Polycarboxylic Acid Ion-Exchange Resin Adsorbates for Taste Coverage in Chewable Tablets

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Abstract □ High potency adsorbates of methapyrilene, dextromethorphan, ephedrine, and pseudoephedrine were prepared by column procedures using a polymethacrylic acid ion-exchange resin. Taste evaluation of the adsorbates showed a significant reduction in bitterness of the drugs. Coating the adsorbate particles with a 4:1 ethylcellulose–hydroxypropylmethylcellulose mixture reduced the bitterness further. Taste coverage was maintained after incorporation of the coated adsorbate into chewable tablets. *In vitro* release-rate studies showed immediate and complete drug elution from uncoated adsorbates. Release from coated adsorbates varied with the extent of coating. *In vivo* drug availability was demonstrated by LD_{50} tests in mice and rats and by a urinary excretion crossover study in humans.

Keyphrases □ Tablets, chewable—improved palatability, coating-dependent release rates □ Taste coverage, chewable tablets—ion-exchange resins □ Bioavailability—chewable tablets, coating effect □ Timed-release tablets—coated drug–carboxylic ion-exchange resin absorbates □ Ion-exchange resins, polycarboxylic acid—taste coverage, chewable tablets

The adsorption of bitter drugs onto synthetic ion-exchange resins to achieve taste coverage has been well documented (1–7). With amine-containing drugs, polysulfonic acid resins are more efficient than polycarboxylic acid exchangers for this purpose since their lower pKa (approximately 2 *versus* 5–6) yields a stronger drug–resin bonding. However, this stronger bonding results in a slower *in vivo* elution of drug from the polysulfonic acid resins, a principle that has been utilized in sustained-release dosage forms (8–10). In addition, the exchange capacities of the latter resins are usually lower than those of the polycarboxylic acid exchangers (4–5 *versus* greater than 10 meq./g.), with the result that a lower quantity of drug may be adsorbed.

Previous studies in this laboratory on the interaction of amine drugs with polycarboxylic acid ion-exchange resins (11) indicated that these resins may be quite useful in taste coverage. These studies indicated that saliva, with an average pH of 6.7 and a cation concentration of 40 meq./l. (12), would only elute a limited percentage of drug from a polycarboxylic acid resin adsorbate. However, rapid and quantitative elution would occur as soon as the adsorbate is exposed to the low pH of the stomach. These studies also revealed that drugs containing tertiary amine groups give much higher selectivity coefficients than those with primary, secondary, or quaternary amines. Thus, taste coverage should be most efficient with tertiary amine drugs.

The particle coating of polycarboxylic acid ion-exchange resin adsorbates was also considered as a method for achieving taste coverage. Two recent patents described related procedures. In one (13), anion-exchange resins without drugs were coated for palatability; the other (14) dealt with coating of cation-exchange resin adsorbates for slow drug release. In such a method, the resin could be considered primarily a carrier for the drug in the coating step. Although this process would be more complex and expensive than direct coating of crystals, there could be several advantages:

1. The taste coverage ability of the uncoated adsorbate could be additive to that of the coating.
2. Polymer coatings could adhere more effectively to ion-exchange resin particles than to crystals.
3. The desired narrow particle-size range could be obtained by proper selection of the resin.
4. The resin particles could be more compact and have less surface area than most crystals.
5. The adsorbate could be less sensitive than pure drug to explosivity due to static charge.
6. The extremely rapid elution rate in acid could make the drug available more rapidly in the stomach.
7. The water adsorptive and swelling properties of the polycarboxylic acid ion-exchange resins could hasten tablet disintegration and thus provide drug availability without chewing.

This paper describes taste coverage studies with drug adsorbates made with a polymethacrylic acid ion-exchange resin. Four bitter drugs were selected for this evaluation. They included two with tertiary amine groups (methapyrilene and dextromethorphan) and two with secondary amines (ephedrine and pseudoephedrine).

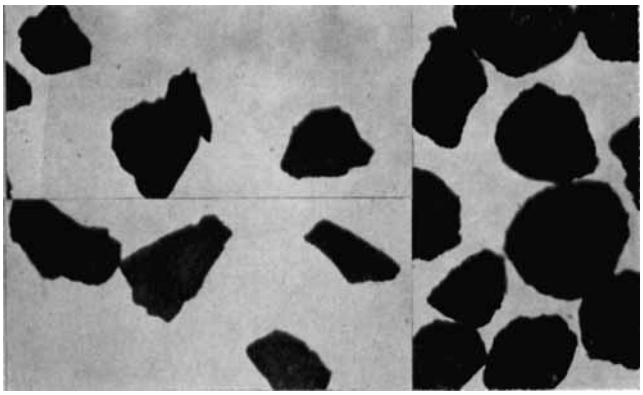

Figure 1—*Comparison of coated and uncoated pseudoephedrine adsorbate particles. Photograph on left shows uncoated adsorbate while the right photograph shows adsorbate with 31.0% coating.*

EXPERIMENTAL

Resin—In all studies, a polymethacrylic acid ion-exchange resin with a particle-size range of 72–147 μ, a crosslinkage of 4–5% divinylbenzene, and an exchange capacity of greater than 10 meq./g., was used.

Adsorbate Preparation—Approximately 400 g. of resin was slurried 30 min. in 4 l. of 1 *N* NaOH. The slurry was then transferred to a 10.2-cm. (4-in.) diameter, 1.5-m. (5-ft.) glass column equipped with a coarse fritted-glass disk at the bottom. The resin was then

Table I—Drug–Resin Adsorbate Preparation

Drug	Salt Used	Resin Cycle	Grams Drug Used per Gram Resin	Influent Concentration, mg./ml.	Yield[a], %	Adsorbate Potency[b], mg./g.
Methapyrilene	HCl	Na	1.12	50	99.9	496
Dextromethorphan	HBr	Na	1.44	20	98.4	522
Ephedrine	Base	H	1.89	50	96.3	645
Pseudoephedrine	HCl	Na	3.97	50	37.9	552

[a] Yield was drug adsorbed divided by drug added and determined from total drug in effluent. [b] Adsorbate potency is milligrams drug base per gram of dried adsorbate.

Table II—Bitterness Evaluations for Ephedrine Derivatives

Form[a]	Dosage[b]	Coating[c], %	Bitterness Level[d] after 10 sec.	1 min.	2 min.	5 min.	10 min.	15 min.
U	P	0	>3	>3	3	2½	1½	½
UA	P	0	2	1½–2	1½	½–1	)(	0
CA	P	23.4	)(	½	½	)(	0	0
CA	P	34.2	)(–½	½	)(	)(	0	0
CA	P	38.6	)(	)(	0	0	0	0
CA	P	42.0	0	)(	0	0	0	0
UA	T	0	1–1½	1½	1	)(–½	0	0
CA	T	23.4	½	½	½	)(	)(	0
CA	T	34.2	)(–½	)(	)(	)(	0	0
CA	T	38.6	)(–½	½	½	)(	0	0
CA	T	42.0	0	0	0	0	0	0

[a] U = drug base; UA = uncoated adsorbate; CA = coated adsorbate. [b] P = particles; T = chewable tablets. [c] Percent of coated adsorbate weight. [d] 3 = strong bitterness; 2 = moderate bitterness; 1 = slight bitterness;)(= threshold.

backwashed 1 hr. with water using a peristaltic pump. Four liters of 1 *N* NaOH was then pumped downflow at a rate of 4 l./hr., followed by 5 l. of water, 8 l. of 1 *N* HCl, 5 l. of water, 8 l. of 1 *N* NaOH, and 5 l. of water. The calculated amount of drug that would yield an adsorbate containing 50–60% drug was dissolved in water and pumped downflow at 4 l./hr. followed by 5 l. of water. Excess liquid was drained from the resin bed by suction, and the wet adsorbate was transferred to glass pans. It was then dried in a vacuum oven at 50° to constant weight.

Coating Procedure—The dextromethorphan, ephedrine, and pseudoephedrine adsorbates were coated to several different coating levels by a procedure similar to that described by Coletta and Rubin (15), using an air suspension coater. Based on their results, a 4:1 mixture of ethylcellulose–hydroxypropylmethylcellulose was selected as the coating material and used in all cases. Figure 1 compares coated adsorbate particles with uncoated adsorbate to emphasize the efficiency of the coating. The percentage coating for each sample was determined by assaying for drug before and after coating. Generally, the values obtained corresponded to those calculated from the amount of coating material added.

Tableting Procedure—A calculated weight of adsorbate, containing 11.67 g. of dextromethorphan, 20.48 g. of ephedrine, 21.94 g. of methapyrilene, or 49.15 g. of pseudoephedrine, was blended 20 min. in a twin-shell V blender with 7 g. of magnesium stearate and enough pregranulated mixture to make 700 g. The pregranulation was made by massing a mixture of 700 g. of mannitol, 292 g. of sucrose, and 8.0 g. of cyclamate sodium with alcohol, granulating through a 6-mesh screen, drying at 50°, and screening through a 16-mesh screen. The drug blend was compressed on a 16-station rotary compressing machine[1] to give approximately 1000 tablets weighing 700 mg. each.

Release-Rate Studies—Drug release from uncoated adsorbates was determined by adding 100 mg. of adsorbate to a 25-ml. test tube, followed by 10 ml. of 0.08 *N* HCl. The mixture was immediately stirred on a mixer[2] for the specified time and then rapidly filtered. Eleven different time periods, from 5 to 600 sec., were used with each adsorbate. The filtrates were then assayed by UV spectroscopy (11).

Drug release at pH 6.7 was determined by adding 500 mg. of adsorbate to a test tube, followed by 10 ml. of a pH 6.7 phosphate buffer (0.04 *N* in sodium ion). The mixture was immediately stirred on a mixer[2] for 1 min., rapidly filtered, and assayed.

Release from coated adsorbates and tablets was determined by adding 3.00 g. of adsorbate or eight gently crushed tablets to a 500-ml. conical flask suspended from a wrist-action shaker[3] into a 37° water bath. Three hundred milliliters of either 0.08 *N* HCl or simulated intestinal fluid USP (pancreatin omitted) was added, and the flask was shaken for 24 hr. Thirteen 5-ml. samples of solution were removed periodically from 5 min. to 7 hr., and a final sample was obtained at 24 hr. These were assayed by UV spectroscopy after the required dilutions.

Taste Evaluation—All taste evaluations were made by a trained flavor profile panel (16), using at least seven members for each sample. A time–intensity method (17) was used, in which a sample equivalent to a normal dose was held in the mouth (chewed in the case of tablets) for 10 sec. Bitterness levels were recorded immediately

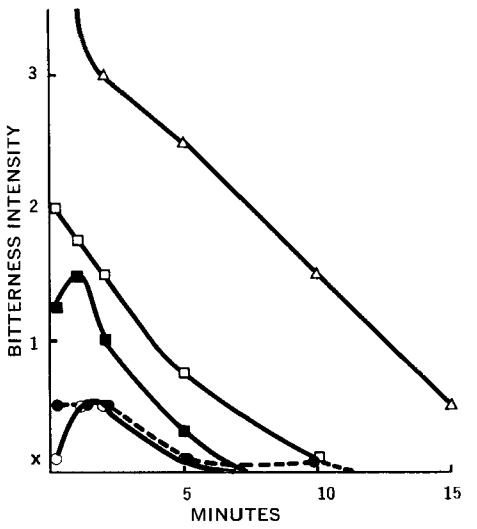

Figure 2—*Bitterness intensity curves for various ephedrine dosages. Key: △, ephedrine base; □, uncoated adsorbate; ■, uncoated adsorbate tablets; ○, 23.4% coated adsorbate; and ●, chewable tablets containing 23.4% coated adsorbate.*

[1] Stokes B-2, F. J. Stokes Corp., Philadelphia, Pa.
[2] Vortex Genie, Scientific Products, Evanston, Ill.
[3] Burrell Corp., Pittsburgh, Pa.

Table III—Bitterness Evaluations of Dextromethorphan Derivatives

Form[a]	Dosage[b]	Coating[c], %	Bitterness Level[d] after 10 sec.	1 min.	2 min.	5 min.	10 min.	15 min.
HBr	P	0	>3	>3	2½	1½	1	½
UA	P	0	2	2	1½	½	)(	0
CA	P	25.4	½	)(–½	)(	)(	0	0
CA	P	34.6	)(–½	)(	)(	0	0	0
CA	P	40.6	)(	)(	0	0	0	0
UA	T	0	1½	1½	1½–2	1½	1	)(
CA	T	25.4	)(–½	½	)(	)(	)(	0
CA	T	34.6	)(	)(–½	)(–½	)(	0	0
CA	T	40.6	)(	)(	)(	)(	0	0

[a] UA = uncoated adsorbate; CA = coated adsorbate. [b] P = particles; T = chewable tablets. [c] Percent of coated adsorbate weight. [d] 3 = strong bitterness; 2 = moderate bitterness; 1 = slight bitterness;)(= threshold.

Table IV—Bitterness Evaluations of Pseudoephedrine Derivatives

Form[a]	Dosage[b]	Coating[c], %	Bitterness Level[d] after 10 sec.	1 min.	2 min.	5 min.	10 min.	15 min.
HCl	P	0	>3	>3	>3	2	1	1
UA	P	0	2	2½	2	1½	—	—
CA	P	21.0	1	1½	1	½	)(	0
CA	P	25.4	)(	½	)(	)(	0	0
CA	P	31.0	)(	)(	0	0	0	0
CA	T	25.4	½	1½	1½–2	1½–2	½–1	)(

[a] UA = uncoated adsorbate; CA = coated adsorbate. [b] P = particles; T = chewable tablets. [c] Percent of coated adsorbate weight. [d] 3 = strong bitterness; 2 = moderate bitterness; 1 = slight bitterness;)(= threshold.

and then at 1, 2, 5, 10, and 15 min. Bitterness intensity values were based on a 0–3 scale, with 3 being strong bitterness (0.20% caffeine solution), 2 being moderate (0.10% caffeine), 1 being slight (0.05% caffeine), and being threshold (0.001%).

Determination of LD_{50}—Groups of either 10 female Swiss-Webster mice, 16–24 g. in weight, or six Sprague-Dawley male weanling rats, 40–70 g., were given various doses of the drugs suspended or dissolved (1–10%) in a 0.5% methylcellulose solution. The animals were observed for at least 7 days. The LD_{50} and associated confidence limits were calculated according to the method of Litchfield and Wilcoxon (18).

Urinary Excretion Study—Eight human subjects were used for this study. Four subjects were administered single 60-mg. doses of pseudoephedrine base in capsules; the other four received coated pseudoephedrine adsorbate (60 mg. drug) incorporated into chewable tablets. Urine samples were collected at 0–2, 2–4, 4–8, 8–12, and 12–24 hr. One week later, the subjects were crossed over and the sequence was repeated. The urine samples were assayed by GLC (19).

RESULTS AND DISCUSSION

Selection of the resin was based primarily on its particle-size range. Attempts to use resins with particles smaller than 72 μ presented considerable difficulty in the column operations. Although particles larger than 147 μ function better in column operations, their large size makes them too gritty for incorporation into chewable tablets.

A column procedure was found necessary to obtain adsorbates with the high drug concentrations desired. Batch operations gave both lower potency adsorbates and lower yields. These findings are consistent with the selectivity coefficients obtained for these drugs in an earlier study with carboxylic acid ion-exchange resins (11). Table I summarizes the results obtained in the preparation of the drug–resin adsorbates by column procedures.

The adsorption technique for each drug was adjusted to allow for variations in the physical constants of the drugs. The most efficient loading procedure would be to use the drug base and the resin on the acid cycle. However, only ephedrine base had sufficient solubility for such a procedure. In using soluble salts of the other three drugs, it was necessary to put the resin in the base form. If left in the acid form, the acid generated by adsorption would rapidly elute part of the drug and reduce yields. Nearly quantitative yields were obtained with dextromethorphan and methapyrilene. However, to get the desired high potency with pseudoephedrine, a large excess of drug was necessary. This resulted in a substantially reduced yield. The differences in adsorptive characteristics between these drugs can be attributed to the greater affinity of the resin for tertiary amines than secondary amines. At pH 5.5, the selectivity coefficients obtained for methapyrilene and dextromethorphan were, respectively, 24 and 43 times greater than that obtained for pseudoephedrine (11). Since ephedrine has a selectivity coefficient similar to pseudoephedrine, it too would have given poor yields if a drug salt and sodium cycle

Table V—Bitterness Evaluation of Methapyrilene Derivatives

Form	Dosage	Bitterness Level after 10 sec.[a]
HCl salt	Particles	>3
Uncoated adsorbate	Particles	1
HCl salt	Tablets	>3
Uncoated adsorbate	Tablets	2

[a] 3 = strong bitterness; 2 = moderate bitterness; 1 = slight bitterness.

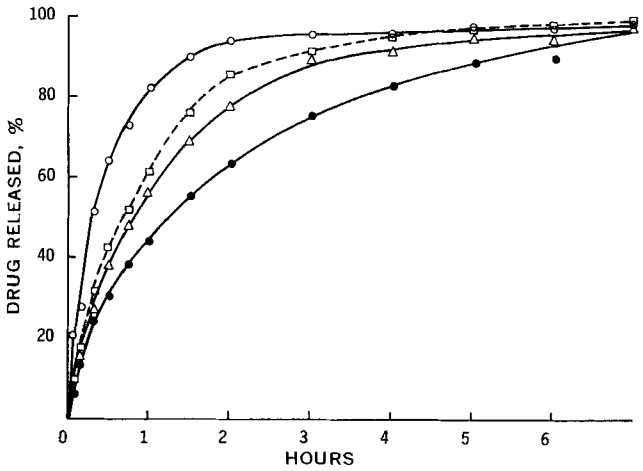

Figure 3—*Release of ephedrine from coated adsorbates in 0.08* N *HCl. Key:* ○, *23.4% coating;* □, *34.2% coating;* △, *38.6% coating; and* ●, *42.0% coating.*

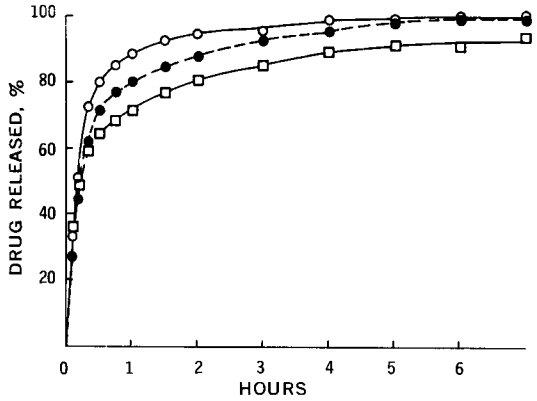

Figure 4—*Release of dextromethorphan from coated adsorbates in 0.08* N *HCl. Key:* ○, *25.4% coating;* ●, *34.6% coating; and* □, *40.6% coating.*

resin were used. Generally, the drug was added to the resin column as a 5% solution. However, the lower solubility of dextromethorphan hydrobromide would allow this concentration only by maintaining the solution temperature above 50°. It was found more convenient to reduce the influent concentration to 2% and accept the large volume increase.

Taste evaluations for the pure drugs, adsorbates, and coated adsorbates are shown in Tables II–V. In all samples except methapyrilene, time–intensity values were obtained to include aftertaste in the evaluation. Figure 2 graphically shows a comparison of the bitterness levels obtained from various ephedrine forms. In all cases, the pure drugs were extremely bitter. Adsorption onto the resin reduced the bitterness to some extent. This finding is consistent with the expectation that saliva would only elute a limited percentage of drug from the uncoated adsorbate. Table VI shows the percentages eluted from 500 mg. of adsorbate by 10 ml. of pH 6.7 (0.04 *M*) buffer in 1 min. These percentages were only slightly affected by exposure times above 30 sec., indicating that these numbers are close to equilibrium values. The larger percentages obtained with ephedrine and pseudoephedrine again emphasize the stronger bonding between the resin and tertiary amines.

Particle coating the adsorbates gave further bitterness reduction, with the extent of this reduction being dependent on the coating level. In all cases, a coating level of about 25% appeared to be sufficient to reduce bitterness to less than 1 (slight bitterness) on the intensity scale. Incorporation of the adsorbates into chewable tablets generally had little effect on the taste coverage. However, in some cases the bitterness levels were increased. This result can be attributed to rupture of the coating either during tablet compression or chewing. Incorporation of flavoring or sweetening agents into the tablet formula would be beneficial in counteracting this effect.

Availability of drug from the adsorbates was demonstrated in a number of *in vitro* experiments. Table VI shows the drug-release characteristics from uncoated adsorbates in several different solu-

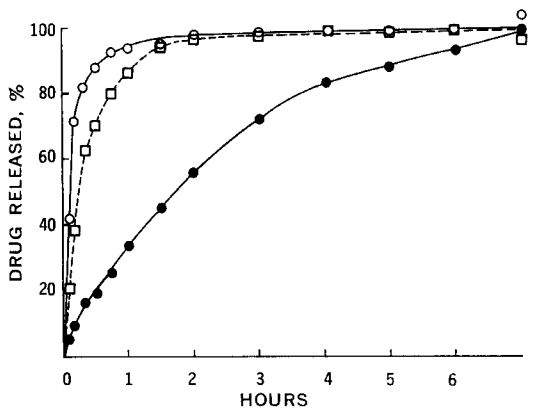

Figure 5—*Release of pseudoephedrine from coated adsorbates in 0.08* N *HCl. Key:* ○, *21.0% coating;* □, *25.4% coating; and* ●, *31.0% coating.*

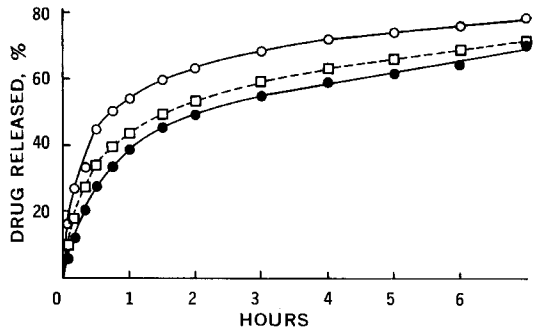

Figure 6—*Release of ephedrine from coated adsorbates in simulated intestinal fluid. Key:* ○, *23.4% coating;* □, *34.2% coating; and* ●, *42.0% coating.*

tions. In 0.08 *N* HCl, the elution half-lives were all below 15 sec. while 90% of the drugs were eluted in 0.8–2.2 min. Essentially complete drug release occurred within 15 min. Completion was demonstrated by eluting no additional drug when the resin particles were filtered and reslurried with fresh acid solution. This rapid and complete drug elution in 0.08 *N* HCl is due to the high pKa of the polymethacrylic acid ion-exchange resins. Assuming a pKa similar to the 4.85 reported by Gustafson (20) for this type of resin, only 0.022% of the potential anionic sites would be dissociated at pH 1.2, and less than 0.05% of the drug in the adsorbates would remain ionically bonded.

Table VI also shows the equilibrium distribution of drug in simulated intestinal fluid using 10 mg. of adsorbate/ml. of solution. Although the mixtures were allowed 24 hr. for equilibration, the reactions were again very rapid and essentially complete within 15–30 min. The equilibrium values varied with the drug, with greater than 90% eluted from the two secondary amine adsorbates and less than half from the tertiary amine adsorbates. Although drug availability might be affected by incomplete elution in the intestine, such a possibility appears remote. *In vivo* equilibrium percentages would be substantially higher than those shown in Table VI, since adsorbate concentrations in the body should be well below the 10 mg./ml. used to obtain the listed values. Lower adsorbate concentrations would result in an increase in the number of eluting cations per unit adsorbate weight and, thus, a shift in equilibrium. In addition, the rapid equilibration rates would cause continuous elution of drug from the resin to maintain equilibrium as the drug in solution is absorbed into the blood.

Drug release from the adsorbates was slowed considerably by the introduction of coating. Figures 3–5 show the release from coated adsorbates in 0.08 *N* HCl. The curves demonstrate that the release rate from a given adsorbate is governed primarily by the coating level. However, a comparison of the figures indicates that the drug used also has an effect; identical coating levels on different adsorbates will not necessarily yield similar release rates. This may be due to variability in physical constants of the drugs (solubility, diffusivity, selectivity coefficient, *etc.*) or simply the effect of the drug

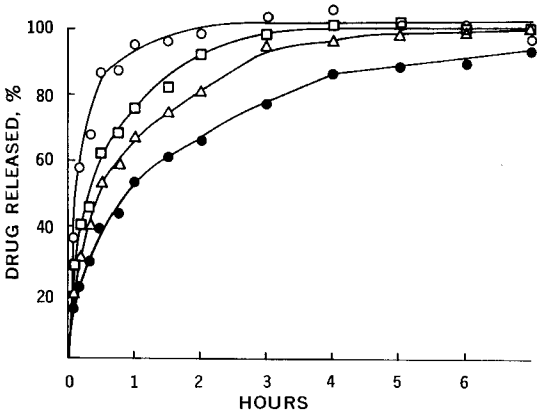

Figure 7—*Release of ephedrine from crushed tablets made from coated adsorbates in 0.08* N *HCl. Key:* ○, *23.4% coating;* □, *34.2% coating;* △, *38.6% coating; and* ●, *42.0% coating.*

Table VI—Release of Drug from Uncoated Adsorbates in pH 6.7 Buffer, 0.08 *N* HCl, and Simulated Intestinal Fluid

Drug	Percent Released after 1 min. in pH 6.7 Buffer	$t_{1/2}$ in 0.08 *N* HCl, min.	$t_{90\%}$ in 0.08 *N* HCl, min.	Percent Released after 24 hr. in Simulated Intestinal Fluid
Ephedrine	26.7	0.2	1.0	98.1
Dextromethorphan	4.89	0.1	0.8	30.4
Pseudoephedrine	32.1	0.1	1.1	92.5
Methapyrilene	3.43	0.2	2.2	45.5

on coating efficiency. As in the case of uncoated adsorbates, drug release in simulated intestinal fluid proceeded to equilibrium rather than completion. The equilibrium percentages for all coated adsorbates were similar to the values shown in Table VI for uncoated adsorbates. In addition to incomplete elution, the release rates for attaining equilibrium were slower. This is exemplified in Fig. 6 with coated ephedrine adsorbates. Although equilibrium for these samples was close to complete elution, the percentages released at each time interval were substantially less in simulated intestinal fluid than in 0.08 *N* HCl. This may have been due to a lower drug concentration of the solution within the coated resin particles caused by either decreased drug solubility or lower elution efficiency at pH 7.5 *versus* pH 1.2.

Drug release from ground tablets formulated from the coated adsorbates was slightly faster than that obtained from coated adsorbate particles. Figure 7 shows release curves from ephedrine tablets formulated from coated adsorbate. Since the rate increases obtained from tablets (Fig. 7 *versus* Fig. 3) are most pronounced in the early stages, it is most likely that coating rupture of some particles occurs during tablet compression or grinding. This effect would also be obtained when these tablets are chewed.

Acute oral toxicity tests in mice and rats were used to determine *in vivo* availability of drug from the resin adsorbates (Table VII). The high LD_{50} of the pure resin indicated that its contribution to toxicity should be minimal. The small differences in the LD_{50} values between drug salts and uncoated adsorbates (within confidence limits) implies that resin adsorption does not affect drug availability. Similarly, pseudoephedrine was available from crushed tablets made from coated adsorbate to the same extent as the drug base. However, the LD_{50} for coated pseudoephedrine adsorbate particles was substantially increased. This suggests a reduction of the peak blood level concentration, although not necessarily a decrease in total availability.

Total availability of drug from coated adsorbate was demonstrated in a crossover urinary excretion study in humans. Figure 8 compares the cumulative recovery of drug from pseudoephedrine base capsules and coated drug adsorbate formulated into chewable tablets. The results show slower, but complete, availability of drug from the coated adsorbate. Since the 31% coated pseudoephedrine

Table VII—Comparison of LD_{50} Results between Pure Drugs and Drug Adsorbates

Sample	Animals	LD_{50}, mg./kg.	95% Confidence Limits, mg./kg.
Resin	Mice	>10,000	—
Pseudoephedrine hydrochloride	Mice	371	275–530
Uncoated pseudoephedrine adsorbate	Mice	500	431–580
31% Coated pseudoephedrine adsorbate	Mice	910	812–1020
Pseudoephedrine base	Rats	660	537–812
Coated pseudoephedrine adsorbate (tablets)	Rats	680	577–803
Dextromethorphan hydrobromide	Mice	250	223–280
Uncoated dextromethorphan adsorbate	Mice	210	190–234

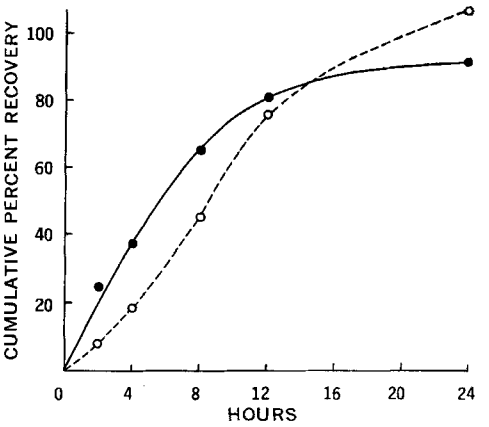

Figure 8—*Urinary excretion study of pseudoephedrine dosages administered to humans. Key:* ●, *pseudoephedrine base capsules; and* ○, *tablets containing 31% coated pseudoephedrine adsorbate.*

adsorbate used in this test was among the slowest releasing samples tested (Fig. 5), it probably represents maximum *in vivo* availability delay. Coated adsorbates with faster *in vitro* release rates should give more rapid and similarly complete availability.

Examination of the urinary excretion curves along with the *in vitro* results indicates that the coated drug–carboxylic acid ion-exchange resin adsorbates might be useful for sustained release as well as taste coverage. Whereas the use of sulfonic acid ion-exchange resins for this purpose appears to be primarily dependent on equilibrium phenomena, release from the coated adsorbates is primarily dependent on the coating level. Thus, desired drug release rates should be attainable by control of the coating level.

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