Ion Exchange Resin Salts for Oral Therapy I

Carbinoxamine

By DAVID A. SCHLICHTING

Six new carbinoxamine cation exchange resin salts have been prepared. The degree of dissociation under simulated gastrointestinal tract conditions has been studied. It has been found that salts formed with resins having a pKa less than 5.2 are most adaptable to slow elution and, hence, sustained release of carbinoxamine. A more detailed investigation of salts of polystyrene sulfonic acids was made. Conditions regarding resin loading, per cent of cross linking of resin, efficiency of exchange, and the presence of added free acid resin were considered for attaining slow dissociation characteristics. Pharmacological tests of antihistamine activity are described. A new *in vivo* method of determining total drug release from an ion exchange salt is described and related to an *in vitro* method. The preparation of dosage forms and their stability is briefly discussed.

MOST ANTIHISTAMINIC agents have a central nervous system side effect. Frequently, a parasympatholytic effect is associated with them. The majority of these agents have a duration of action of about 4 hours or less (1). In the treatment of many conditions requiring antihistamines, a sustained antihistaminic effect is sought. If near optimal release of medicament can be achieved, then sustained drug blood levels and a reduction in side effects would be anticipated. Consequently, the possibility of achieving controlled and sustained release of the antihistamine carbinoxamine, 2-[*p*-chloro-α-(2-dimethylaminoethoxy)benzyl]pyridine, was investigated. A study was made of insoluble cation exchange resin salts, their formation, and dissociation under *in vitro* simulated gastrointestinal tract conditions and an *in vivo* test. Carbinoxamine maleate is a water-soluble, readily absorbed amine salt of proved clinical utility as an antihistaminic agent. A 4 to 8-mg. dose gives an effective clinical response and is recommended by the manufacturer to be taken three to four times a day.

Use is made of insoluble, synthetic cation exchange resins for salt formation and release-rate evaluation. They allow for utilization of numerous variables. Resins of varying functional anions, pKa values, cross linkages, and particle sizes are available. These variables are utilized in the following experiments in an attempt to prepare salts of carbinoxamine that release the drug slowly.

EXPERIMENTAL

Materials.—The insoluble, synthetic cation exchange resins used are described in Table I with information from the manufacturers as to their characteristics.[1] Future reference to these resins by capital letter will refer to Table I.

Resin Salt Formation.—Preparation of the carbinoxamine salts of the various resins was accomplished in the usual manner employing either batch or column processes (2). Carbinoxamine, its maleate, and its hydrochloride were used in aqueous and water-alcohol solutions in concentrations varying from about 1 to 20%. Quantities of carbinoxamine varying from two and one-half times the theoretical capacity to one-fourth of the capacity were used. Figure 1 exemplifies the rate of salt formation and is typical of this specific reaction as well as others studied.

Assay.—Assay of the various salts formed was accomplished by column elution with 5 to 10% hydrochloric acid. Elution with 2–300 ml. of acid over about a 24-hour period of time was found to be adequate. A Beckman spectrophotometer, model DU, was used for assay, reading at 263 mμ. Minor modifications were necessary when the resin salt was formulated in tablet and suspension dosage forms. Table II gives the results of the assays of carbinoxamine salts of the resins described in Table I.

Release Rates.—Time-release relationships were studied by subjecting a 40–100 mg. sample of the resin salt to 75 ml. of U.S.P. simulated gastric fluid without pepsin for one hour at 37.5 ± 3°. After 1 hour, the eluate was removed and assayed and was replaced by 75 ml. of U.S.P. simulated intestinal fluid without pancreatin. Aliquots, 5 to 10 ml., of this latter fluid were removed and assayed periodically and fresh replacement samples were added. The method is of the type described by Chaudhry and Saunders (3) as the replacement closed tube method.

The test apparatus used for time-release rates utilized 2.2 × 9-cm. glass tubes. They were fitted with 100-mesh stainless steel screens at the bottom and hooks at the top. Test samples were placed in such tubes. The tubes were hooked onto the arm of a U.S.P. device for raising and lowering tubes (4).

Received April 19, 1961, from McNeil Laboratories, Inc., Philadelphia, Pa.
Accepted for publication May 8, 1961.

[1] The materials and information were kindly supplied by Chemical Process Co. (Duolite), Dow Chemical Co. (Dowex), National Aluminate Corp. (Nalcite), and Rohm and Haas Co. (Amberlites).

TABLE I.—DESCRIPTION OF INSOLUBLE, SYNTHETIC ION EXCHANGE RESINS STUDIED

Code	Name of Resin	Chemical Description Main Constituent	Approx. % Cross Linkage with Divinyl Benzene	Particle Size Range, U. S. Std.	Approx. Exchange Capacity, Meq./Gm. Dry Basis	Approx. pK, 1 *M* NaCl
A	Amberlite IR-120	Polystyrene sulfonic acid	8–10	30–40	5	1.3
B	Dowex 50 W X 8	Polystyrene sulfonic acid	8	50–100	5	1.3
C	Dowex 50 W X 12	Polystyrene sulfonic acid	12	50–100	5	1.3
D	Duolite C-3 (H)	Phenol formaldehyde sulfonic acid	None	16–50	3 (Sulfonic)	1.3
E	Amberlite XE-89 (H)	Poly acrylic acid	5–7	16–50	6–7	5.2
F	Amberlite XE-96 (H)	Poly methacrylic acid	4–6	16–50	10	6.0
G	Amberlite XE-64 (H)	Poly methacrylic acid	4–6	100–325	10	6.0
H	Amberlite EM-267 (H)	Poly acrylic:sulfonic acids in 7:3 ratio	11.5	16–50	$-CO_2H$ 9.8 $-SO_3H$ 2.1	5.2 1.3
I	Nalcite X-219 (Na)	Sodium polystyrene phosphonate	...	16–50	5–6	3.2 7.6

TABLE II.—ASSAY AND RELEASE OF CARBINOXAMINE FROM VARIOUS RESIN SALTS

Salt of Resin Tested	% Carbinoxamine in Salt	Total Release Rate, % 1 hr.	2 hr.	4 hr.	5 hr.	6 hr.	7 hr.	8 hr.
A	21.9	5	32	50	..	58	..	61
B	23.6	2	25	40	..	44	..	47
C	18.7	1	19	30	..	35	..	36
D	8.4	19	45	56	..	61	..	62
E	54	99	99	99	..	99	..	100
F	21.4	89	92	91	..	91	..	..
G	24.2	90	95	94	..	96	..	..
H	9.6	37	40	49	56	56	56	..
I	32.5	72[a]	76	83	86	87	..	..

[a] A 0.5-Gm. sample studied for 4½ hours in gastric fluid and 1½ hours in intestinal fluid.

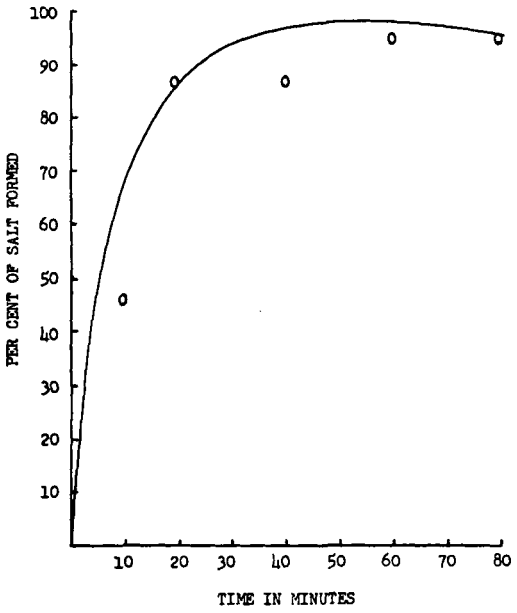

Fig. 1.—Reaction rate at room temperature between a 2.8% aqueous carbinoxamine maleate solution, equivalent to 25% of the theoretical capacity of the resin, and resin A.

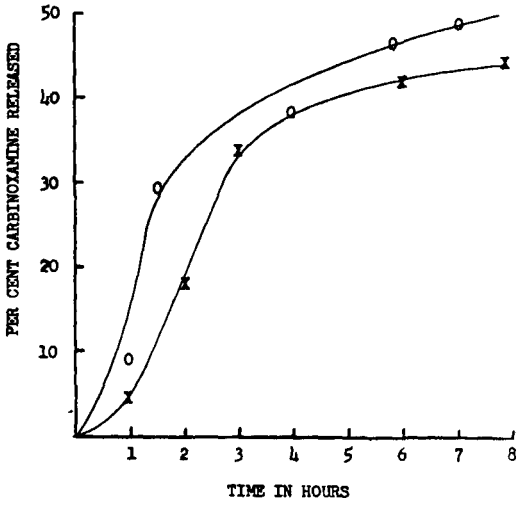

Fig. 2.—Rate of dissociation of two salts assaying 25.0 and 25.6% carbinoxamine, respectively. O, Surface area = 1,463 mm.²/100 mg.; X, surface area = 758 mm.²/100 mg.

The tubes containing samples were allowed to move up and down in individual 4 × 15-cm. test tubes containing 75 ml. of eluant maintained at 37.5 ± 3°. Table II describes the release rates of the various resins described in Table I.

In 5 morphine-chloralose anesthetized dogs, a 0.7 mg./Kg. dose of carbinoxamine, given intraduodenally as the maleate salt, showed maximal response to intravenous histamine in an average time of 33 minutes. The elapsed time from the average maximal response until histamine response returned to one-half the control response averaged 101 minutes. In 4 morphine-chloralose anesthetized dogs, a 2 mg./Kg. dose of carbinoxamine on resin, intra-

duodenally, showed maximal response to intravenous histamine in an average time of 74 minutes. The elasped time from the average maximal response until histamine response returned to one-half the control response averaged one 106 minutes.[2] Assuming about 50% dissociation of the resin salt, the prolonged protection is significant.

An *in vivo* study of total release of carbinoxamine from polystyrene sulfonic acid in a healthy adult male was accomplished. A sample of resin A salt, shown in Fig. 2 as X—X, containing 33 mg. of carbinoxamine was ingested 5 hours after the evening meal and 8 hours before the morning meal. A portion was recovered from the feces about 24 hours later and was isolated and assayed for carbinoxamine remaining on the resin. It was found that this dose released 53% of the carbinoxamine in a normal gastrointestinal tract compared to 44% released by the *in vitro* test method reported.

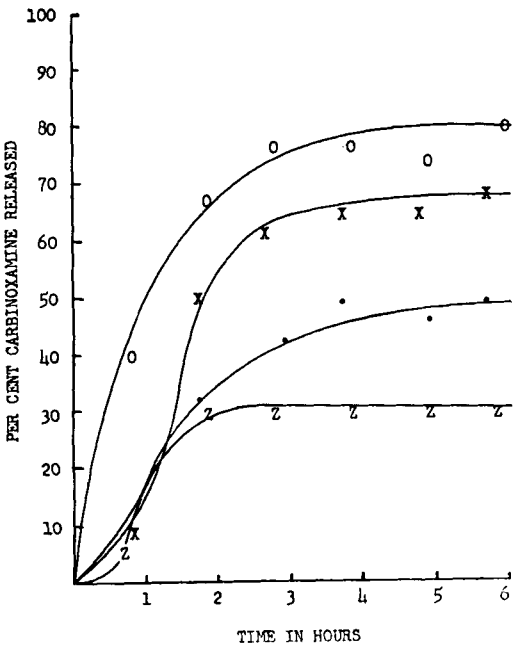

Fig. 3.—Rate of dissociation of smaller than 80-mesh samples. O, Sample 65% converted to salt form; X, same salt plus equal weight of resin A acid; Z, same salt plus three times the weight of resin A acid; ●, sample 47% converted to salt form.

RESULTS AND DISCUSSION

Several variables were shown to have important effects on dissociation of the resin salts as reported in Table II. Resins having a pKa 5.2 or greater release carbinoxamine too rapidly for sustained action, e.g., resins E, F, and G. Resins having a pKa less than 5.2 release carbinoxamine in a more desirable manner for sustained release effect, e.g., resins A, B, C, D, and H. For those resins having two pK values, the overall effect is between the two values. Resin A gives time-release characteristics closest to a straight line function and reacts efficiently with carbinoxamine. Increase in cross linkage of the polymers reduces both the efficiency of salt formation and of dissociation. Figure 2 shows the effect of surface area on release characteristics. Doubling of the surface area increased the dissociation *in vitro* by about 5% in this test. Figure 3 shows that partial loading of resin A or introduction of acid resin A in the presence of resin salt A gives results similar to those reported by Chaudhry and Saunders (3). However, the salt plus equal weight of resin releases more than expected.

Tablets were formulated and it was found that the salt of resin A, ground to smaller than 40 mesh, could be compressed well when aluminum hydroxide or dicalcium phosphate was used as the main tablet diluent and gelatin solution was used in granulation. Such tablets, colored with pigments or other tablets coated with sugar, showed no alteration in assay or release characteristics on storage for 3 months at about 40°.

It was found that the salt of resin A, ground to smaller than 80 mesh, could be suspended well in tragacanth or Carbopol 934[3] sols. The effect of pH on release was studied and indicates that a weak ionic aqueous suspension would release little or no carbinoxamine between pH 3 and 5. Assay and release characteristics of suspensions showed no alteration on storage for 3 months at about 40°.

SUMMARY AND CONCLUSIONS

Six new insoluble synthetic cation exchange resin salts of carbinoxamine have been prepared and evaluated. Salt formation and dissociation were studied and polystyrene sulfonic acid was found to be superior. Retardation of dissolution occurred, however, with all salts made from resins having a pKa less than 5.2. For the preferred acid salt it was found that: particle size plays a minor role in dissolution rate, partial salt formation or the presence of added free acid markedly alters dissolution rate, and increased crosslinking of the resin reduces the dissolution rate. In anesthetized dogs it was shown that the resin salt protected against histamine for a significantly longer time than carbinoxamine maleate. A new *in vivo* test method of total release was compared with the *in vitro* test method used and they were found to be of the same order of magnitude. Tablets and suspensions of the resin salt have been prepared and found to be stable over a period of 3 months at about 40°.

REFERENCES

(1) Goodman, L. S., and Gilman, A., "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1955, p. 659.
(2) Kunin, R., and Myers, R. J., "Ion Exchange Resins," John Wiley & Sons, Inc., New York, N. Y., 1950.
(3) Chaudhry, N. C., and Saunders, L., *J. Pharm. and Pharmacol.*, **8**, 975(1956).
(4) "United States Pharmacopeia," 15th rev., Mack Publishing Co., Easton, Pa., 1955, p. 937.

[2] The assistance of Mrs. R. G. Peterson is gratefully acknowledged.

[3] Kindly supplied by the B. F. Goodrich Co.