9) have agreed with their results. Boyd, Adamson and Myers derived the following equation for a particle diffusion exchange process:

$$F = \frac{Q_t}{Q_\infty} \quad 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{e^{-n^2 B t}}{n^2} \qquad \text{Eq. 1}$$

where F is the fractional adsorption or desorption value, Q_t is the quantity of drug adsorbed or released at time t and Q is the quantity constant at time t:

$$B = \frac{\pi^2 D_i}{r^2} \qquad \text{Eq. 2}$$

where D_i is the effective diffusion coefficient of the exchanging ions in the resin particle and r is the radius of the resin particle. After

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integration with respect to Bt and a Fourier transformation the final workable equation is:

$$Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi\left(1 - \frac{\pi F}{3}\right)^{\frac{1}{2}} \qquad \text{Eq. 3}$$

This equation holds true if F is equal to or less than 0.85. Reichenberg (8) derived the following equation when F is greater than 0.85:

$$Bt = -\log e \frac{\pi^2}{6}(1-F) \qquad \text{Eq. 4}$$

If the calculated Bt value is plotted against time, a straight line passing through the origin should be obtained if the exchange process is particle diffusion controlled.

From 1950 to the present, there have been a number of papers reporting the use of ion exchange resins in combination with drugs, including quinine (10), cinchona alkaloids (11), phenylpropanolamine and chlorpheniramine (12), levamisole (13) and codeine (14). Uses of ion exchange resins in the pharmaceutical industry include taste masking, drug stabilizers, tablet disintegrants and drug delivery systems.

EXPERIMENTAL

Materials

Amberlite XE-364R, IRP-69, IR-120 PLUS and IR-122[a], Dowex 50W X4 and X8[b], hydrochloric acid[c], potassium chloride[c], propranolol hydrochloride[d] and sodium chloride[c].

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a. Rohm & Haas Company, Philadelphia, PA
b. The Dow Chemical Company, Midland, MI
c. Fisher Scientific Company, Fair Lawn, NJ
d. Cosma S.P.A., Italy

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Equipment

Fisher Magnetic Stirrer[c], Hanson Dissolution Apparatus[e] and Spectronic 2000[f].

Determination of Particle Size

The particle size and distribution of the six cation exchange resins were determined by microscopy. A total of five hundred particles were counted for each determination.

Preparation of Drug-Resin Complex

A 50 mg/ml aqueous solution of propanolol hydrochloride was mixed with a known weight of ion exchange resin, using a magnetic stirrer, for two days. At appropriate time intervals, samples were taken to determine the adsorption profile. After two days the drug resin complex was filtered through a sintered glass funnel and the filtrate assayed spectrophotometrically at a wavelength of 288.1 nm. The drug resin complex was then rinsed with distilled water and the filtrate assayed for propranolol content. The total amount of drug adsorbed by the resin was calculated by subtracting the amount of propranolol in solution after filtering and rinsing from the initial propranolol concentration, 50 mg/ml.

Desorption of the Drug from the Resin

The rotating paddle method as described by the USP XX (15) was used. A 50 mg sample of drug-resin complex was added to a modified gastric fluid containing 62.55 mEq of Na^+, 14.94 mEq of K^+ and 0.175

e. Hanson Corporation, Northridge, CA
f. Bausch & Lomb, Rochester, NY

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mEq of H^+ per 900 ml, adjusted to a pH of 1.2. The gastric fluid was maintained at 37 ± 0.5°C and the paddles were rotated at 50 rpm.

RESULTS AND DISCUSSION

The physical characteristics of crosslinkage, particle size and capacity for the six strongly acidic cation exchange resins with varying degrees are presented in Table I. While the percent crosslinkage effects the adsorption capacity of the resin and the rate of exchange, particle size effects only the rate of exchange. The total cation exchange capacity is the maximum achievable capacity for the exchanging ions, measured in milliequivalents (mEq) per gram of dry resin or per milliliter of wet resin.

The particle size distribution of the Amberlite and Dowex 50W Type exchange resins are shown in Figures 1 and 2, respectively. The Amberlite resins had statistically similar average particle sizes except Amberlite XE-364R which had a significantly larger particle size than Amberlite IRP-69 and Dowex 50W X4 which had a significantly smaller particle size than Dowex 50W X8.

The adsorption study for the six cation exchange resins was conducted over a two day period. A typical adsorption profile is seen in Figure 3. Table II lists the final percent capacity occupied by propranolol for each resin.

Clearly, propranolol occupied significantly less of the capacity of Amberlite IR-122, a 10% crosslinked resin, compared to Amberlite IRP-69 and slightly less than Amberlite IR-120 PLUS, both 8% crosslinked resins. The percent capacity occupied by propranolol with Amberlite

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TABLE I

Physical Properties of the Six Strongly Acidic Cation Exchange Resins Studied

Cation Exchange Resins	Percent Crosslinkage	Mean Particle Size (Microns)	Total Cation Exchange Capacity (m Eq/g dry resin)
Amberlite XE-364R	4	104.55	5.0
Amberlite IRP-69	8	74.49	4.3
Amberlite IR-120 PLUS	8	88.12	4.3
Amberlite IR-122	10	93.86	4.3
Dowex 50W X4	4	112.56	5.0
Dowex 50W X8	8	137.32	5.0

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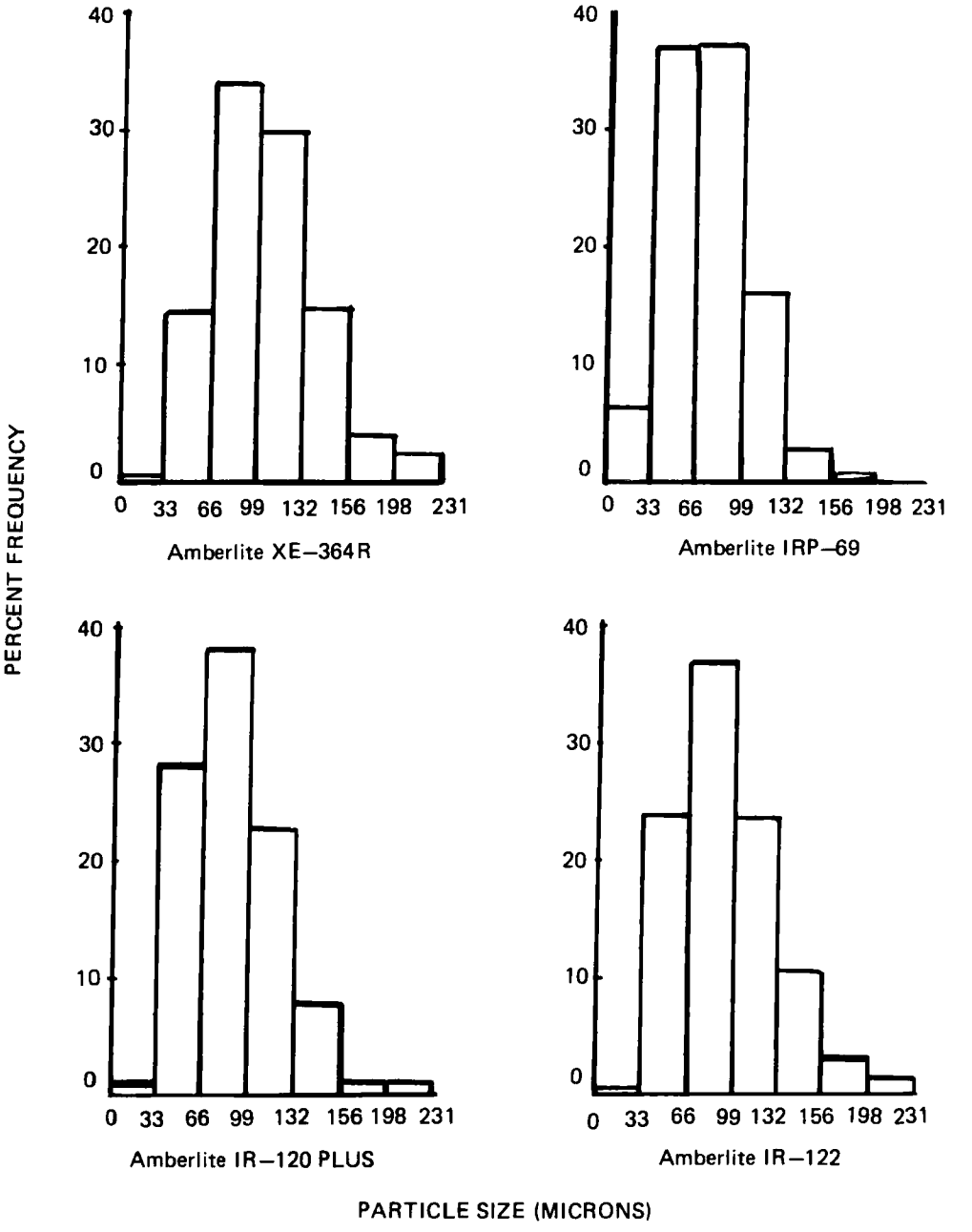

FIGURE 1

Histogram of Particle Size Distribution of Amberlite Resins

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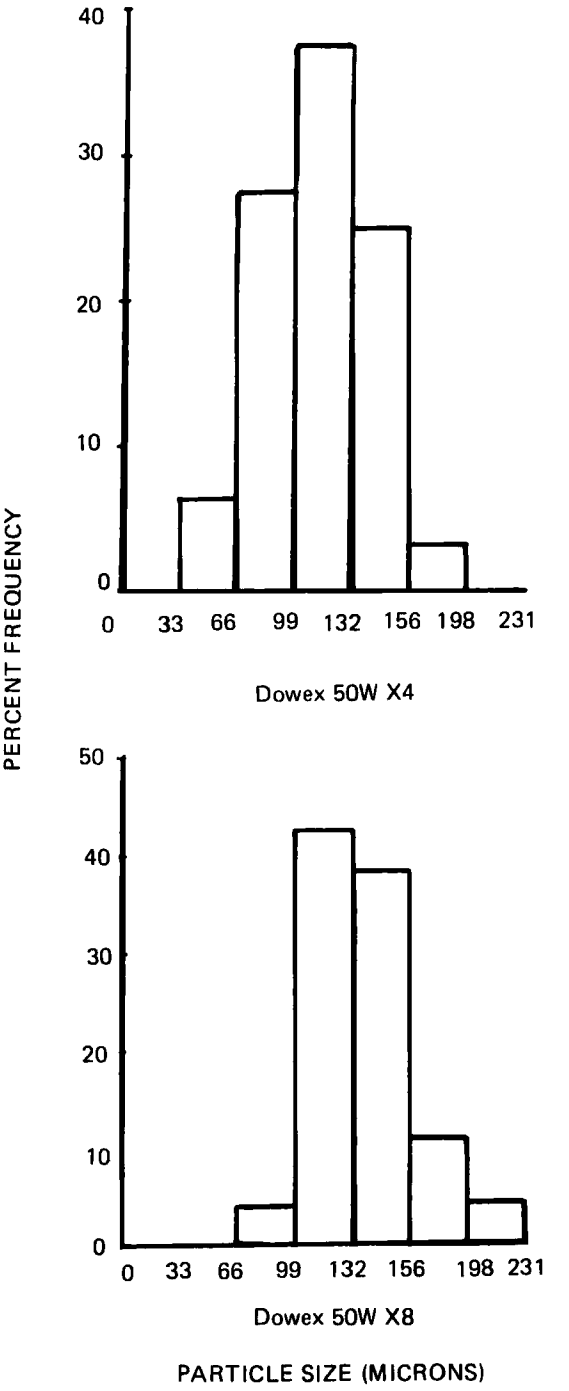

FIGURE 2

Histogram of Particle Size Distribution of Dowex 50W Type Resins

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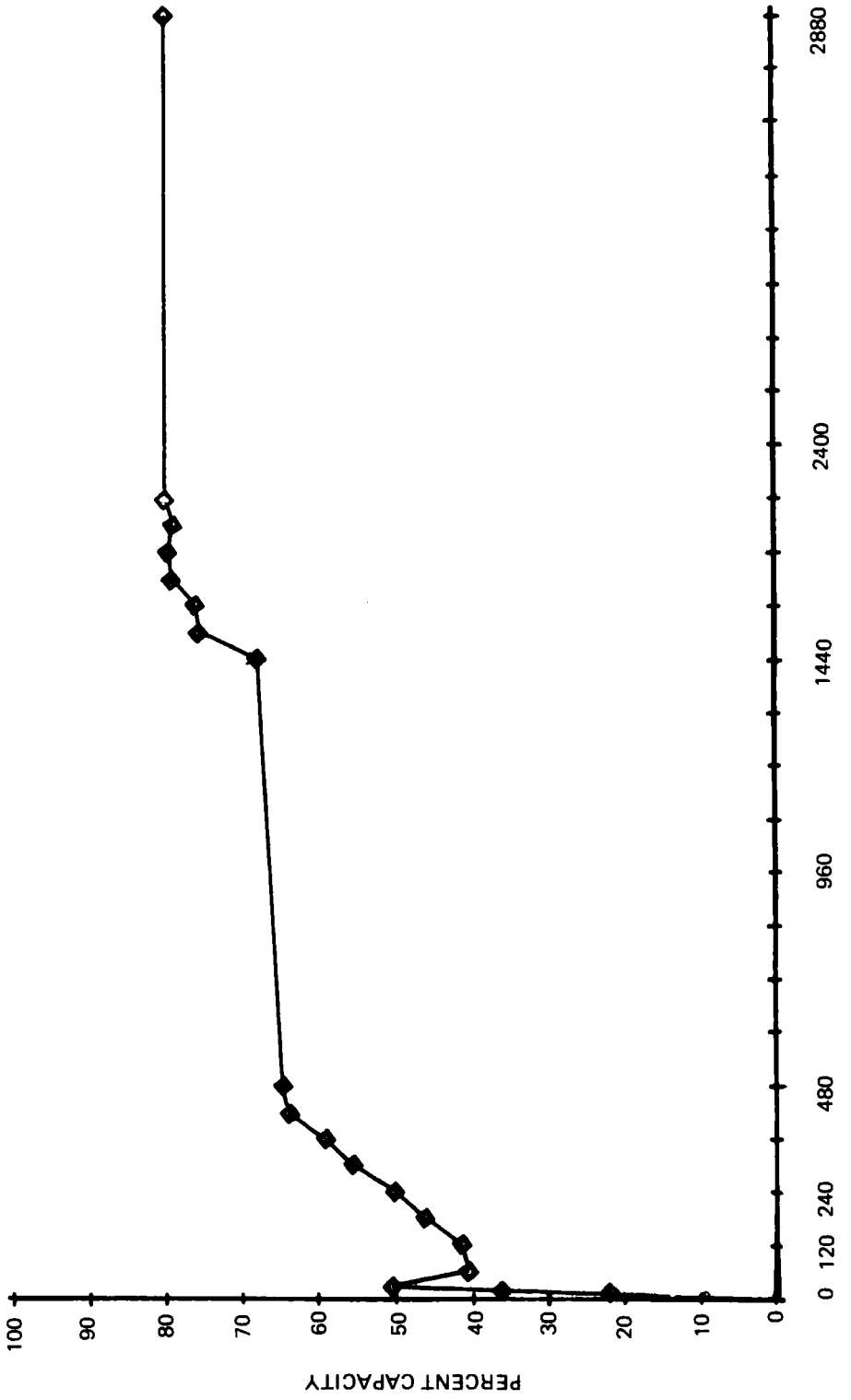

FIGURE 3

Two Day Adsorption Profile of Amberlite IRP-69

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TABLE II

Final Percent Capacity Occupied by Propranolol in Each Cation Exchange Resin

Cation Exchange Resin	Percent Capacity Occupied by Propranolol
Amberlite XE-364R	66.71
Amberlite IRP-69	81.03
Amberlite IR-120 PLUS	69.05
Amberlite IR-122	67.20
Dowex 50W X4	83.84
Dowex 50W X8	55.27

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XE-364R was lower than with the other Amberlite resins although it was expected to be higher. A possible explanation is that, during the milling process of the resin, a physical change may have occured resulting in a lower capacity for Amberlite XE-364R.

Dowex 50W X4 total percent capacity occupied by propranolol was significantly higher than Dowex 50W X8 due to the difference in percent crosslinkage of these resins.

The particle diffusion kinetics of the adsorption exchange reaction, over the first eight hours, was studied according to the Boyd, Adamson and Myers model (7). Observation of the adsorption profile (Fig. 3) appears to indicate two adsorption phases, the first over the initial 30 minutes and the second from the first to the eighth hour. A

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Bt vs. time curve was plotted to determine the exchange rate constant, B, and the diffusion coefficient, D_i, for each adsorption phase. A typical Bt versus time curve is shown in Figure 4 and the exchange rate constants and diffusion coefficient of each resin are presented in Table III. As can be seen, all of the Amberlite resins had the same adsorption exchange rate constants and diffusion coefficients in each adsorption phase. This may be due to the insignificant difference in particle size and the small difference in percent crosslinkage of the Amberlite resins.

Dowex 50W X4 had a faster adsorption exchange rate constant and higher diffusion coefficient for both adsorption phases. This is due to the lower percentage of crosslinking and particle size of Dowex 50W X4 compared to Dowex 50W X8. In addition, the desorption characteristics of propranolol from the drug resin compelx were studied. In preliminary experiments, complete drug release could not be attained; therefore, three alternative dissolution methods were evaluated. The ionic concentration of the exchanging ion was increased, an aqueous solvent was changed to an organic solvent and an alternative dissolution method, other than the USP methods, was tried. None of these three alternates achieved complete release of the drug from the cation exchange resins. Several previous studies have reported similar results. Schacht and coworkers (13) only reached about 80% release of levamisole using Dowex 50W type cation exchange resins. Raghunathan et al (12) also had less than 100% drug release with phenylpropanolamine (60%) and chlorpheniramine (50%) in 500 ml of

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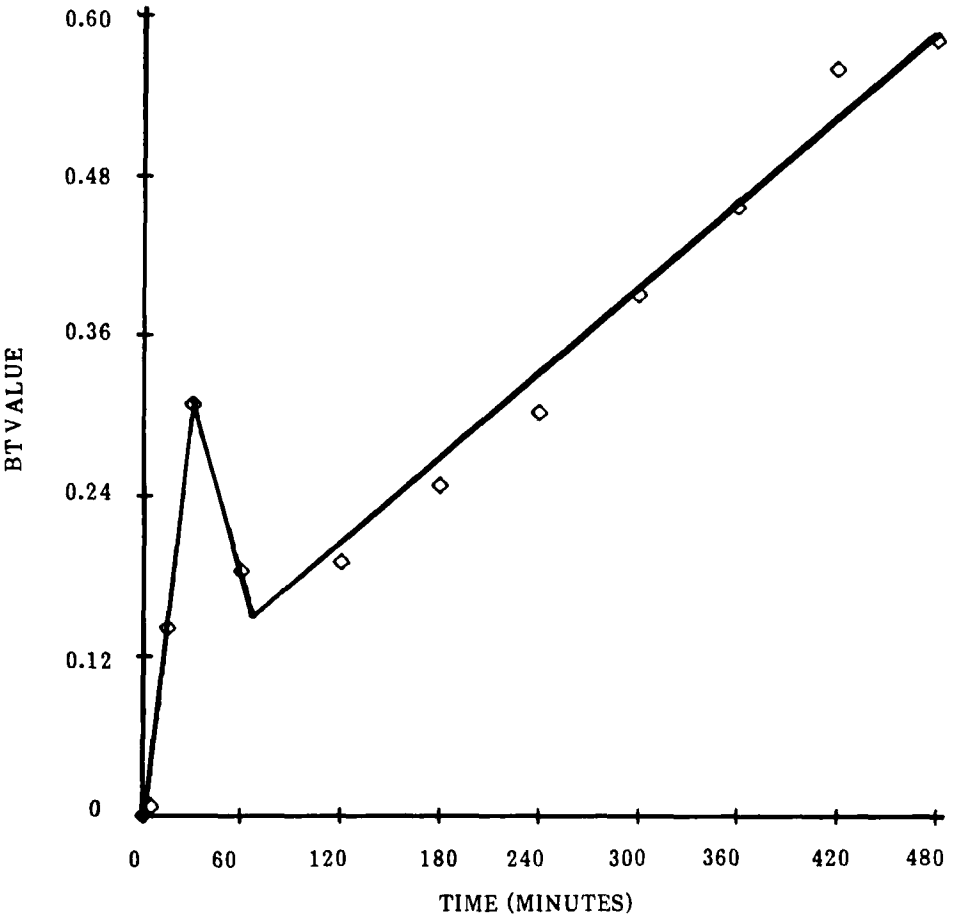

FIGURE 4

Boyd, Adamson and Myers Particle Diffusion Curve of Initial and Secondary Adsorption Phase: Amberlite IRP-69

0.1N HCl when the drugs were complexed with Amberlite IRP-69. There were studies using propranol complexed with Dowex 50W type resins (Gyselinck, 16), and Amberlite resins (Jayaswal, 17). Gyselinck achieved 80% release, based on a reported Bt value, and Jayaswal had less than 40% drug release when propranolol was complexed wtih Amberlite IR-120.

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TABLE III

Adsorption Exchange Rate Constants and Diffusion Coefficient of the Six Cation Exchange Resins

Cation Exchange Resin	Initial		Second	
	Exchange Rate Constant (B) (min^{-1})	Diffusion Coefficient (D_i) ($\mu m^2/min$)	Exchange Rate Constant (B) (min^{-1})	Diffusion Coefficient (D_i) ($\mu m^2/min$)
Amberlite XE-364R	4.64×10^{-3}	5.138	5.39×10^{-4}	0.597
Amberlite IRP-69	1.0×10^{-3}	6.183	1.07×10^{-3}	0.600
Amberlite IR-120 PLUS	8.88×10^{-3}	6.986	6.83×10^{-4}	0.537
Amberlite IR-122	7.00×10^{-3}	6.326	4.33×10^{-4}	0.391
Dowex 50W X4	8.41×10^{-3}	16.035	1.55×10^{-3}	1.968
Dowex 50W X8	6.90×10^{-3}	8.785	3.08×10^{-4}	0.588

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Since this investigation could not achieve total drug release, the remaining dissolution testing was carried out using the USP parameters previously described. The dissolution profiles of the Amberlite resins and of the Dowex 50W type resins are shown in Figures 5 and 6, respectively.

The kinetics of the desorption process was investigated by determining the exchange rate constants and the diffusion coefficients for a particle diffusion release model. From the fractional dissolution value, a corresponding Bt value was obtained and plotted against time for each resin. These curves were sigmoidal in nature but only the linear portion of the curve was used to determine the exchange rate constant, B. The linear portion of the curve was determined by doing a series of linear regressions and comparing the correlation coefficients using a Z test. A typical Bt vs. time curve is seen in Figure 7. Table IV lists the exchange rate constant and diffusion coefficient for each resin studied and the time period of the constant exchange. While the exchange rate constants of the 8% crosslinked resins, Amberlite IRP-69 and IR-120 PLUS, were the same, both of these resins had a significantly faster exchange rate than Amberlite IR-122 due to the difference in percent crosslinking. Dowex 50W X4 had a significantly faster exchange rate than Dowex 50W X8 due to its smaller particle size and lower degree of crosslinking.

Amberlite IRP-69 and IR-122 had essentially the same diffusion coefficients, 3.109 and 3.304 um^2/min respectively. These were higher than Amberlite IR-122, 1.126 um^2/min, due to the difference in percent

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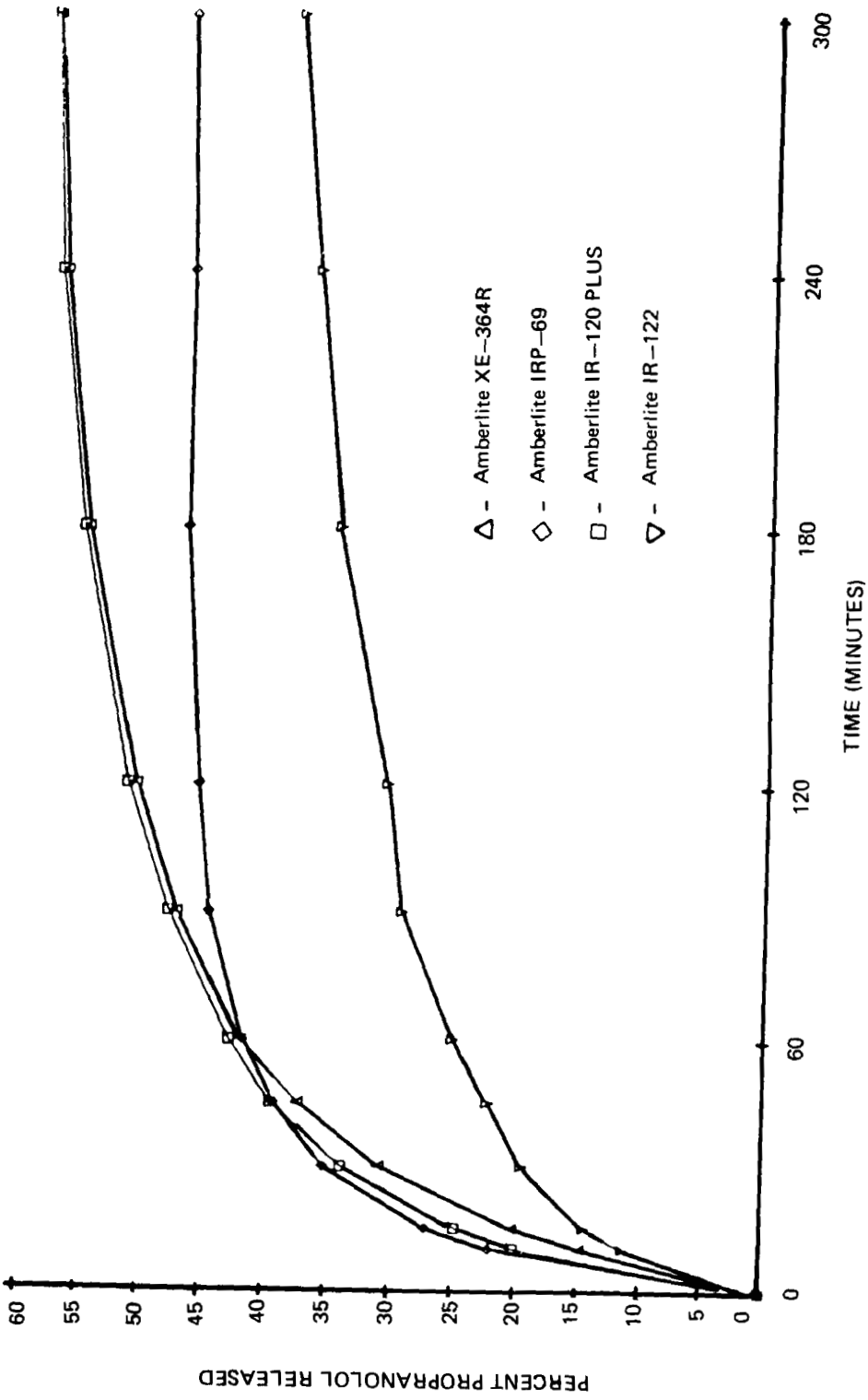

FIGURE 5

Dissolution Profile of Amberlite Resins

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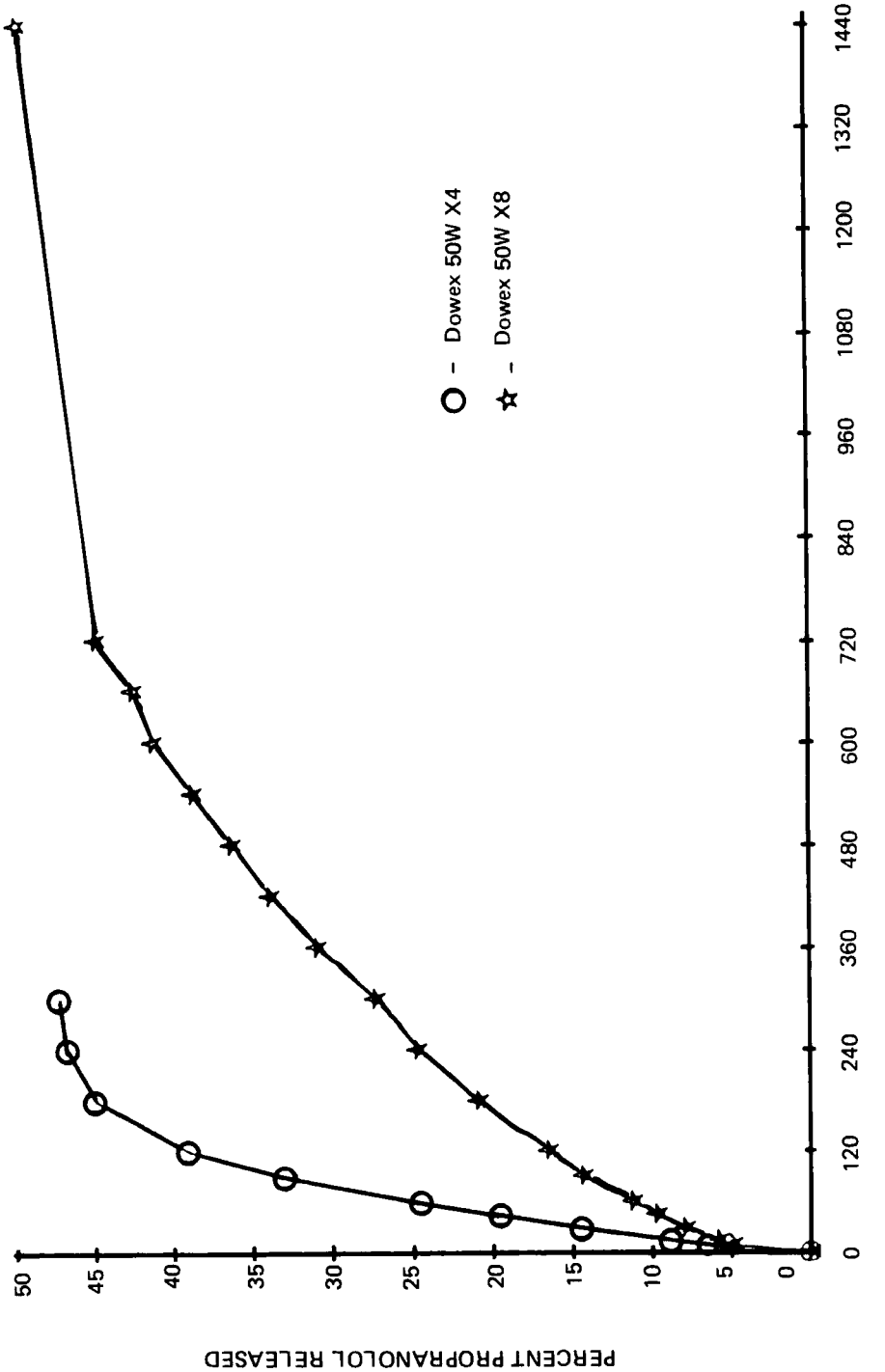

FIGURE 6

Dissolution Profile of Dowex 50W Type Resins

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FIGURE 7

Boyd Adamson and Myers Particle Diffusion Curve
Desorption Study: Amberlite IR-120 PLUS

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TABLE IV

Desorption Exchange Rate Constants, Diffusion Coefficients and Time Period of the Linear Portion of the Boyd, Adamson and Myers Particle Diffusion Curve for the Ion Exchange Resins Studied

Cation Exchange Resin	Exchange Rate Constant (B) (min^{-1})	Diffusion Coefficient (D_i) ($\mu m^2/min$)	Time Period of the linear portion of the curve (min)
Amberlite XE-364R	3.59×10^{-3}	3.891	6-60
Amberlite IRP-69	5.53×10^{-3}	3.109	4-15
Amberlite IR-120 PLUS	4.20×10^{-3}	3.304	4-30
Amberlite IR-122	1.28×10^{-3}	1.156	5-30
Dowex 50W X4	1.69×10^{-3}	2.155	30-120
Dowex 50W X8	3.68×10^{-4}	0.723	300-720

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crosslinking. Dowex 50W X4 had a significantly higher diffusion coefficient, 2.115 um^2/min, than Dowex 50W X8, 0.723 um^2/min due to its smaller particle size and percent crosslinking. No definite conclusions can be made about Amberlite XE-364R due to the probable change in the physical characteristics of the resin during milling; however the in vitro release was too rapid for a sustained release effect.

The conclusions based on the in vitro dissolution studies clearly show that all but Dowex 50W X8 had a rapid release of propranolol. In vivo studies would have to be conducted to determine if propranolol complexed with strongly acidic cation exchange resins is an effective sustained release drug delivery system by itself or if the drug-resin complex would need to be coated to be effective as in the case of the "Pennkinetic" system.

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