DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(9-11), 2047-2066 (1987)



# DRUG-DELIVERY BY ION-EXCHANGE.

## PART III: INTERACTION OF ESTER PRO-DRUGS OF PROPRANOLOL WITH CATIONIC EXCHANGE RESINS.

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**Summary**

The interaction of a series of O-n-acyl propranolol pro-drugs with strong cation exchange resins is reported and various variables which control loading and release profiles have been investigated. pH has little practical effect on the loading efficiency under the conditions used but standardisation of experimental details for the measurement of in vitro liberation profiles must be undertaken. In particular, stirring speeds of 200-300 rpm were necessary to ensure the independence of release profile and agitation. Additionally, the dissolution medium may not provide sink conditions throughout the full dissolution process if pH variation does not take into account solubility differences between analogues. Ionic strength also influences release rates and attempts to examine the effects of pH must also control this variable. The proportion of cross-linking agent in the resin plays an important role. Increasing the cross-linking delays considerably the release of drug from the matrix and is a useful parameter in optimising controlled delivery. The loading efficiency of the resin is reduced, however, as the cations are excluded from parts of the resin due to a reduction in pore diameter. In contrast, the particle size of the resin has little influence upon loading

efficiencies but larger particles significantly delay the release of drug. The effect of O-n-acyl chain-length on the loading and release profiles was determined by molecular size. As groups increased in size the loading was inhibited and release rates were reduced. Again, this enables some control of release profiles but the approach is most suitable for drugs which are active at low doses which allow full use of these variations without the necessity for large amounts of resin in the delivery system.

**Keywords**

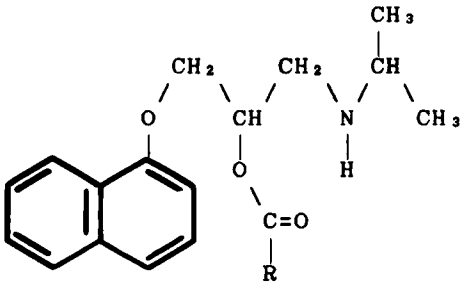
Controlled-release, ion-exchange resins, pro-drugs, propranolol, resinates.

## INTRODUCTION

The controlled delivery of drugs has long been an objective of pharmaceutical formulators and many strategies have been adopted to achieve this goal. For oral delivery, systems which are based upon ion-exchange resins[1] have shown promise. The method has usually been adopted for basic drugs in the cationic form which interact with a cationic ion-exchange resin to form an insoluble drug-resinate complex. Such complexes have been used to serve as a depot for drug delivery,[2] to aid taste-masking of unpleasant principals[3], to enhance stability profiles[4] and to decrease toxicity.[5,6] Indeed, the first reports of ion-exchange drug delivery systems appeared only a short time after the synthesis of the full range of polystyrene-based resins.[7] A significant attribute of this delivery system is that drug release is initiated by the penetration of competing cations into the resin. Liquid formulations, prepared with low-ionic strength vehicles, suffer minimal leaching during storage and do not release the drug until the ions of the gastro-intestinal tract are encountered. Rates of delivery have generally been too rapid for true controlled release and coating of the resin particles has been adopted to provide a diffusional barrier to the drug. Advantages of this design include independence of release rates on factors such as pH, gastro-

intestinal fluid volume, enzyme levels and matrix composition which may influence drug release from other systems.[8-11]

Propranolol has appropriate pharmacokinetic and activity profiles to make it a suitable candidate for controlled-release systems and various studies using this, and related drugs, in association with ion-exchange resins have appeared.[12-19] These studies have generally examined differences in the ion-exchange component of the system and workers have demonstrated the potential utility of this delivery system. To further this approach, and to examine the possible role of the physico-chemical properties of the drug molecule, we have previously described the synthesis and properties of a series of O-n-acyl ester pro-drugs of propranolol (1-8).[20] In this paper we examine the interaction of these compounds with strong cationic exchange resins and the release of drug from the drug-resinate complex.



| | R |
|---|---|
| 1, | $CH_3$ |
| 2, | $C_2H_5$ |
| 3, | $C_3H_7$ |
| 4, | $C_4H_9$ |
| 5, | $C_5H_{11}$ |
| 6, | $C_7H_{15}$ |
| 7, | $C_9H_{19}$ |
| 8, | $(CH_3)_3C$ |

## 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 orthophosphoric acid, containing diethylamine as moderator

and were delivered at 1 mL $min^{-1}$. Mobile phase compositions were as follows:

| | | |
|---|---|---|
| I | $CH_3CN$:0.03M $KH_2PO_4$:0.8% $H_3PO_4$:$H_2O$ (54:23:1:22; | pH=2.8) |
| II | $CH_3CN$:$Et_2NH$:88% $H_3PO_4$:$H_2O$ (65:0.15:0.1:34.75; | pH=2.8) |
| III | $CH_3CN$:$Et_2NH$:88% $H_3PO_4$:$H_2O$ (65:0.2:0.1:34.7; | pH=2.8) |
| IV | $CH_3CN$:$Et_2NH$:88% $H_3PO_4$:$H_2O$ (85:0.4:0.15:14.45; | pH=2.8) |

| | |
|---|---|
| Propranolol, O-acetyl ester, ethyl paraben: | I or II |
| Propranolol, O-propanoyl- to O-hexanoyl esters, and Et paraben: | III |
| O-octanoyl- and O-decanoyl esters: | IV |

Ion-exchange resins were the Dowex strong cation exchange series based upon polystyrene sulphonic acid with variable cross-linking (1-12% divinylbenzene) and of various particle sizes (50-500 mesh, 300-20 μm) or a weak Amberlite cation exchanger based upon methacrylic acid cross-linked with divinylbenzene (200-400 mesh, 75-40 μm). Moisture contents of the resins, both before and after loading, were determined using a Baird and Tatlock Karl Fischer AF3 auto-metering and titration unit. Particle size distributions were measured directly with a nest of micro-sieves (20-500 μm).

## Methods

### Purification of the Resins

Resins were purified and loaded by an adaptation of the technique reported by Gyselinck et. al..[14] For large particle size resins (50-100 mesh, 300-130 μm) a column process was used. A slurry of the ion-exchange resin (2g in 20 $cm^3$ of double distilled water), with well-defined particle size, cross-linking and moisture content, was introduced into a glass column fitted with a tap and a plug of glass wool. The resin was washed consecutively with methanol (50 $cm^3$), benzene (50 $cm^3$), methanol (50 $cm^3$) and double distilled water (50 $cm^3$) to remove organic and coloured impurities. The resins were then activated by three treatments with alternate aliquots of 1M NaOH and 1M HCl and finally the resin, in the acid form, was washed with double distilled water and dried. For smaller resin particles (200-500 mesh, 75-20 μm) the same purification process was used but, due to the lower permeability of the resin bed, particles were

stirred with the appropriate liquid phase for at least 5 minutes. The particles were separated by centrifugation and decantation.

### Preparation of Drug-resin Complexes

An accurately weighed amount of drug (2g in most instances) was dissolved in acidified aqueous dimethylformamide (DMF; 10 $cm^3$, 50%, pH=3.0) and the solution was passed through a column of the appropriate resin (equivalent to 1g of anhydrous resin). The eluate was recycled through the column several times until the pH had fallen to about 1.7 and the UV spectrum of the drug solution showed no further loss of drug to the resin. The eluate was collected to enable the loading of the resin to be estimated from UV absorbance measurements. The drug-resin complex was washed three times with cooled, boiled, double distilled water, once with acetone (25 $cm^3$) and the product was dried at 25-30 °C overnight. For smaller particle sizes a batch method was used in which the above treatments were applied but the resins were stirred with the drug solution until equilibration had taken place (3 hr). The drug resin complex was separated by centrifugation (4000 rpm for 10 min.) and washed as before.

### Dissolution Tests

A modified gastric juice, pH=1.6, was prepared by dissolving sodium chloride (21.6 g) in 0.16M HCl (1L). The pH and the concentrations of ions in this solution are equivalent to those reported by Harrison for gastric juice.[21] A McIlvaine phosphate-citrate buffer (pH=7.4), adjusted to an ionic strength of 0.1M with KCl, was used to simulate intestinal fluids.[22] McIlvaine buffer, at constant ionic strength, was also used to study the effect of pH variability on the release rate of drug from the resinate. The release of drug from the resinate or coated resinate was monitored using either a continuous-flow spectrophotometric method, when chemically-stable systems were studied, or by hplc analysis, principally for the release of propranolol esters at high pH (7.4) when degradation may occur. The integrity

of the compounds used in the continuous-flow system was always checked by hplc at the end of each run.

In the continuous-flow system the selected dissolution medium (1L) was maintained at 37°C in a jacketed cylindrical container, equipped with a close-fitting cover, by means of a Churchill recirculating thermostatic bath. A three-bladed stainless steel stirrer, the blades 2 cm from the bottom, was placed centrally and rotated at 300 rpm by a Heidolph electric motor. The dissolution medium was recirculated through the quartz (1 cm) flow cell of a Cecil CE272 UV spectrophotometer, operated at 0.5-2 AUFS at 290 nm, by means of an electric pump (FMI model, Fluid Metering Co.). Fluid connections were through teflon tubes (1 mm ID) and the outlet from the dissolution vessel was fitted with a sintered glass sparger to prevent withdrawal of ion-exchange particles. This apparatus, without recirculation through the spectrometer, was also used for the hplc analyses. In this case samples (1 $cm^3$) were withdrawn at 5-10 minute intervals through a cotton wool plug, to prevent entrainment of particles. This was added to the internal standard (ethyl paraben, 8 mg in 100 $cm^3$ 0.1M HCl; 1 $cm^3$) and 20 µL aliquots were injected onto the column. All standard solutions were prepared in solvents similar to the dissolution medium in use to minimise UV or sample-solvent effects.[23] Withdrawn samples were replaced with equivalent volumes of the same solvent at 37°C. In both methods the dissolution was initiated by adding the appropriate drug-resin complex (250-500 mg) to the equilibrated dissolution medium.

## RESULTS AND DISCUSSION

### Effect of pH on Loading

The loading of propranolol and its derivatives onto an ion-exchange resin is an equilibrium process which depends upon the presence of the cationic form in solution. This is dictated by the pH of the solution which may, therefore, exert an influence on the loading efficiency. Moreover, the penetration of larger ions into the resin may also be

depressed by kinetic effects and competition with other ions present in the solution may also be observed. To investigate this behaviour a 100-200 mesh (150-75 μm) Dowex strong cationic exchange resin (1g of dry resin, moisture content 55%) with 8% cross-linking agent was loaded with propranolol hydrochloride (500 mg in 10 $cm^3$ of 50% acidified DMF) using the batch method. The pH of the solutions was adjusted by means of 1M HCl. Results are displayed in Table 1, together with the percentage of drug released in one hour from 250 mg of the loaded resin into the simulated gastric medium (1L). Small differences only are noted under the conditions reported. As the pH increases the fraction of propranolol protonated will decrease and reduce the interaction with the resin. The pH values used here still favour large degrees of protonation (for $pK_a$=9.45, $\alpha$[pH=5.96]=99.8%) and only marginal differences are to be expected. Indeed, the observed trend, although small, opposes this effect. This is most probably due to those solutions of lower pH containing higher concentrations of competing ions which marginally inhibit the interaction with the resin. No significant differences were noted in the release profiles of the resins loaded at these various pH values. The range pH=2-4 provides satisfactory loading with minimal variation and hence a value of pH=3.0 was chosen for all loading purposes.

**Effect of Stirring Speed**

Various methods have been described in the literature for the in vitro dissolution testing of drug resinate

**Table 1.** Effect of pH of loading solution on the interaction of Propranolol HCl with a Dowex 50WX8 cationic resin.

| pH | Propranolol Loaded (mg) onto Resin | Propranolol Released (%) after 60 min | Moisture (%) Content of loaded resin |
|---|---|---|---|
| 2.03 | 299.3 | 86.2 | 15.2 |
| 3.03 | 300.6 | 89.0 | 11.0 |
| 4.00 | 302.9 | 88.7 | 11.6 |
| 4.64 | 310.0 | 88.4 | 12.2 |
| 5.96 | 323.0 | 87.0 | 16.3 |

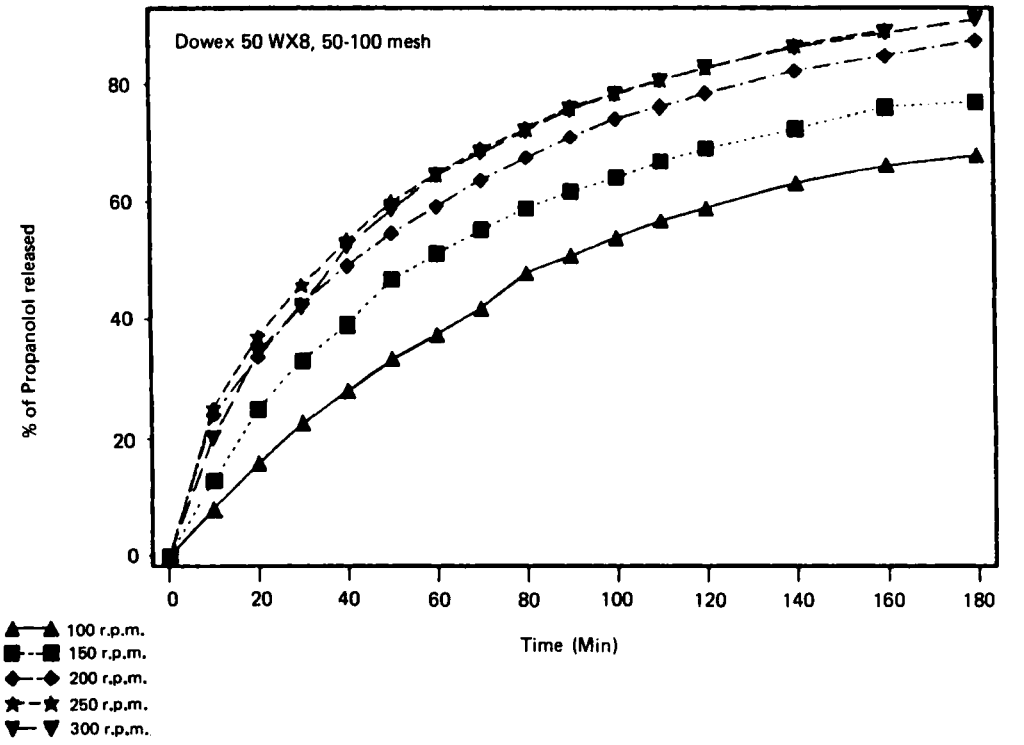



Figure 1. Effect of stirring speed on release profile of propranolol from 250 mg Dowex 50WX8 ( μm) resinate into simulated gastric medium (1L, pH=1.6, 37°C).

preparations[24-31] but despite attempts to develop a standard system[27] none has as yet been universally accepted. The release of drug from the resinate complex is frequently controlled by the diffusion of liberated drug through the resin matrix.[15,19,32-34] Such models assume that sink conditions are established in the receiver phase. The use of a large volume (1L) of the low pH (1.6) medium ensures that the basic propranolol pro-drugs do not approach solubility limited release. A less obvious problem is the stirring speed used in the dissolution tests. This, too, is an important variable and its effect has been monitored in the release of propranolol loaded from a solution of 2g of the hydrochloride in 50% acidified DMF at pH=3.0 onto 1g dry weight equivalent of a Dowex 50WX8 resin of mesh size 50-100 (300-150 μm) using the column method. Figure 1 illustrates

the influence of stirring speed on the release characteristics of the drug-resinate. At low speeds (100-150 rpm) the drug resinate particles were not efficiently stirred and drug release was retarded. This may be due to a hydrodynamic interface between the resinate particles and the solvent which provides a diffusional barrier between the dissolution medium and the resinate particles. At higher speeds (250-300 rpm) the release of the drug was independent of stirring speed due to the more efficient agitation reducing the diffusional barrier. To ensure that formulation and system variables, rather than diffusion-controlled dissolution profiles, were monitored a stirring speed of 300 rpm was chosen for all experiments described in this work.

**Effect of pH on Release**

A claimed advantage of ion-exchange delivery systems is that the release of drug is independent of the pH of the dissolution medium. This prospect was investigated by loading O-pivaloylpropranolol HCl (1g in 5 $cm^3$ 50% acidified DMF, pH=3.0) onto 1g dry weight equivalent of the strong cation exchanger Dowex 50WX8 (55% moisture) and the weak Amberlite cation exchanger (10%moisture), both of 200-400 mesh size (75-40 μm). The batch method was used and equilibration took about 3 hours. The observed loadings were 18.7% and 29.9% respectively. The increased affinity shown by the weak exchanger is probably a consequence of the higher exchange capacity of this resin exhibited when suitable pH values maintain it in the anionic form. Figure 2 shows the release profiles for these resinates in both acidic and basic dissolution media. The release of drug is markedly faster from the Amberlite system and a small difference between the two media is also apparent. The discrepancy for the strong exchange system is equivalent to respective $t_{\frac{1}{2}}$ values for release of 13.8 and 26.3 minutes. This may be a direct result of pH involvement as the solubility of O-pivaloylpropranolol in the more alkaline medium is substantially reduced compared to the acid solution. The capacity of the dissolution medium for the ester is about 62 $mgL^{-1}$ and some 47 mg of drug are available for release.

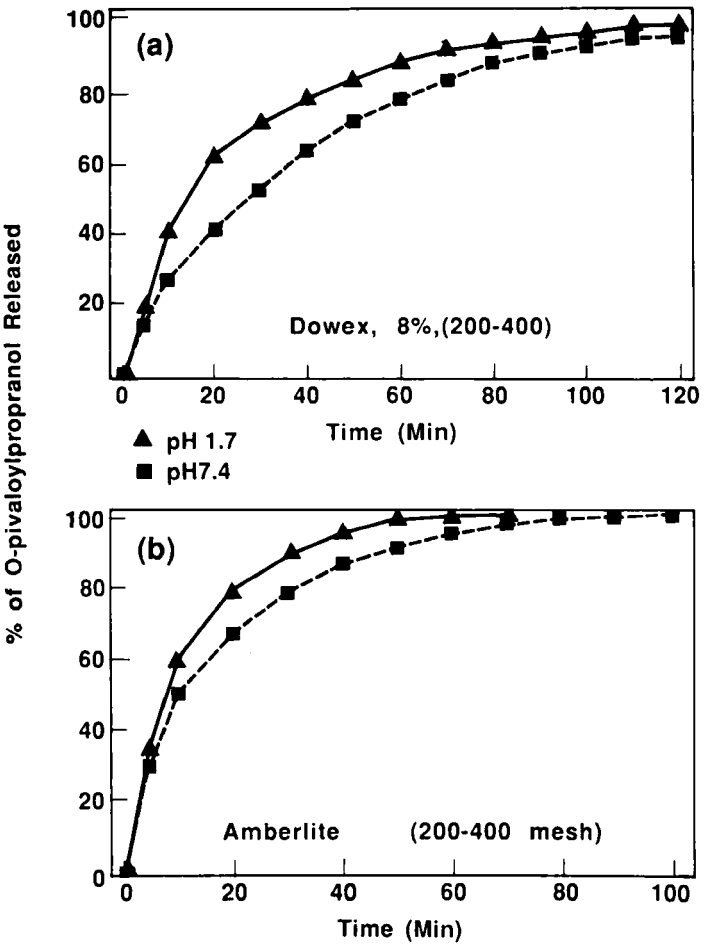



**Figure 2.** Effect of pH on the release of O-pivaloyl-propranolol from Dowex 50WX8 and Amberlite resins (250 mg) into simulated gastric fluid (1L, pH=1.6) and McIlvaine buffer (1L, pH=7.4, μ=0.1M) at 37°C.

These experiments are not under sink conditions for a large part of the profile and thus inhibition of the release may ensue. Additionally, a mismatch in the ionic strengths of the two media may be present due to the different ions present in each. Repeat experiments, following the release of propranolol from a strong cation exchanger as above but using a McIlvaine buffer range of pH=2-6, adjusted to constant ionic strength, demonstrated the independence of

**Table 2.** Effect of ionic strength on the release of O-Pivaloylpropranolol into McIlvaine buffer (1l, pH=3.0, 37°C).

| Time (min) | % O-Pivaloylpropranolol Released | | |
|---|---|---|---|
| | μ = 0.077 | 0.5 | 1.0M |
| 10 | 39 | 40 | 55 |
| 20 | 54 | 58 | 66 |
| 40 | 66 | 69 | 76 |
| 60 | 70 | 72 | 84 |
| 90 | 74 | 79 | 91 |

release rate and pH with dissolution profiles being superimposable. Nevertheless, under some circumstances this relationship clearly is invalid and requires to be confirmed for the system under investigation.

**Effect of Ionic Strength**

To study the ionic strength effect further the release of O-pivaloylpropranolol from a resinate was investigated using McIlvaine buffers (1l, pH=3) with ionic strengths of 0.077, 0.5 and 1M. Data are displayed in Table 2 and show that a increasing ionic strength enhances the liberation of drug from the resinate. This effect confirms that the influx of competitive ions influences the rate of drug delivery from the resin. Such effects are of importance in designing *in vitro* dissolution tests, particularly if different solvents or pH values are used, but may also have implications for *in vivo* use in patients with pH or ion-balance problems such as those found in achlorhydria.

**Effect of Cross-linking**

Ion-exchange resins are available with various proportions of cross-linking agent with 1-12% divinylbenzene being common in the Dowex series. This parameter influences the porosity and swelling properties of the resin. Low cross-linking agents swell markedly upon hydration while the

higher grades have a tighter pore structure. Shrinkage of the resin when the cationic form is brought into contact with acid solutions may also occur.[35-36] This may cause a reduction in pore diameter and lead to the entrapment of large ions.[32] The diffusional release of drugs from resins often follows the relationship:

$$F = 1 - \frac{Q_t}{Q_0} = 1 - \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left[ - \frac{\pi^2 n^2 D.t}{d_p^2} \right]$$

where F is the fraction of drug released from the resinate at time t, $Q_0$ the initial drug content of the resinate ($g.g^{-1}$), $Q_t$ the drug content of resinate at time t ($g.g^{-1}$), D the diffusion coefficient of drug within resin ($m^2.min^{-1}$), $d_p$ the mean diameter of resin particles (m) and t the = time into dissolution (min). A B term ($B = \pi^2 D/d_p^2$) is also defined.

This suggests that the diffusion coefficient, dependent upon the resin and molecular properties, and the particle size of the resin are important factors in determining release from resinates. To reveal such effects with the propranolol pro-drugs, O-pivaloylpropranolol (500 mg) in 50% acidified DMF (5 $cm^3$, pH=3) was loaded onto 1g dry weight equivalent of Dowex 50W resin (100-200 mesh, 150-75 μm) with various degrees of cross-linking using the batch technique.

Data are recorded in Table 3 and show that cross-linking has a dramatic effect upon the loading efficiency with a three-fold reduction in drug content across the range studied. The quoted volume capacities of cationic exchange resins significantly increases with cross-linking, an effect which is largely caused by swelling differences. It is likely, however, that the effect observed here is due to a reduction in pore size which prevents access of the large pro-drug molecule to the ionic sites held deep within the resin. In parallel, the moisture content of the resinates is also dependent upon the degree of cross-linking.

The release of drug from these resinates (250mg) into simulated gastric juice (1L, pH=1.6, 37°C) was also studied. Dissolution profiles are presented in Figure 3 and show that

Table 3. Effect of amount of cross-linking agent on the loading of O-pivaloylpropranolol onto Dowex 50W cationic exchange resins (100-200 mesh, 150-75 μm).

| Cross-linking agent (%) | O-pivaloylpropranolol content (%) | Moisture content (%) |
|---|---|---|
| 1 | 32.7 | 80 |
| 2 | 29.7 | 79 |
| 4 | 25.6 | 65 |
| 8 | 16.2 | 56 |
| 12 | 10.2 | 44 |

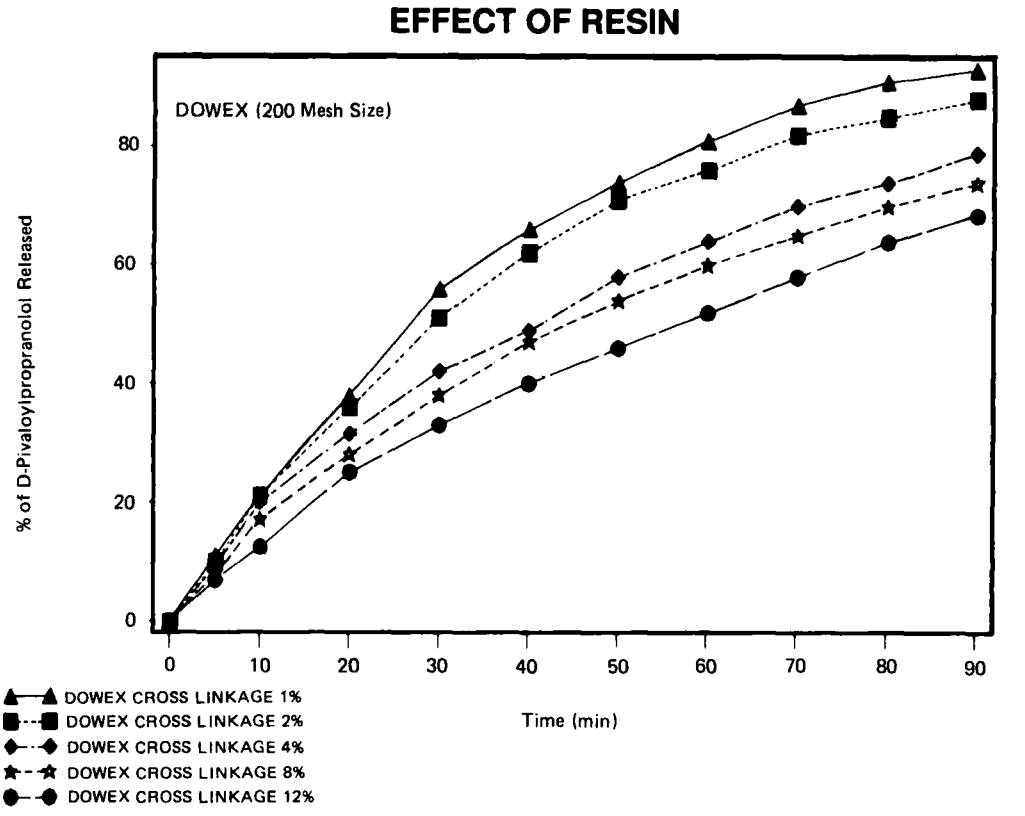



Figure 3. Effect of amount of cross-linking agent on the release of O-pivaloylpropranolol from Dowex 50W resinates (250 mg, 100-200 mesh, 150-75 μm) into simulated gastric medium (1L, pH=1.6, 37°C).

the release rates are also dependent upon the degree of cross-linking. These show considerable variation with $t_{\frac{1}{2}}$ values for release being 26.3, 28.9, 40.7, 44.0 and 57.2 minutes as the cross-linking agent increases from 1% through 2, 4 and 8% up to 12%. These data suggest that the bound pro-drug is not limited to unhindered ionic sites but is also involved with less-accessible centres which offer resistance to diffusion. This may suggest a difference in the swelling behaviour of the resin during loading and during dissolution which results in the pro-drug being entrapped within the resin matrix, the effect becoming more pronounced as cross-linking increases. Cross-linking is clearly an important parameter in modifying release rates provided the lower loadings available with lower porosities may be tolerated.

**Effect of Particle Size**

The rates of ion-exchange interactions are increased as the bead diameter decreases due to a reduction in the diffusive path length. This can be confirmed for the propranolol series by loading 1g dry weight equivalent of Dowex 50WX8 resin (55% moisture) in 100-200 mesh (150-75 μm) and 200-400 mesh (75-40 μm) with O-pivaloylpropranolol (500 mg) in 50% aqueous DMF (5 $cm^3$, pH=3) for 3 hours. Little difference in the loading capacity of either resin was observed with values of 16.2% (larger size) and 18.7% (smaller size) being recorded.

These data are in accord with those of Gyselinck et. al.[14] who have earlier demonstrated that particle size has little effect upon the amount of drug bound to an ion-exchanger but that variables such as cross-linking, and temperature were important. The liberation of drug from these resins was, however, significantly different. Results are illustrated in Figure 4 which shows that the smaller resinate particles delivered the drug much more rapidly ($t_{\frac{1}{2}}$, 15.1 min) than those with the larger distribution ($t_{\frac{1}{2}}$, 46.6 min), in accord with models of diffusional release of exchangeable ions.

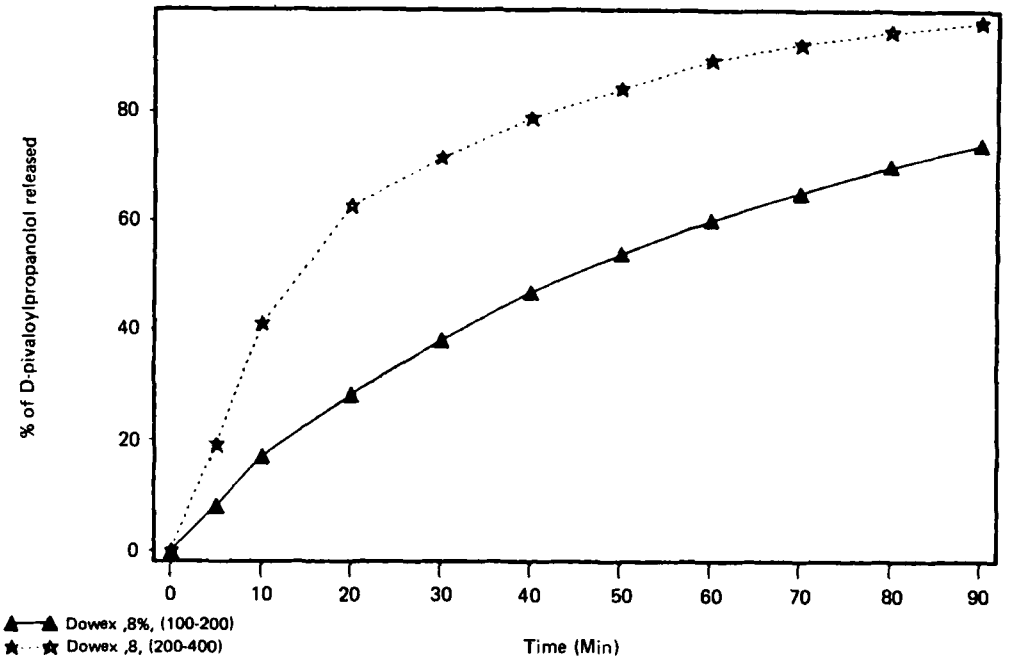



**Figure 4.** Effect of the resin particle size on the release of O-pivaloylpropranolol from its Dowex 50WX8 resinate (250 mg) into simulated gastric juice (1L, pH=1.6, 37°C).

### Effect of Chain Length

The loading efficiency of cationic drugs onto ion-exchange resins depends upon the molecular dimensions of the drug and its relationship with the porosity of the resin matrix. We have already demonstrated this type of interaction in the variation of loading and release profiles as cross-linking within the resin matrix is increased. The range of propranolol pro-drugs available here has been synthesised to provide appropriate physico-chemical and kinetic properties for these pro-drugs.[20,37] The influence of the structural variation in the ester side chain has been studied by interacting solutions of the O-n-acyl propranolols [acetyl (1), propanoyl (2), butanoyl (3), valeroyl (4), and hexanoyl (5)] in 50% acidified aqueous DMF (pH=3) with Dowex 50WX8 resin (1g dry weight equivalent, 50-100 mesh, 300-150 μm) by the column method. Table 4 records the loading in the

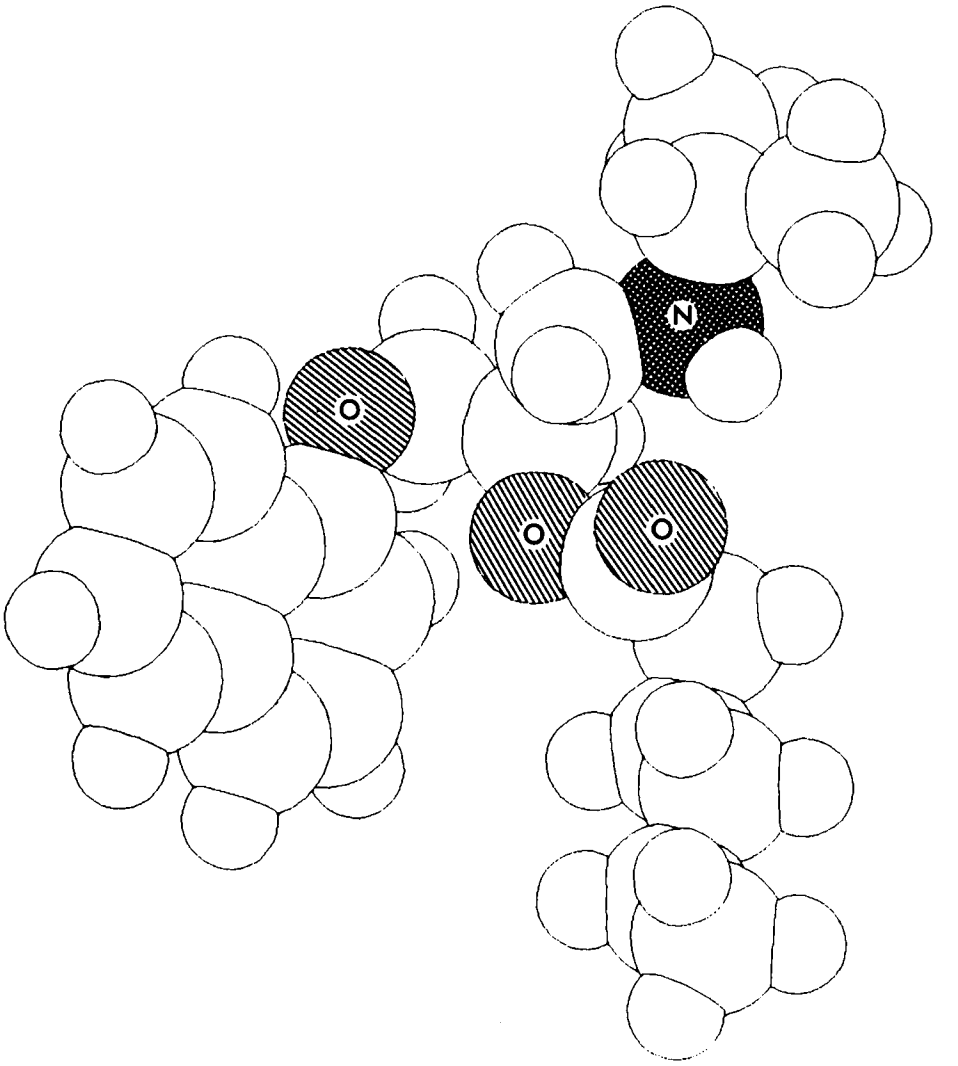



Figure 5. CHEM-X representation of O-n-hexanoylpropranolol.

Table 4. Loading of O-n-acyl propranolol pro-drugs onto Dowex 50WX8 cation ion-exchange resin.

| Propranolol Ester | Drug Content in Resinate (%) |
|---|---|
| Acetyl | 17.5 |
| Propanoyl | 14.5 |
| Butanoyl | 12.0 |
| Valeroyl | 10.1 |
| Hexanoyl | 8.9 |

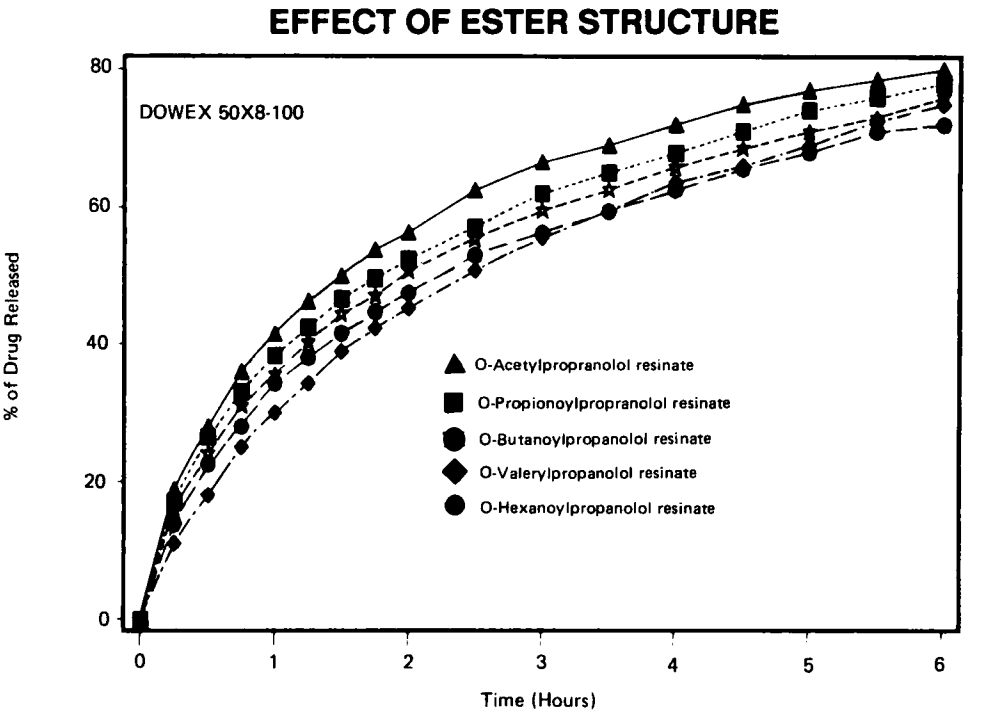



Figure 6. Effect of ester structure on the release of O-n-acylpropranolols from Dowex 50WX8 resinates (250 mg, 50-100 mesh, 300-150 μm) into simulated gastric medium (1L, pH=1.6, 37°C)

respective systems and shows that as the ester function increases in size less drug may be complexed with the resin. This behaviour suggests that the system is behaving analogously to the changes in cross-linking, described above, with larger cations unable to penetrate smaller pores within the matrix. In an attempt to furnish a relationship describing this behaviour, resort was made to the molecular modelling program CHEM-X (Chemical Design Ltd., Oxford) which can provide 3-dimensional representations of molecules and undertake appropriate calculations thereon. The propranolol esters were modelled using this package, assuming staggered conformations of the n-acyl side-chains (Figure 5) and the volume of the structure (V) was calculated. This cube root of this parameter, to model the average radius of the

molecule, was related to the loading, converted to molar terms, by the equation: Loading (%M) = 0.376 - 0.0404 $\sqrt[3]{V}$ (r = -0.966).

The rather poor fit could be due to several factors including problems in calculation, shape factors, hydration and pore size distribution and the empirical equation, relating the loading to carbon number (n), is equally valid: Loading (%M) = 0.0722 - 0.00831 n (r = -0.984).

The release of pro-drug into simulated gastric juice (pH=1.6) from these systems is displayed in Figure 6.

Considerable retardation is observed for the pro-drugs compared to propranolol which has a $t_{\frac{1}{2}}$ for release of some 41 minutes under these conditions. The corresponding values for the pro-drugs, from acetyl to hexanoyl are 1.48, 1.81, 1.94, 2.20 and 2.46 hours. This system, which combines larger particle-resins with drug derivatives with slower elution profiles offers a possible way in which controllable drug delivery may be obtained without the necessity of coating the particles. The use of particles larger than about 120 μm in suspension systems may generate a gritty texture in the product. Smaller sized resin particles may also be rendered suitable for controlled-release by coating procedures and results, and those describing the degradation kinetics of these pro-drugs will be described later.

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