Sustained-Release Drug Delivery System I: Coated Ion-Exchange Resin System for Phenylpropanolamine and Other Drugs

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Abstract ☐ Ion-exchange resin–drug complexes have been used to formulate sustained-release products of acidic and basic drugs. However, sustained release may be difficult to achieve due to many variables. A novel technique is reported that minimizes these variables by providing a polymeric film coating to the ion-exchange resin–drug complex particles, making drug release from these particles diffusion controlled. Direct application of an atomized polymer solution to the fluidized ion-exchange resin–drug complex particles was ineffective in controlling drug release since the coating came off in the dissolution medium due to swelling and fracturing of the particles. Pretreatment of the ion-exchange resin–drug complex particles with an agent such as polyethylene glycol was essential for the particles to retain their geometry and coating during dissolution. With divinylbenzenesulfonic acid resin complexed with phenylpropanolamine as a model, mixtures of ethylcellulose-coated and uncoated resin–drug complex particles were prepared. These mixtures gave varying drug release profiles that showed rank-order correlation with plasma concentration profiles obtained in bioavailability studies with suspension dosage forms.

Keyphrases ☐ Phenylpropanolamine—microencapsulated with ion-exchange resin, new sustained-release delivery system, effect of particle size, coating, and dosage form on bioavailability ☐ Drug delivery systems—sustained release of phenylpropanolamine, ion-exchange resin–drug complex ☐ Microencapsulation—symposium, sustained-release delivery system for phenylpropanolamine, coated ion-exchange resin–drug complex

Ion exchangers are solid and suitably insolubilized high-molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stoichiometric, with the displacement of one ionic species by another on the exchanger (1). The commercial availability of insoluble exchange resins having one functional group caught the attention of pharmaceutical scientists and resulted in several patents (2–10).

Keating (2) listed the following advantages of adsorbing basic nitrogen-containing drugs onto sulfonic acid cation-exchange resins and using them in dosage forms: (*a*) prolong availability by releasing the drug from the complex over 12 hr in the GI tract; (*b*) reduce toxicity by slowing drug absorption; (*c*) increase stability by protecting the drug from hydrolysis or other degradative changes in the GI tract; (*d*) improve palatability; and (*e*) enable formulation of liquid and solid sustained-release dosage forms.

BACKGROUND

Schlichting (11) evaluated carbinoxamine–resin complexes of polystyrenesulfonic acid (pK 1.3), phenol formaldehydesulfonic acid (pK 1.3), polyacrylic acid (pK 5.2), polymethacrylic acid (pK 6.0), polyacrylic acid–sulfonic acid (7:3 ratio), and polystyrene phosphonate (pK 3.2). The polystyrene sulfonic acid salt of the drug showed the most retardation in the release of carbinoxamine. Increased resin cross-linking also decreased the dissolution rate. Resins with a pK value of 5.2 and greater showed no retardation of dissolution.

Koff (5) described the use of coating with castor wax to improve the palatability and stability of a highly acidic cation-exchange resin complexed with amotropine. Macek *et al.* (6) improved the gritty and astringent taste of finely divided polystyrene divinylbenzene copolymer anion-exchange resin intended for swallowing by coating the particles with an acrylic polymer cross-linked with allyl sucrose. Borodkin and Sundberg (7, 8) coated 72–147-μm particles of polymethacrylic acid–ion-exchange complexes of basic drugs with an ethylcellulose–hydroxypropyl methylcellulose (4:1) mixture using an air suspension coater to overcome the bitterness of the drugs.

Clark (9) applied the enteric-coating agent cellulose acetate phthalate on 0.1–1-mm diameter pellets of cation-exchange adsorbate of drugs in a coating pan. No dissolution data were presented.

Jungmann (10) spray dried a slurry of codeine–resin adsorbate in a solution of the coating agent, a copolymer of acrylic acid esters and methacrylic acid esters modified with ammonium groups. At 13.3% drug load and 20% level of coating, the 2-hr release was ~70%.

In an attempt to formulate sustained-release dosage forms of phenylpropanolamine using the sulfonic acid cationic resin system, sufficient retardation in drug release could not be obtained. Application of a diffusion barrier coating on the resin–drug complex was attempted using an air suspension technique. This report presents the results of this work.

EXPERIMENTAL

Materials—*Resins*—A gel-type divinylbenzenesulfonic acid cation-exchange resin consisting of spherical particles (590–840 μm) was used as the model large-particle resin[1]. The model small-particle resin was obtained by grinding these spherical particles[2]; these particles ranged in size from 37 to 150 μm. These resins are approved for pharmaceutical use by the Food and Drug Administration.

Drugs—Phenylpropanolamine, a sympathomimetic amine drug [biological half-life of 3.9 hr in humans, pK of 9.4 (12)] was the first drug used in this coating investigation. Other drugs used were dextromethorphan, pseudoephedrine, ephedrine, and phentermine. The results obtained with phenylpropanolamine and dextromethorphan are reported here. These drugs were obtained either as bases or their salts from standard suppliers of pharmacopeial quality drugs.

Coating Materials—Ethylcellulose 50 cps[3] was selected as the model diffusion barrier material. A refined vegetable oil[4] was used as a plasticizer.

Auxiliary Agents—Polyethylene glycol 4000[5] was selected to help retain resin geometry during coating and dissolution.

Solvents—The coating solvent was either ethanol or methylene chloride–acetone. These solvents were obtained from reliable commercial supplies of highest purity.

Water—Water was either distilled or deionized as indicated.

Equipment—*Coating Equipment*—The coating experiments were carried out using an air suspension coating apparatus[6].

Dissolution Test Apparatus—The dissolution assembly[7] was essentially the same as described in USP XIX (13).

Procedure for Phenylpropanolamine[8]–Resin Complex—Five hundred milliliters of 0.1 *N* HCl was added to a 1-liter vessel[9] (16 cm high

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[1] Amberlite IR-120, Rohm & Haas Co., Philadelphia, PA 19105.
[2] Amberlite XE-69 (also known as IRP-69), Rohm & Haas Co., Philadelphia, PA 19105.
[3] NF grade, Dow Chemical Co., Midland, Mich.
[4] Durkee Foods Division, SCM Corp., Rockville Center, NY 11570.
[5] Union Carbide Co., New York, NY 10017.
[6] Wurster, Dairy Equipment Corp., Madison, Wis.
[7] Model 72 R 115, Hanson Research Corp., Northridge, CA 91324.
[8] The following material describes the procedures for phenylpropanolamine dissolution. Other drugs were similarly tested spectrophotometrically at suitable wavelengths using appropriate amounts of samples.
[9] Kimble Glass Co., Division of Owens-Illinois, Montclair, NJ 07042.

X 10 cm i.d.). A three-bladed polyethylene propeller stirrer (2.5-cm blade size) was positioned just below the surface of the dissolution medium and rotated at 50 rpm. The temperature of the medium was allowed to rise to 37 ± 0.5°. A filtering device, consisting of an ~1-cm syringe filter holder[10] with a small cotton plug, enabled the dissolution medium to filter into a glass tube from which it was pumped through a polyethylene tube into a 1-cm path flow-through cell of an eight-channel recording spectrophotometer[11] and back to the dissolution vessel for continuous monitoring and recording on a moving chart. The assembly was set up to monitor and record six samples and one standard every 5 min at 257 nm and 0.5A attenuation.

Samples of phenylpropanolamine–resin complex equivalent to 90.6 mg (60 mg for a 5-cm cell) of phenylpropanolamine were added to each dissolution vessel. A phenylpropanolamine standard was run simultaneously. The drug in solution then was expressed as a percentage of the total drug present in the resin complex particles. Earlier experiments were carried out with a two-channel spectrophotometer[12] using a 5-cm flow-through cell at 60 rpm.

Procedure for Phenylpropanolamine–Resin Complex Dosage Forms—*Capsules*—The contents of a single capsule (containing resin complex product equivalent to 30.2 mg of phenylpropanolamine) were emptied into 168 ml of 0.1 N HCl contained in the dissolution vessel, and dissolution started. Several such dissolution runs were set up. The tests were carried out as described previously without the spectrophotometric monitoring. Dissolution was terminated at 0.5, 1, 3, and 5 hr, and the samples were immediately filtered free of the resin particles through medium-porosity sintered-glass funnels. The filtrates were assayed for phenylpropanolamine by the GLC technique to be described.

Suspensions—Fifteen milliliters of the suspension (containing resin complex product equivalent to 90.6 mg of phenylpropanolamine) was transferred to a medium-porosity sintered-glass funnel and washed free of the vehicle with two 30-ml quantities of distilled water. The resin then was transferred quantitatively to the dissolution vessel with 450 ml of distilled water; then 1 N HCl (50 ml) was added, and dissolution started. Several such dissolution runs were set up and completed as described under *Capsules*. The filtrates were assayed for phenylpropanolamine by GLC.

GLC Assay for Phenylpropanolamine—Fifty milliliters of the filtered dissolution medium was added to a 125-ml separator, and 2 ml of 10% NaOH was added and mixed. This mixture then was extracted with four portions of chloroform (20, 10, 8, and 8 ml); the chloroform layers were collected in a 50-ml volumetric flask, and the volume was adjusted. Two microliters of the sample or of a similarly prepared standard (126 μg/ml) was injected in a suitable gas chromatograph[13] for potency assay. The 183-cm × 2-mm glass[14] column was packed with 3% OV-225 on 100–120-mesh Gas Chrom Q, and the flow rate of the helium carrier gas was 40 ml/min. The column oven was maintained at 190°, the injection port temperature was 220°, and the flame-ionization detector was at 290°.

Determination of Water Uptake Time—Five grams of the resin or resin mixture was packed lightly in a 25-ml graduated cylinder with tapping. The initial volume of the mixture was noted. Deionized water (4 ml) was delivered to the top of the packed surface from a pipet held 2 cm away from the surface. The time, in seconds, required for the water layer to disappear completely was noted. At least two determinations were done for each mixture.

Apparent Specific Volume Determination—

1. Five grams of the resin was placed in a 15-ml graduated centrifuge tube. The tube was tapped to allow the resin to settle. When no more settling was noticed, the volume of the resin was noted, and the apparent specific volume of the resin was calculated.

2. Distilled water (10 ml) was added to the 15-ml centrifuge tube containing 5 g of the resin, and the contents were shaken and allowed to settle for 12 hr at either 23 or 97°. The volume of the resin then was determined, and the apparent specific volume of the resin was calculated for each temperature.

3. Melted polyethylene glycol 4000 (10 ml) was added to a centrifuge tube containing 5 g of the resin, and the contents were shaken and allowed to settle for 12 hr at 97°. The volume of the resin then was determined, and the apparent specific volume was calculated.

Microscopic Examination—The particles were examined using a low-power binocular microscope (objective ×3 and eyepiece ×10).

Particle-Size Determination—Two grams of the sample was placed on the top screen of a nest of suitable sieves[15], and the sifter was agitated for 15 min. The weight of the fractions retained on the screens was obtained. Particle sizes (d) at specific weight percents (16, 50, and 84) were obtained from a log probability plot of the data as described by Edmundson (14). These particle sizes are described later as $d16$, $d50$, and $d84$.

Preparation of Resin–Drug Complexes—The resin–drug complexes were prepared by the batch process as described by Keating (2).

The gel-type divinylbenzenesulfonic acid cation-exchange resin (either the large or small particle type) of hydrogen form was slurried in deionized water. Phenylpropanolamine base or any drug in its basic form was added to the resin slurry with agitation. The resin–drug complex was formed by the addition reaction. It was washed free of any unreacted drug with deionized water and dried in a fluid bed drier or tray drier at 60°. The dried, small particle resin–drug complex then was screened through a 60-mesh screen. The large particle resin–drug complex was screened through a 10-mesh screen. A drug load of ~33% was obtained with phenylpropanolamine using either resin.

The gel-type divinylbenzenesulfonic acid cation-exchange resin (either the large or small particle type) of sodium form was slurried in deionized water. Phenylpropanolamine hydrochloride or any drug in its salt form was added to the resin slurry with agitation. The resin–drug complex was formed by the exchange reaction. It was washed free of the exchanged salt and any free drug with deionized water. The washed resin–drug complex was dried and screened as described for a drug in its basic form. A drug load of ~25% was obtained with phenylpropanolamine using the fine particle resin.

Polyethylene Glycol Treatment of Resin–Drug Complex—The resin–drug complex was transferred to a suitable mixer and mixed with an aqueous solution of polyethylene glycol 4000. The ratio of drug–resin complex to polyethylene glycol 4000 varied from 4:1 to 5:1, depending on the resin–drug complex. The polyethylene glycol 4000-treated large particle resin–drug complex was used for coating directly. The treated fine particle resin–drug complex was dried in a fluid bed drier or tray drier to a moisture content of ~6% and then was screened through a 60-mesh screen before being coated.

Preparation of Coated Resin–Drug Complex—The polyethylene glycol 4000-treated resin–drug complex (core material) was transferred to a suitable coating apparatus[6]. A 15.24-cm coater handled ~500–600 g of the core material; a 45.72-cm coating apparatus could handle 15–25 kg. The core material then was coated with ethylcellulose–vegetable oil (2.5:1) in methylene chloride–acetone (10:1). Smaller batches were coated using ethanol as the solvent. The coated materials were screened using vibratory screens.

Preparation of Resin–Drug Complex Mixtures—The drug release rates and assays on the mixture components, *i.e.*, the phenylpropanolamine–resin complex (or any other resin–drug complex) and the coated phenylpropanolamine–resin complex (or any other coated resin–drug complex) were obtained. The ratio of the mixture components required for a desired drug release profile was calculated. Resin–drug complex mixtures were prepared by mixing suitable quantities of coated and uncoated resin–drug complexes. The resin–drug complex mixture was assayed for drug content and drug release rate to determine its suitability for sustained-release dosage form preparation.

Preparation of Capsule Dosage Forms—The fine particle resin–drug complex mixture was mixed with excipients and other drug–resin complexes (if any). The mix then was filled into suitable capsules using a capsule-filling machine. The phenylpropanolamine–resin complex mixture was mixed with excipients and chlorpheniramine–resin complex and filled into No. 3 capsules.

Each capsule contained the equivalent of 37.5 mg of phenylpropanolamine hydrochloride and 4 mg of chlorpheniramine maleate. The adult sustained-release dose was designed as two capsules to be taken every 12 hr, providing drugs equivalent to 75 mg of phenylpropanolamine hydrochloride and 8 mg of chlorpheniramine maleate. The large particle resin–drug complex mixtures were used similarly in the preparation of capsules in earlier developmental work.

Preparation of Suspension Dosage Forms—The fine particle resin–drug complex mixture and other resin–drug complexes (if any) were suspended in a palatable, flavored vehicle containing suitable suspending agents. Phenylpropanolamine–resin complex mixture and chlorpheniramine–resin complex were suspended in a fruit-flavored vehicle. Each
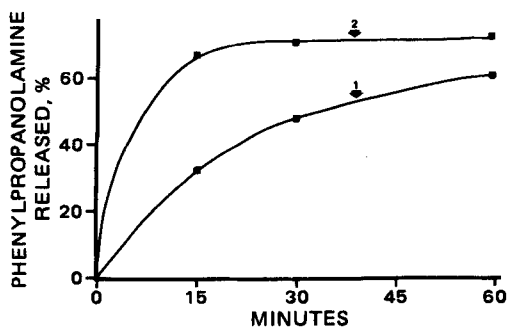
Figure 1—*Mean release profile of pnenylpropanolamine in 0.1 N HCl at 60 rpm. Key: 1, uncoated large particle phenylpropanolamine–resin complex; and 2, uncoated fine particle phenylpropanolamine–resin complex.*

5 ml of this flavored and palatable suspension contained the equivalent of 37.5 mg of phenylpropanolamine hydrochloride and 4 mg of chlorpheniramine maleate. The adult sustained-release dose was designed as 10 ml to be taken every 12 hr, which is equivalent to 75 mg of phenylpropanolamine hydrochloride and 8 mg of chlorpheniramine maleate.

Bioavailability Studies—Details of the bioavailability protocols were reported elsewhere (15).

RESULTS AND DISCUSSION

Variables Affecting Drug Release from Resin–Drug Complex Particles—Figure 1 shows the effect of particle-size differences on the release of phenylpropanolamine in 0.1 N HCl uncoated large resin–drug complex particles (590–800 μm) and uncoated, irregularly shaped resin–drug complex particles with d50 of 80–95 μm. The drug loads in the two resin–drug complexes were ~33%. About 48% drug release was observed in 30 min from the large resin–drug complex particles, whereas 72% was released in the same time from the finer resin–drug particles.

Figure 2 shows the comparative release in 0.1 N HCl of phenylpropanolamine and chlorpheniramine from fine particle resin–drug complexes containing a 25% drug load. Drug release from the chlorpheniramine–resin complex was only 7.5% in 2 hr, indicating that the equilibrium concentration for this complex in 0.1 N HCl was low. Release of phenylpropanolamine, on the other hand, from its resin complex was ~82% in the same time, indicating a high equilibrium concentration for this drug at 0.1 M ionic concentration. Increasing the ionic concentration to 0.4 M shifted the equilibrium concentration toward more complete drug release with the chlorpheniramine–resin complex (Fig. 3); ~72% chlorpheniramine was released in 2 hr. About 98% phenylpropanolamine was released from its resin complex in 2 hr in a 0.4 M dissolution medium.

Chlorpheniramine was completely bioavailable from this resin–drug complex in the present study. However, the significant difference observed in the *in vitro* release of chlorpheniramine due to ionic concentrations was not reflected *in vivo* (15). This result was perhaps due to the continuous absorption of released drug into the blood, resulting in a lower GI drug concentration, which, in turn, permitted more drug release. It was perhaps also due to the higher ionic concentration in the GI tract and to the continuous passage of the resin through the GI tract.
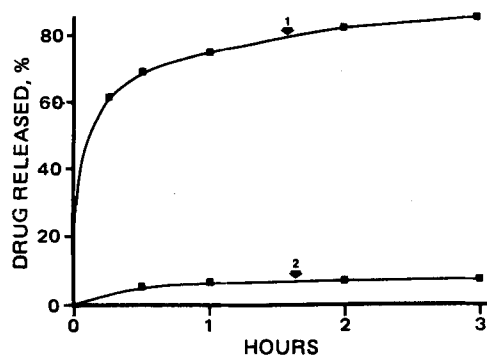
Figure 2—*Mean release profile of phenylpropanolamine and chlorpheniramine in 0.1 N HCl at 50 rpm. Key: 1, uncoated fine particle phenylpropanolamine–resin complex; and 2, uncoated fine particle chlorpheniramine–resin complex.*
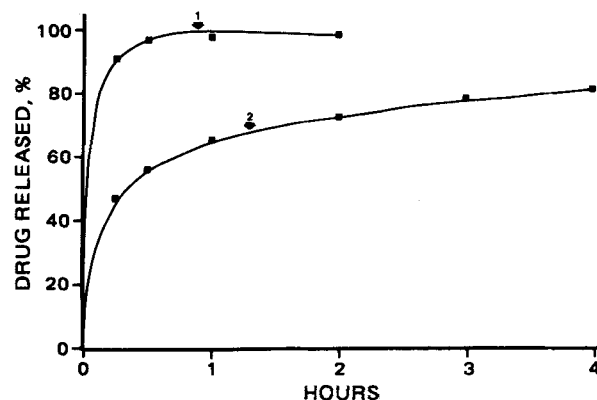
Figure 3—*Mean release profile of pnenylpropanolamine and chlorpheniramine in 0.4 M KCl solution at 50 rpm. Key: 1, uncoated fine particle phenylpropanolamine–resin complex; and 2, uncoated fine particle chlorpheniramine–resin complex.*

Coating Studies—The results indicated the need for a diffusion barrier coating for the phenylpropanolamine–resin complex to modify the drug release profile, particularly with the fine particle drug–resin complex, essential for formulation of a sustained-release liquid dosage form.

Ethylcellulose 50 cps NF was selected as the diffusion barrier film since it is commercially available in pharmaceutical grade. Preliminary studies with the agent indicated the need for a plasticizer to improve film toughness.

Coating by spray drying a suspension of the fine particle resin–drug complex using a coating solution of ethylcellulose in methylene chloride was attempted. The process did not provide efficient coating, and no retardation of drug release was noticed. Therefore, a fluid bed technique was tried using the coating apparatus[6]. Initial experiments were carried out with the large particle phenylpropanolamine–resin complex.

The gel-type divinylbenzenesulfonic acid resins (both the large and fine particles) swell when placed in water and shrink in volume when dried. This property was a disadvantage for obtaining a good diffusion barrier coating on the resin–drug complex particles. The coating peeled from the particles as soon as they were suspended in the dissolution medium because they absorbed the medium too rapidly and became swollen. Attempts to coat the particles in the wet stage (and the swollen form) failed because the particles did not fluidize satisfactorily in the coating apparatus. They also lost water to air by evaporation during fluidization and coating and thus ended up being in their shrunken state. Maintenance of high humidity in the coating chamber helped but did not overcome the problem of fluidization. In any case, the coated particles did not show significant retardation in drug release.

Therefore, it was thought necessary to fill the resin–drug complex matrix, at least partially, with an agent that had hydroalcoholic properties, was a solid and relatively nonvolatile, and was water miscible. The polyethylene glycols and sugars seemed to possess these properties. Polyethylene glycol 4000 was tried as a treatment agent initially, and it improved the coating efficiency and thereby retarded drug release. Other

Table I—Water Uptake Time for Fine Particle Phenylpropanolamine–Resin Complex Pretreated with Various Agents

Agent	Percent Added	Water Uptake Time[a], sec	Water Layer at End of Time
No additive	0	36	None
Polyethylene glycol 4000	2	208	None
	20	1149	Present
Propylene glycol	20	>240	Present
Mannitol	20	96	None
Lactose, anhydrous	20	108	None
Methylcellulose	2	330	None
	20	>600	Present
Gelatin	2	20	None
	20	23	None
Talc	20	73	None

[a] Uptake time (mean value) for 4 ml of water by 5 g of mixture gently packed in a 25-ml graduated cylinder.

Table II—Apparent Specific Volume of Fine Particle Resins or Resin–Drug Complex in Various Media

Material	Medium	Temperature	Apparent Specific Volume, ml/g	Increase in Volume over Volume in Air at Same Temperature, %
Fine particle resin	Air	23°	1.380	—
	Air	97°	1.460	—
	Water	23°	1.750	26.8
	Water	97°	2.100	43.8
	Polyethylene glycol 4000	97°	1.480	1.4
Fine particle phenylpropanolamine–resin complex	Air	23°	1.458	—
	Water	23°	1.875	28.6
Fine particle phenylpropanolamine–resin complex treated with polyethylene glycol 4000	Air	23°	1.620	—
	Water	23°	1.750	8.0

Table III—Water Uptake Time for Ethylcellulose-Coated Large and Small Particle Phenylpropanolamine–Resin Complex

Agent	Water Uptake Time[a], sec	Water Layer at End of Time
Large particle complex		
Without polyethylene glycol 4000	192	None
With polyethylene glycol 4000	580	None
Small particle complex		
Without polyethylene glycol 4000	511	None
With polyethylene glycol 4000	1800	Present

[a] Uptake time (mean value) for 4 ml of water by 5 g of material gently packed in a 25-ml graduated cylinder.

Figure 5—*Mean release profile of phenylpropanolamine in 0.1 N HCl at 60 rpm. Key: 1, uncoated fine particle phenylpropanolamine–resin complex; 2, ethylcellulose-coated fine particle phenylpropanolamine–resin complex without polyethylene glycol 4000 treatment; and 3, ethylcellulose-coated fine particle phenylpropanolamine–resin complex with polyethylene glycol 4000 treatment. The coating level was 11.4% ethylcellulose.*

agents were screened for their suitability for mixing with the resin–drug complex particles by determining their effects on the water uptake time of the resins. Additional studies were carried out with phenylpropanolamine–resin complex treated with polyethylene glycol 4000 to understand the mechanism.
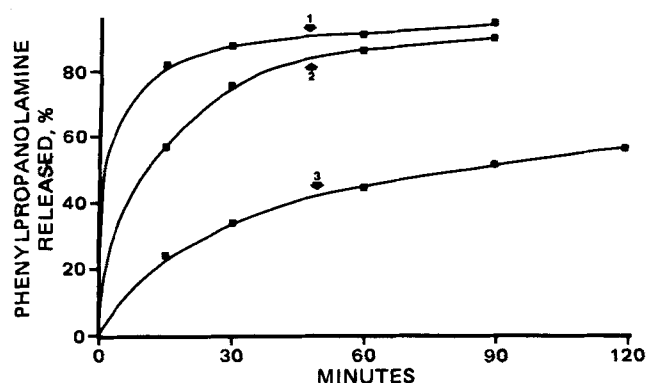
Table I gives the water uptake times for various agents mixed with fine particle phenylpropanolamine–resin complex. Polyethylene glycol 4000, propylene glycol, and methylcellulose increased the water uptake times significantly. Talc, mannitol, and lactose provided some increase. Of the agents tested, polyethylene glycol 4000 retarded the water uptake time the most. Gelatin appeared to decrease the water uptake time.

Table II gives the apparent specific volumes in air and in water for the fine particle resin and the corresponding resin–drug complex of phenylpropanolamine pretreated with polyethylene glycol 4000. The untreated fine particle resin increased in volume in water by 26.8% at 23° and by 43.3% at 97°. The same resin, when placed in melted polyethylene glycol 4000 at 97°, showed an increase of only 1.4% in volume. The fine particle phenylpropanolamine–resin complex treated with 20% polyethylene glycol increased in volume by only 8% when placed in water compared to the 28.6% increase of the untreated material.

Microscopic examination of the coated and uncoated resin–drug complex particles was made. Large particles of phenylpropanolamine–resin complex were spherical in shape. These uncoated particles wetted

easily with water and enlarged in diameter. The ethylcellulose-coated particles were also spherical. They did not wet with water easily, nor did they change in shape or size significantly. The fine particle phenylpropanolamine–resin complex and the corresponding ethylcellulose-coated particles behaved like the spherical resin–drug particles. The coated particles were pretreated with polyethylene glycol.

Table III presents the water uptake times observed with ethylcellulose-coated resin–drug complex particles with and without polyethylene glycol pretreatment. The water uptake times observed for the pretreated particles were much larger than those for untreated particles. These results agree with the microscopic observations.

Drug Release from Coated Resin–Drug Complexes—Figures 4 and 5 show the drug release profiles observed with ethylcellulose-coated phenylpropanolamine–resin complex particles with and without polyethylene glycol 4000 treatment. About 28 and 42% of phenylpropanolamine were released in 1 hr from the coated, treated large particle phenylpropanolamine–resin complex and coated, untreated particles, respectively. These particles were coated with 5.7% ethylcellulose. About 45 and 87% of phenylpropanolamine were released in 1 hr from the coated, fine particle phenylpropanolamine–resin complex treated with polyethylene glycol 4000 and those untreated, respectively. These particles were coated with 11.4% ethylcellulose. The effect of polyethylene glycol
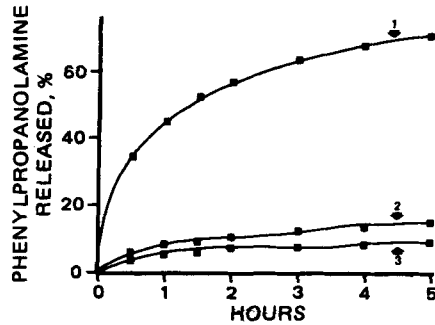
Figure 4—*Mean release profile of phenylpropanolamine in 0.1 N HCl at 60 rpm. Key: 1, uncoated large particle phenylpropanolamine; 2, ethylcellulose-coated large particle phenylpropanolamine–resin complex without polyethylene glycol 4000 treatment; and 3, ethylcellulose-coated large particle phenylpropanolamine–resin complex with polyethylene glycol 4000 treatment. The coating level was 5.7% ethylcellulose.*

Table IV—Phenylpropanolamine Release in 0.1 N HCl from Coated and Uncoated Fine Particle Phenylpropanolamine–Resin Complex Used in Mixtures Listed in Table V

Time Lapsed, hr	Percent Released		
	Coated (Lot 825-594PD)	Coated (Lot 846-715PD)	Uncoated (Lot 842-349RC)
0.5	22.9	27.5	70.3
1.0	31.4	40.6	76.0
2.0	37.3	54.9	79.1
3.0	42.7	61.8	80.5

Table V—Phenylpropanolamine Release in 0.1 N HCl from Phenylpropanolamine–Resin Complex Mixtures Used in Bioavailability Test Suspensions

Time Lapsed, hr	Percent Released									
	Mixture Lot 850-201-PD[a] (Mixture Components: 846-715/842-349; Ratio, % coated to uncoated: 82.5:17.5)		Mixture Lot 850-202PD[b] (Mixture Components: 846-715/842-349; Ratio, % coated to uncoated: 65:35)		Mixture Lot 850-203PD[c] (Mixture Components: 846-715/842-349; Ratio, % coated to uncoated: 45:55)		Mixture Lot 850-204PD[d] (Mixture Components: 846-715/842-349; Ratio, % coated to uncoated: 75:25)		Mixture Lot 843-988PD[e] (Mixture Components: 825-594/842-349; Ratio, % coated to uncoated: 83:17)	
	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.
0.5	35.0	37.6	42.5	42.7	51.1	57.6	38.2	40.3	30.9	26.4
1.0	46.8	48.8	53.0	52.5	60.1	63.9	49.5	50.1	39.0	37.7
2.0	59.1	59.7	63.4	58.8	68.2	73.0	61.0	60.7	44.4	47.2
3.0	65.1	66.5	68.4	64.6	72.1	77.9	66.4	65.7	49.1	51.0
5.0	—	72.6	—	69.9	—	84.4	—	72.8	—	56.0
6.0	—	75.8	—	72.2	—	87.2	—	74.6	—	58.0

[a] Used in Suspension D. [b] Used in Suspension B. [c] Used in Suspension C. [d] Used in Suspension A. [e] Used in Suspension E.

Figure 6—Mean release profile of phenylpropanolamine in 0.1 N HCl at 60 rpm from fine particle phenylpropanolamine–resin complex at various coating levels of ethylcellulose. Key: 1, 11.4%; 2, 21.0%; and 3, 28.25%.
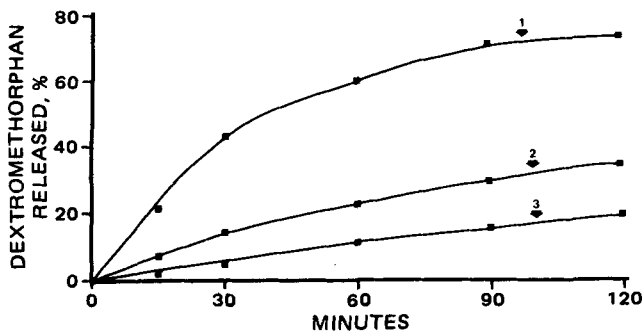
4000 pretreatment is evident in the slower drug release from these coated particles.

Figure 6 shows the effect of ethylcellulose coating levels on the release of phenylpropanolamine from the coated fine particle drug–resin complex. The drug release at the end of 2 hr was 57, 10, and 7.0% with ethylcellulose coating levels of 11.4, 21.0, and 28.3%, respectively. The effect of the coating levels in retarding drug release is evident.
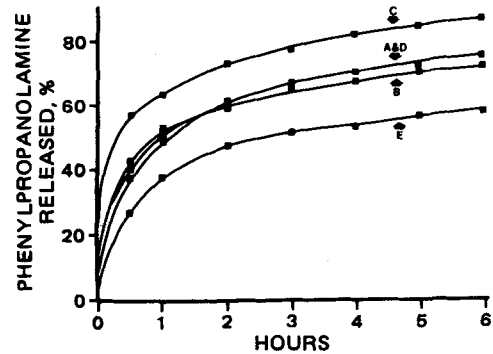
Figure 7 shows the drug release from ethylcellulose-coated and uncoated fine particle dextromethrophan–resin complex. The coated particles were pretreated with polyethylene glycol 4000. Retardation of drug release in the coated particles was seen.

Effect of Coating on Particle Size—The coated fine particle phenylpropanolamine–resin complex particles were generally between 40 and 200 mesh (74–420 μm). For example, a 30-kg batch coated with 11.4% ethylcellulose in a 45.72-cm coating apparatus had particle-size values for d16, d50, and d84 of 184, 123, and 82 μm, respectively. The corresponding d16, d50, and d84 values for uncoated fine particle phenylpropanolamine–resin complex particles were 140, 94, and 61 μm, respectively.

Drug Release from Dosage Forms—Mixtures of coated and un-

Figure 8—Mean release profile of phenylpropanolamine from mixtures of varying ratios of coated and uncoated fine particle phenylpropanolamine–resin complex in 0.1 N HCl at 50 rpm. Key: A, mixture lot 850-204PD used in Suspension A; B, mixture lot 850-202PD used in Suspension B; C, mixture lot 850-203PD used in Suspension C; D, mixture lot 850-201PD used in Suspension D; and E, mixture lot 843-998PD used in Suspension E.

coated fine particle phenylpropanolamine–resin complex were prepared with desirable release profiles. Tables IV and V show the release of phenylpropanolamine from the components and several mixtures used in the preparation of Suspensions A–E for bioavailability studies. The observed release values for the mixtures are in close agreement with the values calculated by adding proportionate release values of components of the mixtures, indicating that mixing of coated and uncoated resin–drug complex is a reliable technique for obtaining desired release profiles.

Figure 8 presents graphically the drug release profiles of the mixtures.

Figure 9 shows the release of phenylpropanolamine from Suspensions A, C, and E made with mixtures shown in Fig. 8. Good agreement of the drug release profiles between the mixtures and the corresponding suspension dosages is seen.

Figure 10 shows the release of phenylpropanolamine from one experimental production batch of capsules and suspensions after storage for

Figure 7—Mean release profile of dextromethorphan in 0.1 N HCl at 60 rpm from fine particle dextromethorphan–resin complex at various coating levels of ethylcellulose. Key: 1, uncoated; 2, 6.22% ethylcellulose; and 3, 8.93% ethylcellulose.
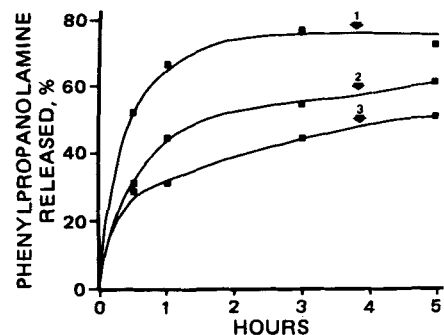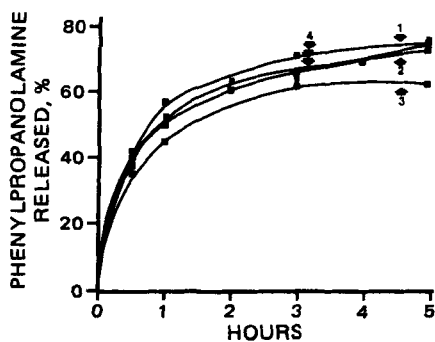

Figure 9—Mean release profile of phenylpropanolamine from Suspensions A, C, and E in 0.1 N HCl at 50 rpm. Key: 1, Suspension C; 2, Suspension A; and 3, Suspension E.

Figure 10—*Mean release profile of phenylpropanolamine from dosage forms in 0.1 N HCl at 50 rpm. Key: 1, capsule lot 855-101PD after 647 days; 2, mixture lot 850-204PD used in Suspension A; 3, suspension lot 847-576PD after 669 days; and 4, mixture lot 846-748PD (initial value at 60 rpm) used in the experimental production batches of capsules and suspensions.*
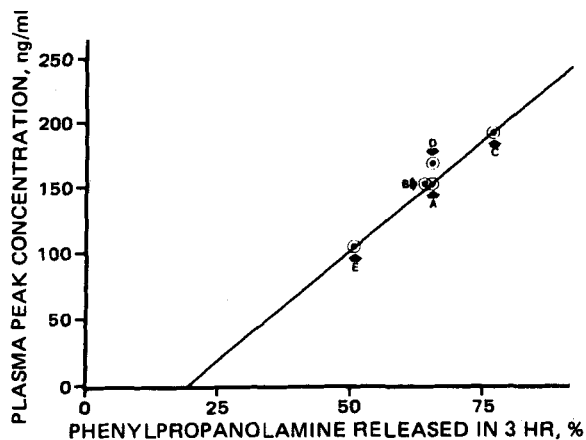
Figure 11—*Relationship between the mean peak plasma concentration for phenylpropanolamine (obtained with Suspensions A–E) and mean 3-hr drug release values for mixtures used in these suspensions as given in Table V.*

647 and 669 days, respectively. The drug release profiles of the mixture used in Suspension A in the bioavailability studies as well as the mixture used in the preparation of the experimental batches are included. Good agreement of the drug release profiles between the mixtures and dosage forms is seen.

Bioavailability Studies—The results of the bioavailability studies were discussed elsewhere (15).

Plasma concentrations of phenylpropanolamine and chlorpheniramine obtained from capsules and suspension dosage forms made with coated and uncoated mixtures of fine particle phenylpropanolamine–resin complex and fine particle chlorpheniramine–resin complex administered

once every 12 hr for 2 weeks (dosage equivalent to 75 mg of phenylpropanolamine hydrochloride and 8 mg of chlorpheniramine maleate) were not significantly different from those obtained with a solution of the drugs administered once every 6 hr (in doses of 37.5 mg of phenylpropanolamine hydrochloride and 4 mg of chlorpheniramine maleate). The resin complex products were sustained-release products providing effective plasma concentrations for 12 hr.

In the variable profile bioavailability study with suspensions of phenylpropanolamine–resin complex mixtures listed in Table V, Suspension C gave the highest plasma phenylpropanolamine peak concentration while Suspension E gave the lowest. Figure 11 shows a plot of the 3-hr *in vitro* release values of phenylpropanolamine for the mixtures *versus* the peak plasma concentrations obtained with Suspensions A–E. There is good correlation between phenylpropanolamine release and plasma peak concentration. Similar correlations were obtained with plots of drug release for 0.5, 1, 2, and 5 hr against the peak plasma concentrations. The areas under the plasma concentration curves and the time to peak obtained with these products also showed rank-order correlation.

The results suggest that a desired plasma concentration profile of phenylpropanolamine may be obtained by mixing coated and uncoated phenylpropanolamine–resin complex in suitable ratios to produce specific drug release profiles. These correlations have been used to help establish product specifications for the finished dosage forms.

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