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DRUG-DELIVERY BY ION-EXCHANGE. PART IV: COATED RESINATE COMPLEXES OF ESTER PRO-DRUGS OF PROPRANOLOL.

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Keywords

Coacervation, controlled-release, gelatin-acacia, ion-exchange resins, propranolol, resinates.

Summary

The micro-encapsulation of cationic exchange resins, loaded with O-n-acyl and O-pivaloyl ester prodrugs of propranolol, by means of gelatin-acacia coacervates is described. Resins loaded at elevated temperatures have delayed release profiles, as have those treated with polyethylene glycol, but drug release still follows particle diffusion models. Drug release from coated resins may be controlled by the weight of coat applied and for a small particle-size pharmaceutical-grade resin the time required for 50% release of complexed propranolol may be extended from 25 minutes to 100 minutes. Double coating procedures may extend this to in excess of 4 hours. The mixing of coated and uncoated particles also offers a means by which release profiles may be controlled and the time necessary for 50% release of O-pivaloylpropranolol may, for example, range from

25 minutes to 250 minutes using mixtures of single-coated particles.

INTRODUCTION

The complexation of drugs with ion-exchange resins[1-3] has proved a promising means of achieving controlled release,[4] of taste-masking[5] and of enhancing stability.[1] In a liquid dosage form the technology is particularly useful for a low ionic strength vehicle does not cause leaching of the drug during storage and release is initiated by an influx of ions on ingestion. To provide an adequate control of release profile the complexed resin beads may be coated.[6-10] Propranolol has received some interest in this respect[11-18] and we have previously described the loading and release of a series of O-n-acyl ester prodrugs of propranolol complexed with cationic exchange resins.[19-21] The release profiles may be further modified by means of coating and this paper records the variation in drug release which may be obtained with a gelatin-acacia coacervation technique.

EXPERIMENTAL

Apparatus

Hplc analyses were undertaken using a system constructed from an Altex 100A dual-piston reciprocating solvent-metering pump and a reversed-phase stainless steel Shandon-type column (10cm x 4.6 mm ID) packed with Hypersil-ODS (5 μm). Samples were introduced by means of a Rheodyne 7125 injection valve, fitted with a 20 μL loop, and detection was accomplished with a Pye LC3 variable wavelength UV detector, fitted with an 8 μL flow cell, and operated at a wavelength of 290 nm with a sensitivity usually of 0.08 AUFS. The mobile phases consisted of aqueous acetonitrile, adjusted to pH=2.8 with phosphoric acid, containing diethylamine as moderator and were delivered at 1 mL min^{-1}.

Methods

Microencapsulation Procedure

The coacervate[22,23] was prepared from 250 mL of 2% m/v of each of aqueous gelatin and aqueous acacia prepared separately at 50°C. A known weight (1-2g) of the drug resin complex was triturated to a paste with the minimum amount of glycerol to ensure that the resin particles were individually separated. More glycerol was added to make the paste more pliant and the mass was then transferred to a 1L vessel. About 30 mL of the acacia solution, maintained at 50°C, was triturated with the resin mass by means of a glass rod to make a uniformed suspension, care being taken to ensure that any aggregates were dispersed. The remaining acacia solution was then added gradually (thermostatic water bath, 50°C) with stirring at 400 rpm. The gelatin solution (250 mL), also at 50°C, was adjusted to pH 3.9 with 1M HCl and this was added gradually, with stirring, to the drug resin complex suspended in the aqueous acacia solution. The pH of the mixture was readjusted to 3.9 with 1M NaOH. Stirring was continued for about 30 minutes.

The capsule wall was rigidified by transferring the vessel to an ice bath, with continuous stirring, and the temperature was allowed to drop to about 5°C over 1 hour. The progress of gelation was followed by microscopic examination every 10°C drop in temperature. Stirring was stopped at 5°C, the microcapsules were allowed to settle and the supernatant fluid was checked for the presence of the drug released by ionic components of the acacia. It was found that less than 1% of drug was leached. After separation of the supernatant fluid, about 50 ml of ice cold isopropanol, for dehydration, was added to the capsules with stirring. The particles were allowed to settle and the supernatant fluid was decanted. The procedure was repeated with another portion of isopropanol. After further decantation, 50 mL of chilled 19% formaldehyde solution in isopropanol was added with stirring to cross-link the capsule

wall. The microcapsules were allowed to settle and the hardening procedure was repeated. The mixture was left with stirring for about 14 h in an ice bath. Mother liquors were then decanted and the microcapsules were washed twice, with decantation, with 50 mL of chilled isopropanol and the slurry of the microcapsules was transferred to a covered dish. The microcapsules were allowed to dry at room temperature over night and were then sieved through a nest of BS1796 microsieves by manual shaking.

Typically, the O-pivaloylpropranolol resin complex (Dowex 50WX2, 100-200 mesh, 2 g, calculated as dry weight) was encapsulated with gelatin-acacia to provide a coat containing a total weight of 10 g of the polymers, providing the core-to-wall ratio of 1:5. To further control delivery, mixtures of coated and uncoated drug resin complexes with ratios of 100:0 95:5, 90:10, 85:15 and 0:100 were also prepared. Additionally, propranolol and O-pivaloyl-propranolol resinates from the pharmaceutical grade resin IRP69 were also encapsulated to provide core-to-wall ratios of 1:6 and 1:12 by weight in the case of the propranolol resinate and 1:4, 1:5 and 1:6 for O-pivaloylpropranolol with fractions between 53 and 90 μm were used for the in vitro dissolution test. The IRP69 resin is a strongly cationic resin with a particle size range of 100-500 mesh with 10% moisture content.

Further coating of encapsulated batches of propranolol and O-pivaloylpropranolol IRP69 resin complexes with a core-to-wall ratio of 1:6 and a particle size of 53-90 mesh was undertaken by re-encapsulation using the same procedure to give a second core-to-wall ratio of 1:1. Release studies on these double coated microcapsules were carried out on the 125-150 μm range.

Treatment of the drug resin complex with polyethylene glycol 4000

The dry O-pivaloylpropranolol drug resinate (Dowex 50WX2, 100-00 mesh, 1 g, calculated as dry weight) was placed in a suitable jacketed cell. The polyethylene glycol (PEG 4000, 100 mg) was added and the mass gently mixed by means of a glass rod during the application of gentle heat. When the polyethylene glycol had completely melted at 50°C the heat was removed and mixing was continued until the temperature returned to room temperature. The coated drug resin complex particles were gently passed through a 100 mesh sieve to remove any agglomerates and 250 mg of this coated resinate was transferred to the dissolution cell.

Effect of Temperature

Resinates were prepared using the batch method at temperatures of 20°C and 90°C and by refluxing the resin with a concentrated aqueous solution of propranolol hydrochloride (1g in 20 mL of distilled water) until equilibrium was achieved. Loadings with amitriptylene hydrochloride, 2g dissolved in 20 mL of 50% acidified aqueous DMF at pH=3, were also used.

Dissolution Studies

The in vitro dissolution tests[21] were performed in simulated gastric juice, comprising sodium chloride (21.6 g) in 0.16M HCl (1L), of pH 1.6 at 37°C. The release of drug from the coated resinate was monitored using either a continuous-flow spectrophotometric method, monitored at 290 nm, or by hplc analysis. The integrity of the compounds used in the continuous-flow system was always checked by hplc at the end of each run.

RESULTS AND DISCUSSION

We have previously shown that the release of drugs from a resinate complex is influenced by such factors as the size

Table 1. Effect of temperature on the loading and release of propranolol from its Dowex 50WX8 (50-100 mesh, 150-300 μm) resinate.

Temperature (°C)	Propranolol loaded onto resin (%)	Propranolol released in 5 h (%)
22	20.0	89.2
90	34.6	77.0
Reflux	50.8	61.5

of the particle bead, the degree of cross-linking and the nature of the drug itself.[21] Another variable which is easily modified is the effect of temperature. The effect of this parameter on the loading and release of propranolol is shown in Table 1.

These results reveal that as the temperature of the loading increases the extent of propranolol incorporation into the resinate is also increased dramatically. These data are parallelled in the release profiles from the resinate in that the samples loaded at higher temperatures show significantly lower release rates. This is probably due to the swelling of the resin particles as a result of both thermal and hydration effects as the temperature increases. An increase in pore diameter provides access to centres of ionic activity, normally unavailable, deep within the resin structure. As the temperature drops on cooling the resin particles shrink and trap the drug within the matrix. This results in an increased load and a reduced release rate. The comparative release profiles of propranolol of the drug resin complex prepared at different temperatures are shown in Figure 1. It has been shown experimentally that all of the drug loaded is released into solution at equilibrium. Similar results were obtained with amitriptylene. Loading at room temperature provided a drug loading of 14.0 % m/m while

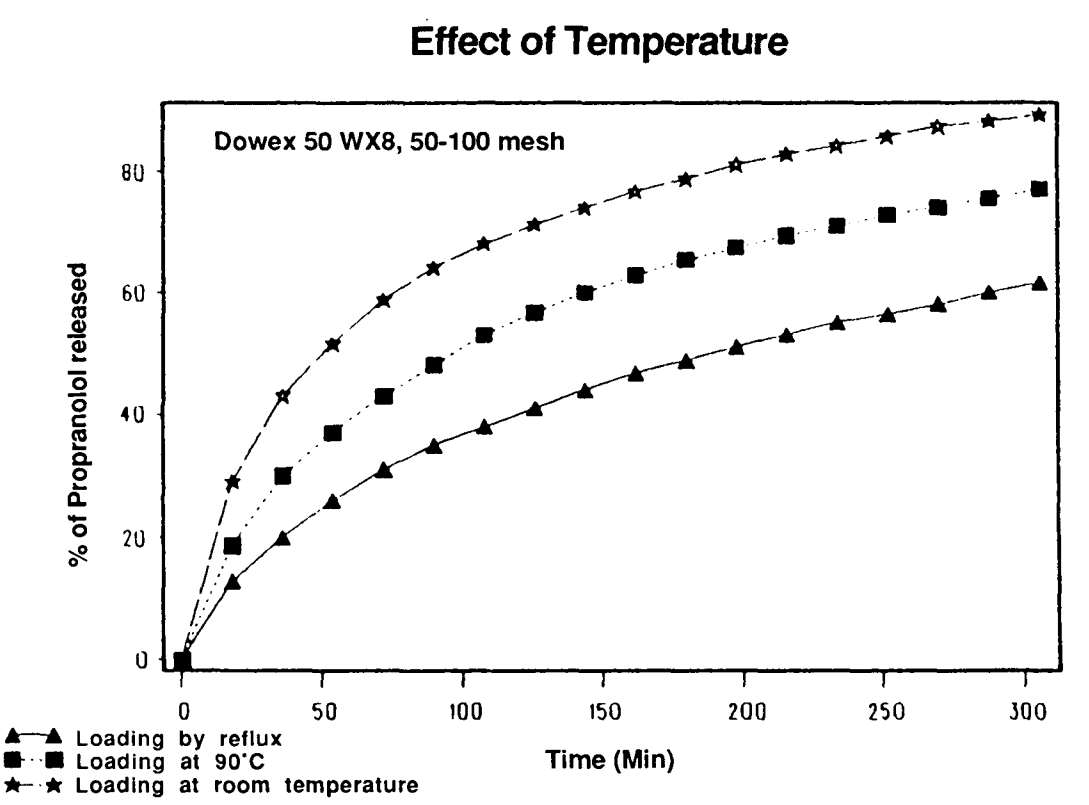

Figure 1. Release profile showing the effect of the loading temperature on the loading and release of propranolol from its Dowex 50WX8 (50-100 mesh, 150-300 μm) resinate.

under reflux enhancement to 29.7% was obtained. The release profiles of the two samples varied less, however, with 58% of amitriptylene released in 5 hours from the room temperature product and 53% from the complex produced under reflux.

Several analyses of the release of drugs from resinate complexes are available[14,15,24-26] and it has been shown that normally release occurs via particle diffusion.[24] The process may be modelled by Equation 1.

$$F = 1 - \frac{Q_t}{Q_o} = 1 - \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left[- \frac{4\pi^2 n^2 D.t}{d_p^2} \right] \qquad (1)$$

with a B term defined as $B = \frac{4\pi^2 D}{d_p^2}$

where:

F = fraction of drug released from the resinate at time t
Q_o = initial drug content of the resinate ($g.g^{-1}$)
Q_t = drug content of resinate at time t ($g.g^{-1}$)
D = diffusion coefficient of drug within resin ($m^2.min^{-1}$)
d_p = mean diameter of resin particles (m)
t = time into dissolution (min).

The variables in this equation are the particle diameter (d_p) and the diffusion coefficient of the drug (D) in the resin. It is possible to calculate the term Bt represented in this equation from a polynomial expression:[25]

$$Bt = 2\pi - \pi^2 F/3 - 2\pi(1 - \pi F/3)^{\frac{1}{2}} \quad \text{when } F \leq 0.85$$

and

$$Bt = -\ln(1 - F) - 0.04977 \quad \text{when } F > 0.85$$

and the plot of Bt against time provides a linear plot if the release of drug is diffusion controlled. Plots of data derived from the release of propranolol from loaded resins at different temperatures are shown in Figure 2.

The linearity of these plots indicate that the release of drugs from the resinate is modelled well by diffusion control in all cases and the temperature effect is merely concerned with enhanced loading in deeply held ionic sights rather than providing an alternative mechanism for release. This approach has the advantage of not only enhancing significantly the extent of drug loading onto the resin but also dramatically increases the period required for its release.

Marketed controlled release ion exchange resin complexes have used the principle of coating the resin beads with ethyl cellulose.[6-8] To prevent disruption of the coat due to

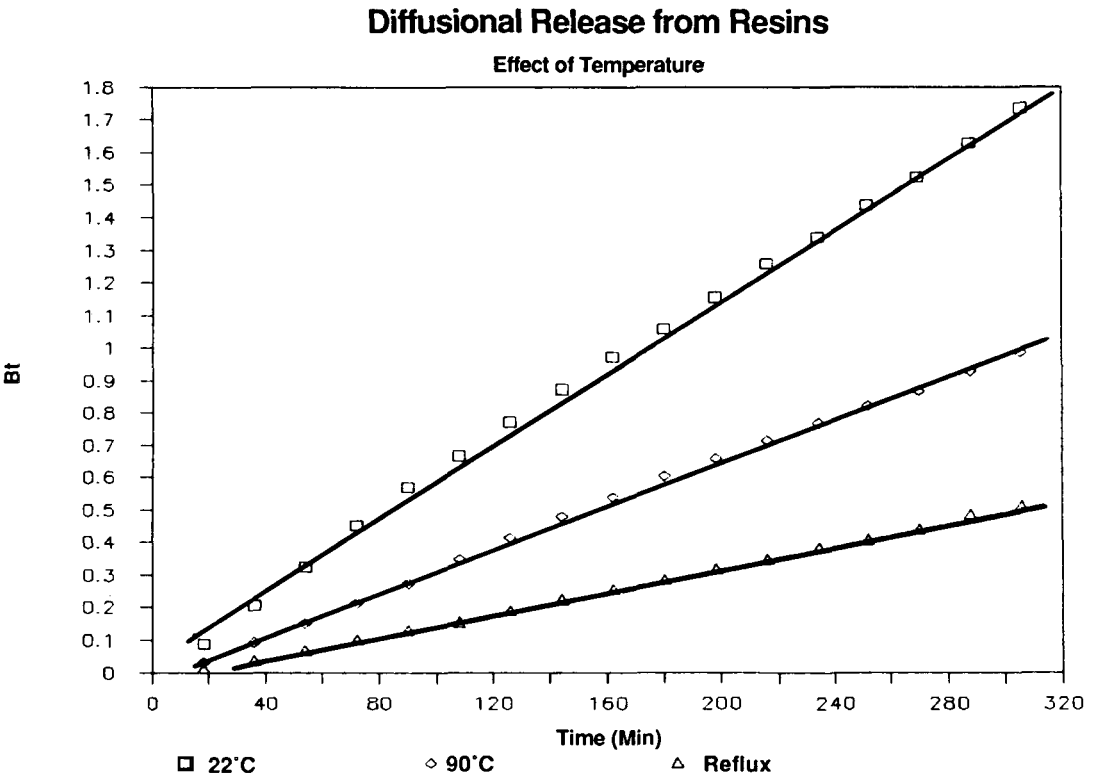

Figure 2. Plot of t versus Bt for propranolol Dowex 50WX8 resinates loaded at various temperatures.

swelling of the dried particles on rehydration, the resin particles are generally maintained in the swollen state by treatment with polyethylene glycol. Figure 3 reveals the effect of loading the drug resin complex with polyethylene glycol without any further treatment.

It is seen that this treatment also causes a reduced rate of release of the drug. Analysis according to Equation 1 shows that this is largely a particle diffusion phenomenon with the diffusion coefficient somewhat reduced due to the replacement of solvent by more viscous polyethylene glycol in the pores of the resin. An alternative coating procedure which overcomes the problems of swelling and fracture is

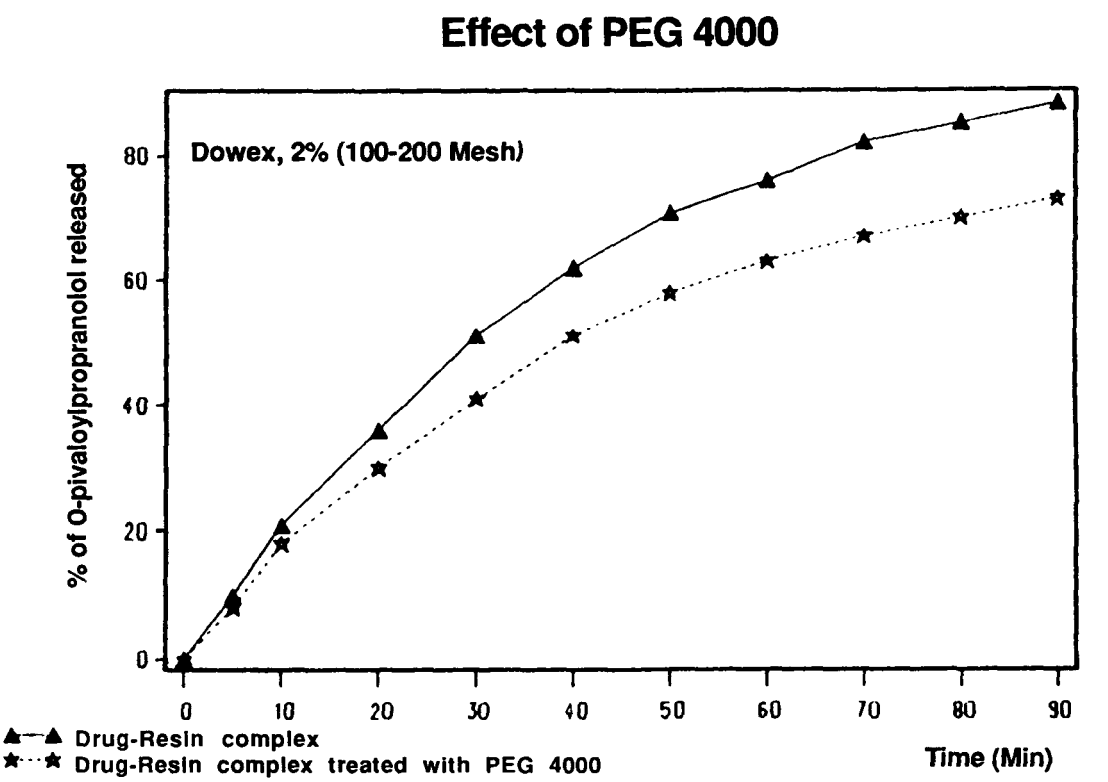

Figure 3. Effect of treatment with PEG 4000 on the release profile of O-pivaloylpropranolol from its Dowex 50WX2 (100-200mesh, 75-150 μm) resinate.

coacervation with gelatin and acacia. Microencapsulation was undertaken using drug-loaded beads and release profiles were monitored. Additionally, to provide further control of the release profiles by increasing the diffusional barrier, the effect of a second coat on the coated drug resin complex was investigated. This process may be advantageous for those resinates prepared with fine particle size resins which release drug rapidly and which can tolerate a significant increase in size without adverse organoleptic properties.

Encapsulation of the O-pivaloylpropranolol resin (Dowex 50WX2 100-200 mesh, 75-150 μm) using a gelatin-acacia

Table 2. The effect of mixing samples of the coated and uncoated resinate complex of O-Pivaloylpropranolol on drug content and dissolution.

Coated Resinate in product (%)	Drug in 1g of mixture (mg)	Drug released in 2 h (%)
100	55	31
95	69	40
90	83	55
85	97	65
0	337	100

coacervate with a core-to-wall ratio of 1:6 was shown to delay the drug release from the coated resinate in simulated gastric juice by about 3 fold compared to release from the uncoated resinate.

In order to control the drug content and the release of drugs from the final preparation, mixtures of coated and uncoated drug resin complexes were blended together with various ratios of coated to uncoated material. The dissolution of mixtures containing 95%, 90% and 85% m/m of the coated resin, diluted with the uncoated product, were undertaken in simulated gastric juice. Table 2 shows the effect of this bi-phasic control system, compared to both coated and uncoated products, and the drug content in the final preparation. The release characteristics of these preparations are graphically presented in Figure 4.

These results are analogous to those quoted for the Pennwalt bi-phasic controlled drug delivery system.[6-8] The major disadvantage of this process was that the drug content in the micro-encapsulated resin drug complex was much reduced. This makes the process more applicable to those drugs with a low therapeutic dose. The more rapid drug release from the uncoated particles provides an initial increase in the availability while the coated particles

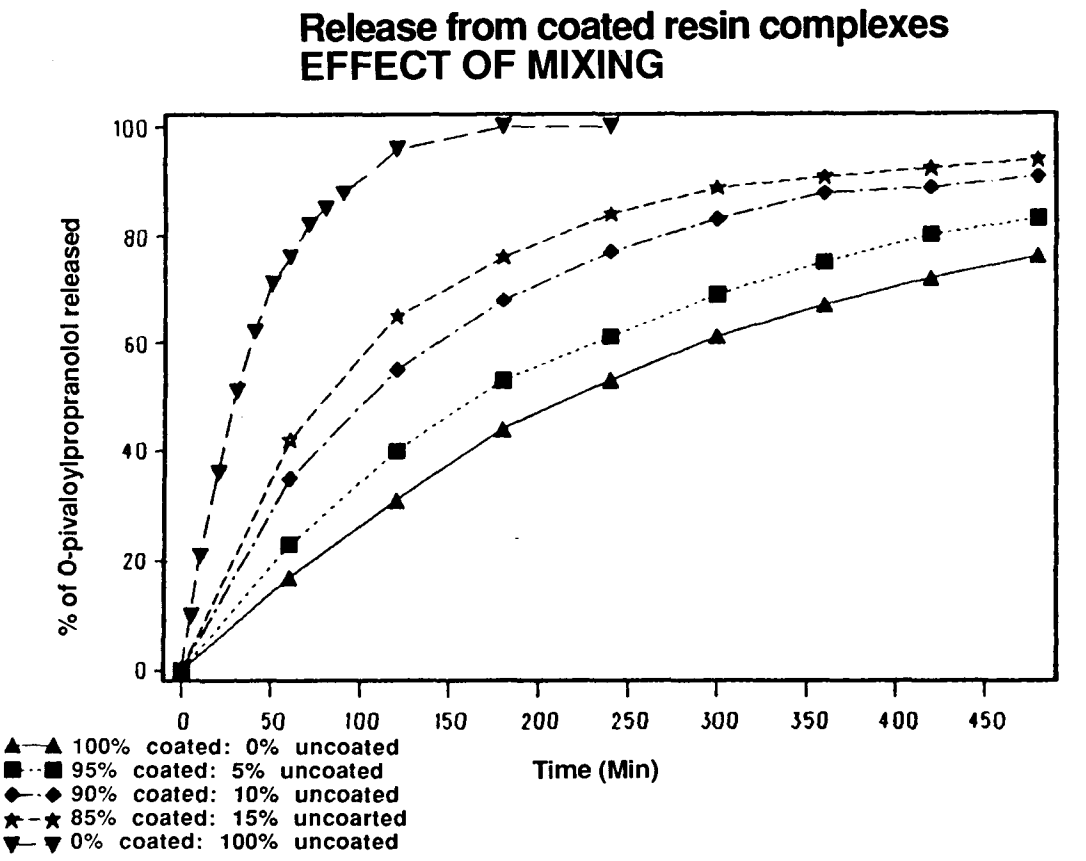

Figure 4. Effect of mixing coated and uncoated particles of O-pivaloylpropranolol Dowex 50WX2 (100-200 mesh, 75-150 μm) resinate.

provide a more sustained profile. For the drug to be displaced from the ion exchange resin, ions from the gastro-intestinal fluid was first diffused through the outer coating and the diffusion of drugs through the semi-permeable coating surrounding the resin particle becomes rate limiting for drug release. By varying the thickness of the coat the rate of drug release can be predetermined and controlled. During passage through the gastro-intestinal tract, ions present in the fluids displaced drug from the ion exchange resin matrix. Since the concentration of ions within these fluids remains

Table 3. Effect of amount of coating on the drug content and release from encapsulated resinate complexes of IRP69 (100-500 mesh, ~20-150 μm) with Propranolol (Propr) and O-Pivaloylpropranolol (O-Piv).

Preparation	Drug Content in 1g (mg)		Drug Released in 1 h (%)	
	Propr	O-Piv	Propr	O-Piv
Uncoated resinate	434.0	395.3	100.0	78.8
Core:Wall 1:4		97.8		56.6
Core:Wall 1:5		90.4		43.4
Core:Wall 1:6	73.0	70.8	85.9	28.2
Core:Wall 1:12	43.0		71.6	
Double coated resinate	40.5	34.5	58.3	23.0

constant, inter-patient variations in rate of drug release are expected to be small.

Drug resin complexes were also prepared for propranolol and O-pivaloylpropranolol using an irregularly shaped, fine particle pharmaceutical grade resin (IRP69, 100-500 mesh, ~20-150 μm). This was encapsulated by gelatin-acacia using various core-to-wall ratios.

Table 3 shows that the increase in proportion of the coating material again decreases the amount of drug content and prolongs the drug release profile as shown in Figure 5.

Tables 4 and 5 show the sieve analysis of the prepared microcapsules for both propranolol and O-pivaloylpropranolol resinates using a nest of BS1796 sieves and manual shaking.

The fraction 53-90 μm from the single coated resinates and the fraction 125-150 μm from the double coated ones were used for the *in vitro* dissolution tests. Microscopic examination of the drug resin complex and the microcapsules were carried out after staining the particles with Sudan III.

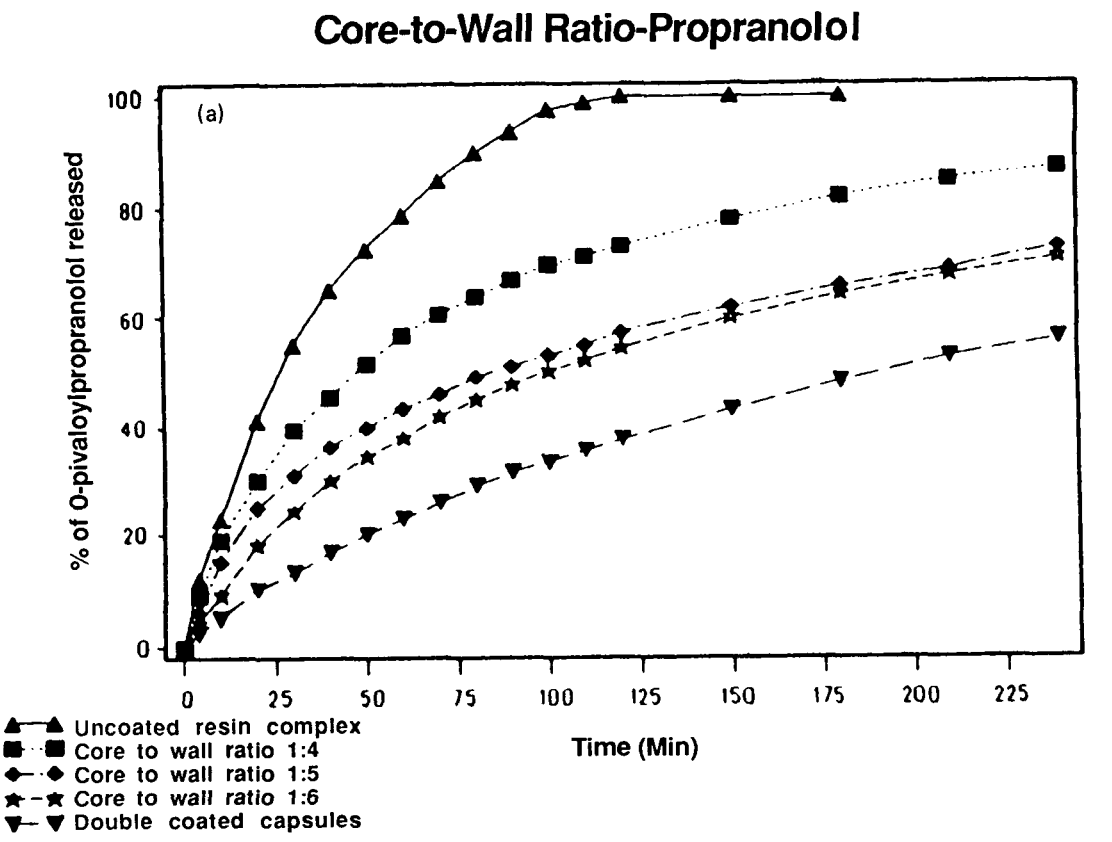

Figure 5. Release profile of [A] Propranolol and [B] O-Pivaloylpropranolol from the IRP69 resinates (100-500 mesh, ~20-150 μm) encapsulated with various amounts of gelatin-acacia.

The resinate particles, triturated with glycerol, are shown to be broken up into microparticles which facilitate encapsulation. The microscopic appearance of the micro-encapsulated drug resin complex before hardening with formaldehyde was translucent, smooth and round. While after hardening the translucency was lost due to dehydration and the resin particles cannot be seen. The appearance of these microcapsules after dissolution in simulated gastric juice

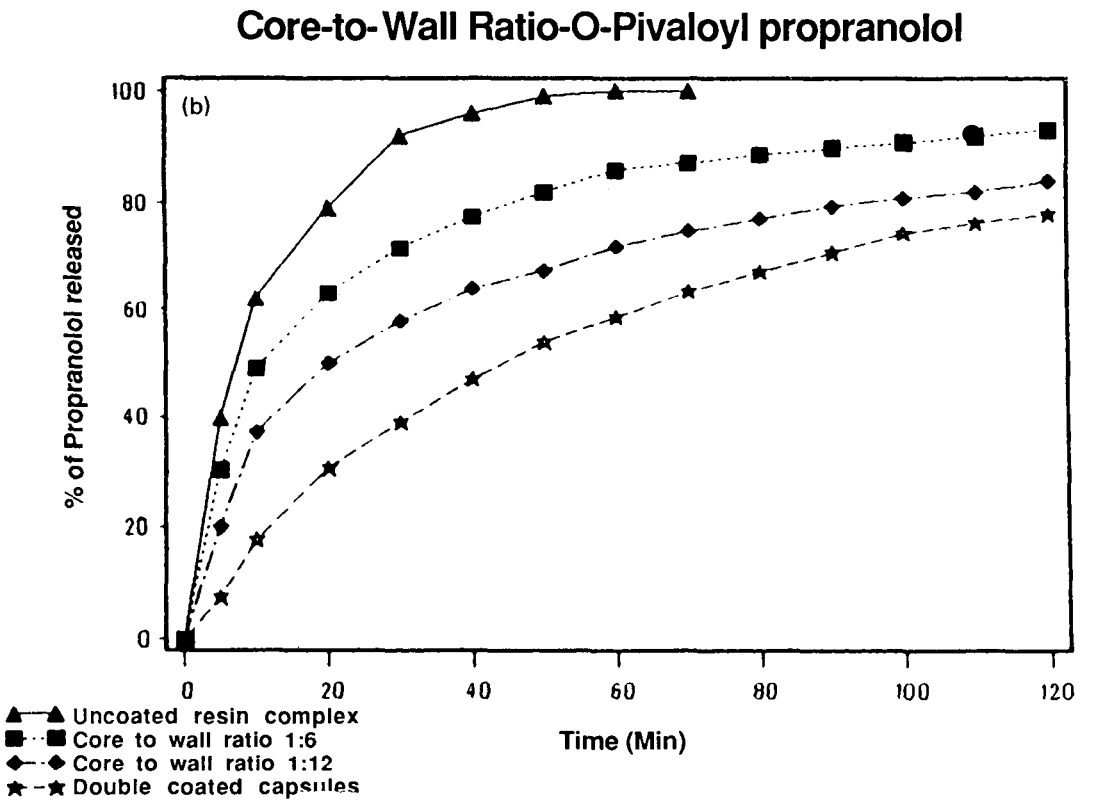

Figure 5 continued

Table 4. Particle size analysis of micro-encapsulated propranolol IRP69 resinate.

Particle Size (μm)	Fraction Retained (weight %) Core-to-Wall Ratio		
	1:6	1:12	Double Coated
>150	0.3	0.5	3
125-150	7.6	0.6	77
90-125	27.9	14.3	22
53-90	56.9	72.0	
38-53	6.5	11.3	
<38	0.8	1.3	

Table 5. Particle size analysis of micro-encapsulated O-pivaloylpropranolol IRP69 resinate.

Particle Size (μm)	Fraction Retained Core-to-Wall Ratio			
	1:4	1:5	1:6	Double Coated
>150	1.9	0.6	0.2	3.0
125-150	6.0	4.7	0.7	67.0
90-125	32.9	25.0	21.5	30.0
53-90	50.2	61.0	65.2	
38-53	5.3	6.7	11.2	
<38	3.7	2.0	0.8	

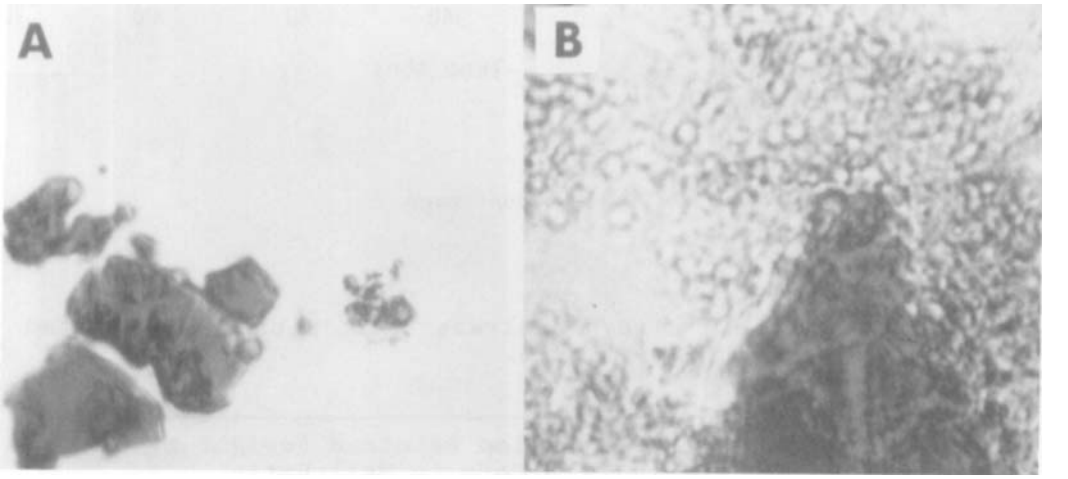

Figure 6. Effect of Micro-encapsulation and Release on Ion-exchange Resins loaded with Propranolol.
[A, original IRP69 small particle-size resin; B, resin complex during trituration with glycerol; C, micro-encapsulated resin prior to hardening; D, encapsulated resin after hardening with formaldehyde for 14 h; E, enacapsulated resin particles after dissolution studies; F, double-coated resin particles].

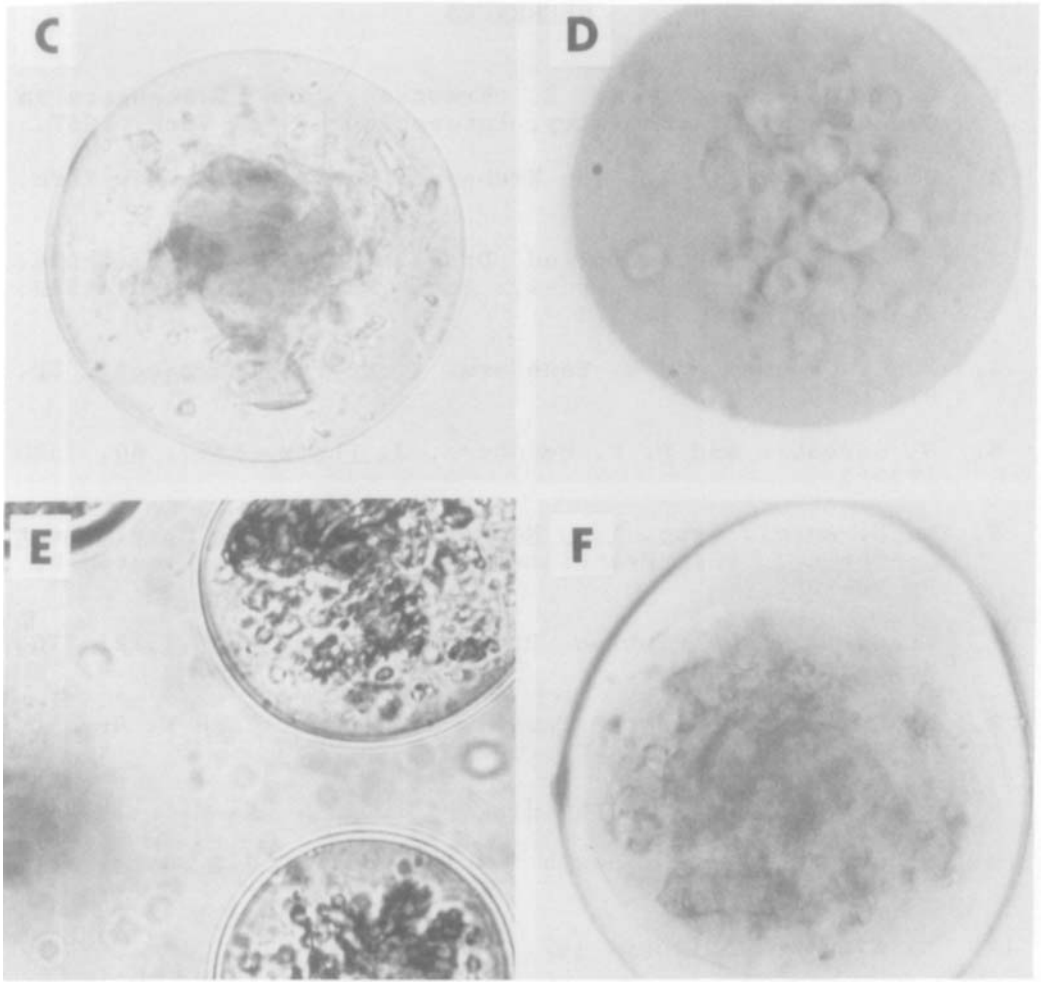

Figure 6 continued

under the microscope shows that the translucency was much greater than before hardening, due to rehydration of the capsules during dissolution. The overall shape of the microcapsules were still intact. The microscopic appearance for the double coated drug resin is shown in Figure 6. Dissolution studies were also carried out in cooled, boiled double distilled water on the uncoated drug resinate complex and the coated ones. No significant release of drug was noted from either system.

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