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DRUG-DELIVERY BY ION-EXCHANGE. PART VII: RELEASE OF ACIDIC DRUGS FROM ANIONIC EXCHANGE RESINATE COMPLEXES

W J Irwin,* R MacHale and P J Watts

Drug Development Research Group,
Pharmaceutical Sciences Institute,
Aston University,
Aston Triangle,
Birmingham, B4 7ET, UK.

Keywords

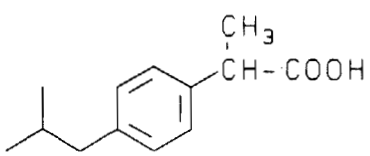
Cholestyramine, dissolution, drug delivery, ibuprofen, ionic exchange resins, resinates.

Summary

The loading and release of ibuprofen, ketoprofen and mefenamic acid from a range of strong anionic exchange resins, including cholestyramine, is described. Release rates into simulated gastric fluid increase with stirring speed up to 300 rpm and decrease as either the particle size of the resin beads or the degree of cross-linking increase. An increase in the temperature of loading enhances the capacity of the resin towards the drug and reduces its release rate. Coating of the resin also enables suppression of drug release to be achieved. The small particle size of cholestyramine enables a rapid release of drug from the resin to be achieved. This rate is significantly greater than that obtained by monitoring dissolution from a drug-lactose dispersion and may indicate that ion-exchange technology may provide an opportunity to overcome poor dissolution characteristics for weekly ionic compounds.

INTRODUCTION

The use of ionic exchange resins[1-3] to modify the pharmaceutical properties of drugs, including release rate,[4] taste-masking[5] and the reduction of toxicity and stability enhancement,[6-8] is a viable formulation opportunity. The development of controlled release systems from liquid dosage forms has received particular attention with practical systems relying upon the influx of ions into the resin to release the drug together with a coating membrane to provide control of release rate.[9-13] Most work has been undertaken following the release of basic drugs from cationic exchange resins[3,14-25] and, in contrast, there is little available information on the application of this technology to the delivery of acidic drugs. The recent report of the interaction of a series of simple aromatic acids with anionic exchange resins[26] prompts us to report the results of some studies of the release of the anti-inflammatory carboxylic acid derivatives ibuprofen (1), ketoprofen (2) and mefenamic acid (3) from a range of anionic exchange resins.



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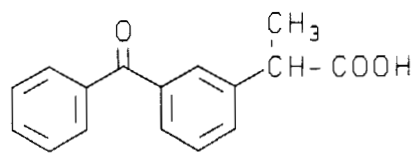

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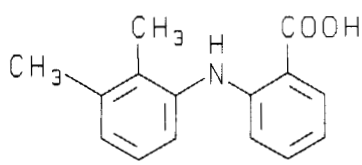

(3)

EXPERIMENTAL

Apparatus

Release experiments were performed using USP flasks and stirrers in a Caleva Model 7SC Dissolution Tester equipped with a Caleva TE-85 Tempette thermoregulator, normally set at 37°C. Solutions were continuously cycled, by means of a Watson-Marlowe 501M multi channel peristaltic pump, through an LKB 4052 TDS Ultrospec 11 Spectrophotometer. Moisture contents were determined with a Karl Fischer AF3 autometering and titration unit and the particle sizes of resins were determined by sieving with a nest of micro-sieves (38-850μm).

Dowex anionic exchange resins with cross-linking (x) equivalent of 2%, 4% and 8% divinylbenzene (DVB) in particle sizes of 200-400 mesh (Dowex x-400; 38-75μm), 100-200 mesh (Dowex x-200; 75-150μm), 50-100 mesh (Dowex x-100; 150-300μm) and 20-50 mesh (Dowex x-50; 300-800μm) were obtained from Sigma. Cholestyramine (Duolite AP 1110) was donated by Duolite.

Methods

Preparation of Resins.

Resins were activated prior to use by successive elution of methanol, distilled water, 1M NaOH and 1M HCl through a bed of the resin held in a column.[21] Volumes of ~30 mL of each were used for each gramme of resin. The treated resin was then washed with distilled water until the eluate was neutral. The small particle-size of cholestyramine (38-63μm) and Dowex 400 mesh (338-75μm) resins prevented column activation and washes were undertaken in a beaker with filtration or centrifugation. Resins were dried at 50°C to constant weight prior to use and were loaded by either the column or beaker method, depending upon the particle size of the resin involved.

Loading of the Resins

Resins containing mefenamic acid were loaded by adding a two-fold excess by weight of the acid (20mL, 10 mg mL^{-1}), dissolved in 0.05M NaOH, to the dry resin (100mg). Absorption profiles were determined by monitoring the loss of mefenamic acid

from solution to provide optimum contact periods. Overnight periods were generally used but, with small particle size or low cross-linking density, loading periods could be as short as 20 min for cholestyramine and 40 min for Dowex 200 with 2% cross-linking. The effects of sodium hydroxide concentration were observed by also loading cholestyramine from solutions of mefenamic acid in 1.0M and 0.1M NaOH and the influence of a drug:resin weight ratio of 1:1 was also examined. In the case of ibuprofen and ketoprofen, the activated, dried resin (0.2-1.0g) was treated overnight with a solution of either ibuprofen or ketoprofen (2x10 mL; 1.5% m/v) in 0.1M NaOH. The loaded resin was collected, washed with distilled water and acetone and then dried overnight. The effect of temperature was monitored by loading the 20-50 mesh (300-850μm), 8% cross-linked resin under reflux.

Microencapsulation Procedure

Cholestyramine resin, loaded with mefenamic acid (1.6g dry weight), was triturated with glycerol to produce a smooth paste which was then further mixed with glycerol (20 mL).[23,27,28] To this suspension, held in a 1L jacketed flask maintained at 50°C, was slowly added aqueous acacia solution (250 mL, 2% at 50°C) to ensure a uniform dispersion. The mixture was stirred at 400 rpm and a solution of gelatin (250 mL, 2% at 50°C, pH adjusted to 3.9 with 1M HCl) was added. The mixture was readjusted to pH 3.9 with 1M NaOH and stirring was continued for 30 min. The suspension was rapidly transferred to an ice-bath and allowed to cool with microscopical observation . At 5°C the microcapsules were allowed to settle and the liquid was decanted. The capsules were washed with two lots of ice-cold isopropanol (50 mL), with stirring, followed by treatment with two lots of a solution of formaldehyde in isopropanol (19%, 50 mL). After the second addition, the suspension was stirred for 2 h to complete the hardening of the coat. The microcapsules were separated by decantation and were washed twice with ice-cold isopropanol (50 mL) and were then allowed to dry at room temperature to yield 9.7g of product.

Release from the Resinates

Release from resinates was undertaken with sink conditions into a simulated gastric medium comprising phosphate-citrate buffer of pH 7.4 adjusted to ionic strengths of 0.1, 0.488 or 1.0. The resinate complex (1g) was added to either 1L or 500 mL of the dissolution medium and the UV absorption was continuously monitored at 285 nm (mefenamic acid), 261 nm (ibuprofen) or 300 nm (ketoprofen). The wavelength and the amount of resin were adjusted so that the absorbance of the dissolution medium did not exceed 3.0 when the resinate was completely exhausted. The sampling line was fitted with an inlet filter to prevent resin particles being swept into the detector. Stirring rates of 150 or 300 rpm were normally used and quantification was established through calibration graphs at the analytical wavelengths. To compare the release of drug from a resinate complex with a typical solid system, a dispersion of mefenamic acid (20mg) and lactose (40mg) was prepared by mixing and the dissolution profile of the mix, under similar conditions, was monitored.

RESULTS AND DISCUSSION

The loading of acidic drugs onto the anionic exchange resins was largely independent of resin particle size but displayed the anticipated reduction with an increase in the degree of cross-linking. The maximum value of loading of ibuprofen and ketoprofen was onto Dowex 2-200 (37.4 and 40.5% by weight of dry resin) which fell to 26.7 and 24.9% when the 8-50 grade was used. Cholestyramine furnished 28.5 and 30.0% loading. Mefenamic acid generally provided more variable loadings with Dowex 8-200 furnishing 18.6% and cholestyramine 45% drug content by dry weight.

The release from the resinate complexes was undertaken in simulated gastric fluid.[22,23] Control of stirring is essential to enable comparison of release rates to be made. Figure 1 records the influence of stirring speed on the release profiles of ketoprofen from Dowex 2-200 resin. Release is mediated by a

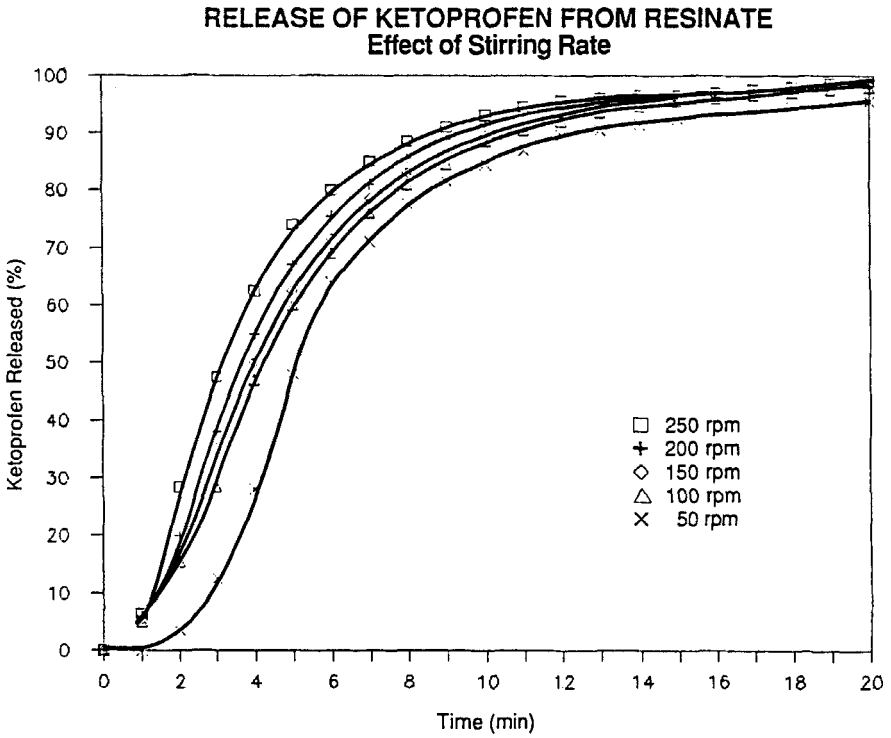

Figure 1. Effect of Stirring Rate on the Release of Ketoprofen from its Dowex 2-200 Resinate Complex.

stationary diffusion layer surrounding the resin particles which is dependent upon stirring rate until 250-300 rpm is reached.

Temperature also has a significant effect on both loading and release of drug from the resinate complex. At 22°C, 24.9% of ketoprofen was loaded onto the Dowex 8-50 resin while in the sample loaded under reflux this was increased to 35.7%. Figure 2 records the influence of this parameter on the release of ketoprofen from this resinate. Here, it is seen that the resin loaded at the higher temperature provides a significantly lower release rate despite having a greater drug content. It is probable that in this case heat expands the resin affording ions access to deeper exchange centres. On cooling, the resin relaxes entrapping the interacting anion and provides a greater diffusional resistance to elution.

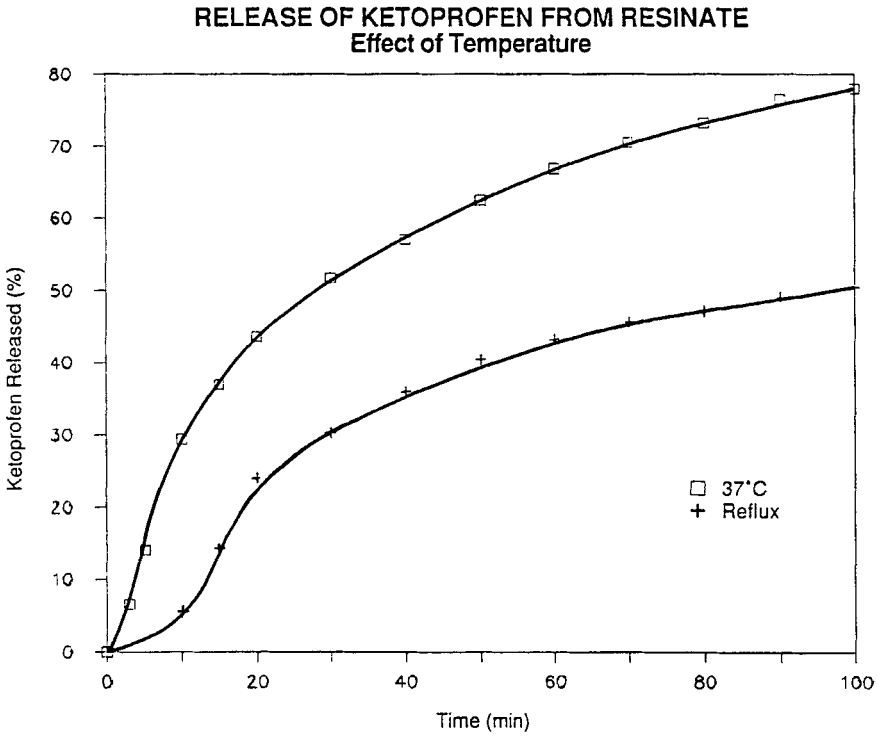

Figure 2. Effect of Loading Temperature on the Release of Ketoprofen from its Dowex 8-50 Resinate Complex.

Cross-linking within the resin may also exert a significant effect on both loading and release. The influence of this parameter is readily seen upon hydration of the resins with small degrees of cross-linking enabling resins to swell significantly. Cross-linking modifies the pore-size within the resin and thus excludes the larger organic anions from access to active exchange centres within narrow pores. In the case of anionic exchange resins, cross-linking is due to both the level of the cross-linking agent and also to the formation of methylene bridges formed from the precursor CH_2Cl residues which are converted into the $-N^+(CH_3)_3$ exchange centres. Degrees of cross-linking in this series of resins are thus inexact. For example, cholestyramine contains some 1-2% divinylbenzene, just sufficient to produce the three-dimensional matrix, but swelling studies suggest cross-linking is nearer to 8%. Loading onto Dowex 200 mesh resin was

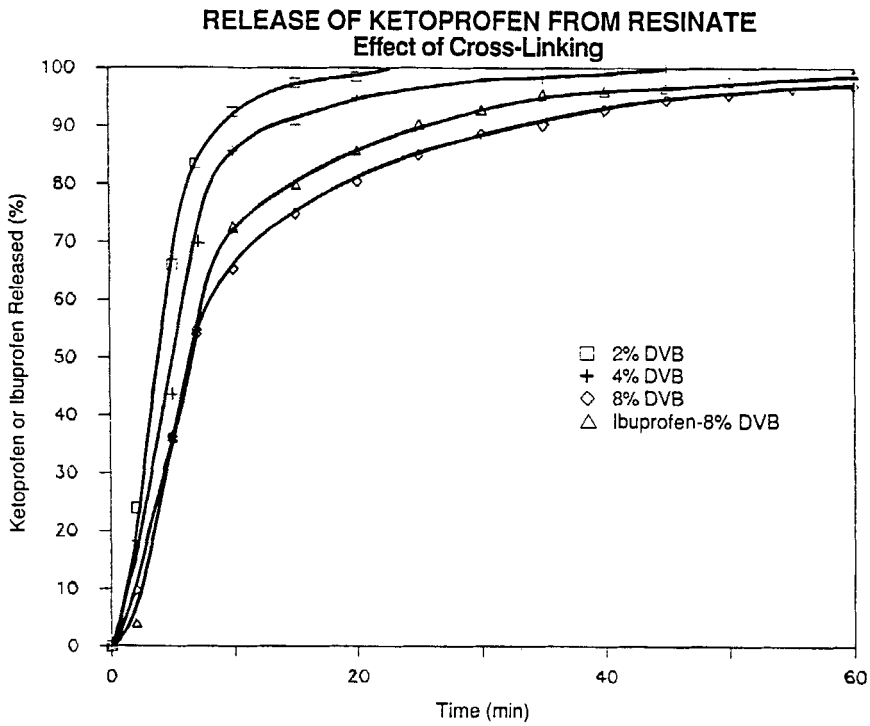

Figure 3. Effect of Degree of Cross-linking on Release of Ketoprofen from its Dowex x-200 Resinate Complex. Also shown is release of Ibuprofen from its Dowex 8-200 Resinate Complex.

almost constant at the 2% and 4% cross-linking levels. With ibuprofen, for example, loadings of 37.4% (Dowex 2-200) and 37.2% (Dowex 4-200) where obtained while values of 40.5% and 38.7% were obtained for ketoprofen. With cross-linking equivalent to 8% divinylbenzene significant reductions were observed with ibuprofen yielding 27.8% loading with that of ketoprofen being reduced to 27.6%. The release of drug from these resinate complexes mirrored these effects. Figure 3 records some typical release profiles from the series of ketoprofen resinates but also includes a curve from ibuprofen released from its Dowex 8-200 resinate. Little difference is seen between the two drugs, although ibuprofen is released slightly faster, but it is clear that as the cross-linking increases the release rate is

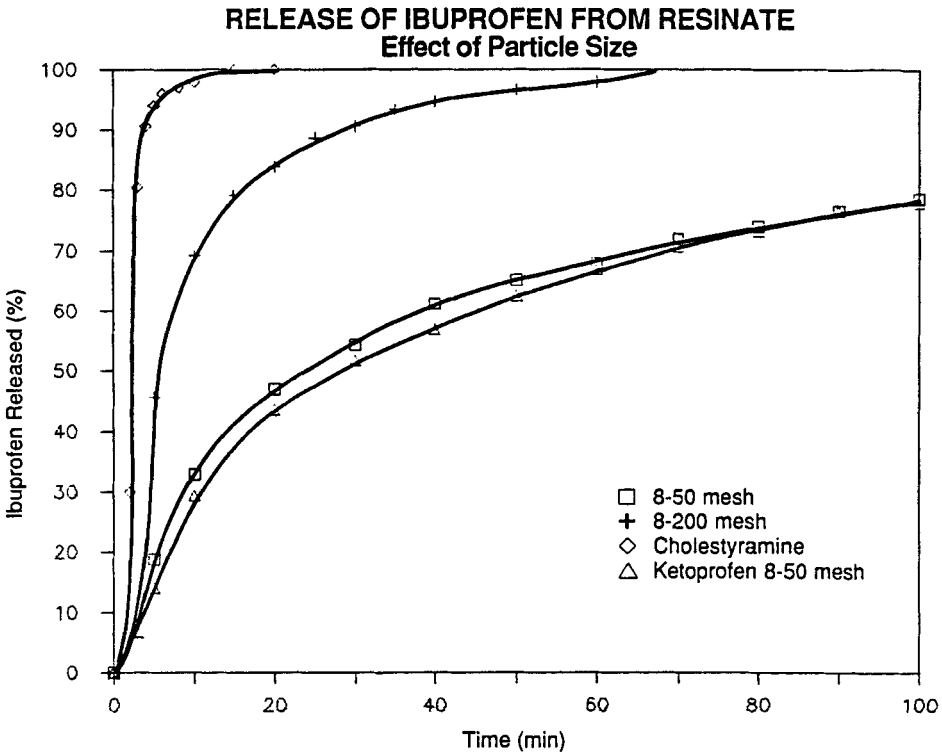

Figure 4. Effect of Particle Size on the Release of Ibuprofen from its Dowex Resinate Complexes. Also shown is release of Ketoprofen from its Dowex 8-50 Resinate Complex.

depressed. Half lives for this release were found to be 10.8 min (2%), 17.3 min (4%) and 25 min (8%) for ibuprofen while the corresponding values for ketoprofen were 10 min, 15.3 min and 33.3 min.

The final variable of significance studied was the particle size of the resin. This is expected to have little influence on the equilibrium loading capacity but a significant effect on release rates due to the greater diffusional pathlengths in the larger particles. Typical loadings for ibuprofen onto Dowex 8-400, 8-200, 8-100 and 8-50 resins, which showed no trend dependent upon particle size, were 26.9±2.4% ($\bar{x}\pm\sigma$) while the corresponding data for ketoprofen gave loadings of 27.9±1.1%. Figure 4 records typical release curves and illustrates the

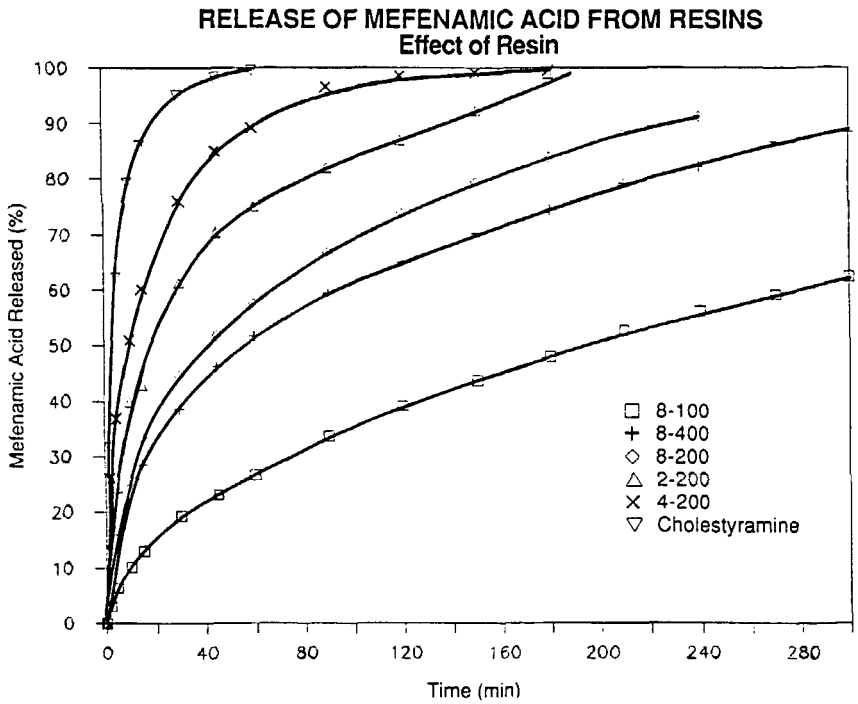

Figure 5. Effect of Particle Size and Degree of Cross-linking on the release of Mefenamic Acid from its Resinate Complexes.

significant difference between ibuprofen liberated from Dowex 8-50 and Dowex 8-200 resinates. The smaller particle size resin provides a release half life of 6 min while the larger extends this period to some 25 min. The curve also illustrates a plot for ketoprofen release, from its Dowex 8-50 resinate, $t_{\frac{1}{2}}$ 28 min, showing again the similar but slightly slower release of this analogue.

Both arylpropionic acid derivatives (1,2) also may be loaded onto cholestyramine with efficiencies similar to those above with ibuprofen providing a 28.9% loading and ketoprofen 25.9%. Cholestyramine is an anionic exchange resin used medicinally in high doses (12-24g daily) to counter excessive blood cholesterol levels. In this rôle it complexes with bile acids preventing their enterohepatic reabsorption and thus depleting the cholesterol steroid pool through the synthesis of new bile acids.

The particle size specification of cholestyramine is within the range 5-150μm (100-500 mesh) but our sample was largely within the 38-63μm range. The small particle size of this resin ensures that release from the complexes is rapid. The curve for the release of ibuprofen from its cholestyramine resinate is also displayed in Figure 4, with a half life of 2.5 min, a value identical to that found for ketoprofen from its cholestyramine resinate.

Analogous results were obtained for mefenamic acid. Figure 5 records release from a series of Dowex resinates which vary in particle size and in degree of cross-linking. This confirms that increases in either particle size (8-400, 8-200, 8-100) or the degree of cross-linking (2-200, 4-200, 8-200) reduces release rates. Little effect in the loading efficiency was observed with a two-fold increase in the weight of resin or on changing the solvent to 0.1M or 1M NaOH.

Quantitative analysis of the release of complexed drug from the ion exchange resinate are available[29-33] and it has been shown that normally release occurs via particle diffusion.[31] Boyd and coworkers have modelled the release process according to 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 rate constant B defined as :

$$B = \frac{4\pi^2 D}{d_p^{\,2}} \qquad (2)$$

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).
n = summation variable incrementing from unity to infinity. In practice, only a few terms are necessary as higher values of n, and of t, reduce the summation term to insignificance.

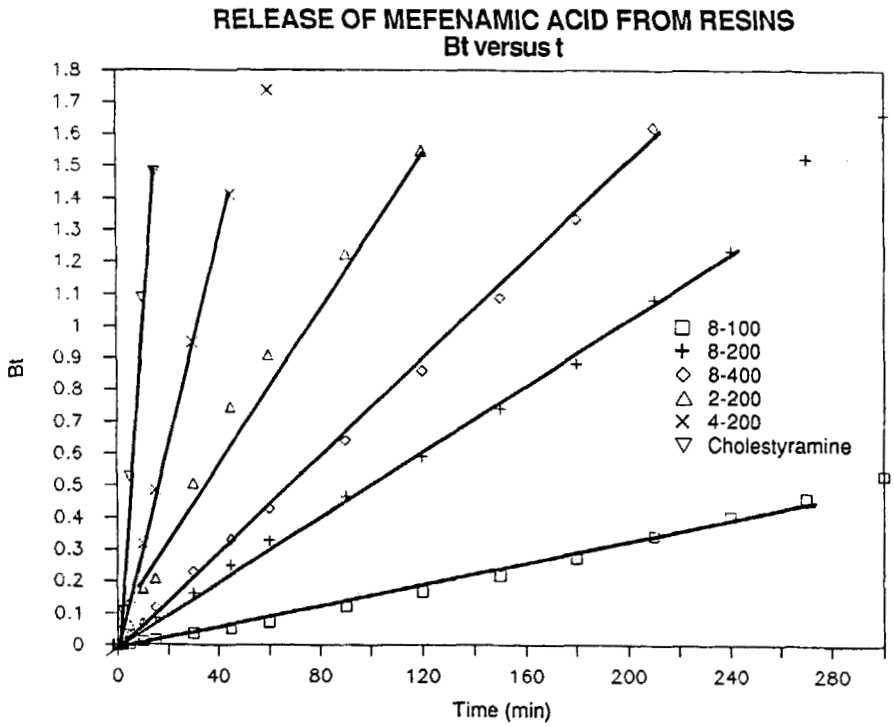

Figure 6. Plots of t versus Bt for the Release of Mefenamic Acid from various Resinate Complexes.

The variables in this equation which control the rate of drug release are the particle diameter (d_p) and the diffusion coefficient of the drug (D) in the resin. Reichenberg has shown that, by means of Fourier analysis and integration, it is possible to calculate the product term Bt represented in this equation from the fractional release (F) using one of two expressions depending upon the magnitude of F:[32]

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

and

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

A plot of time against Bt provides a linear plot if the release of drug is diffusion controlled. The slope of this plot

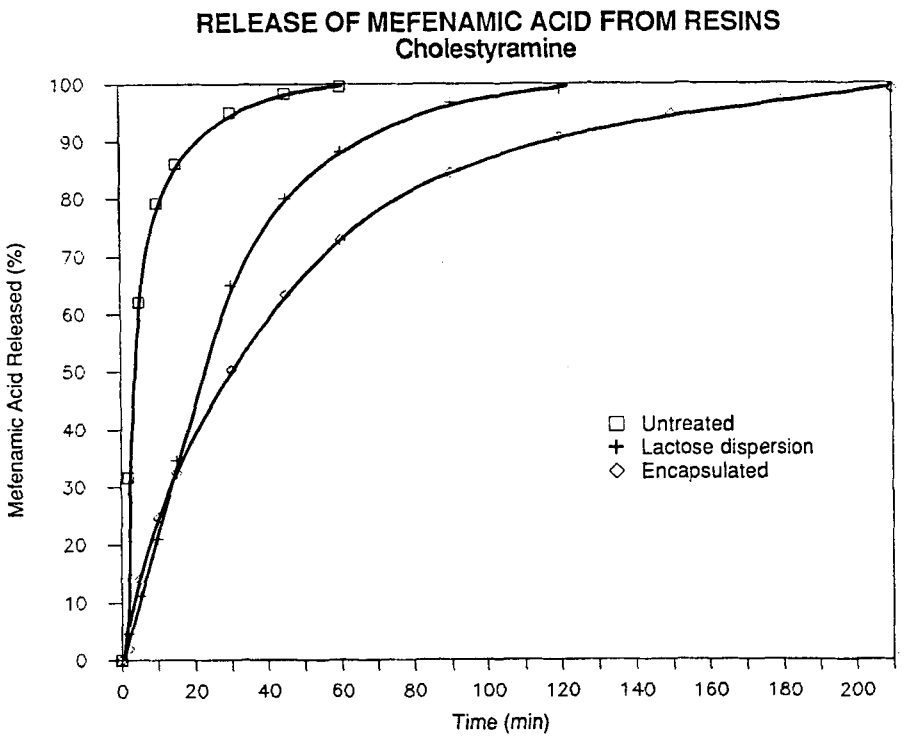

Figure 7. Release of Mefenamic Acid from its Cholestyramine Resinate, untreated and encapsulated, and dissolution from a Lactose Dispersion.

is B and the diffusion coefficient may be evaluated using the relationship in Equation 2.

Treatment of the release data above according to these transformations provides linear plots which confirm that release of these acidic drugs from their resinate complexes is diffusion controlled. This is illustrated in Figure 6, using the data presented in Figure 5, for mefenamic acid.

The mefenamic release data recorded in Figures 5 and 6 also include cholestyramine. A major interest in the use of ion exchange resins in formulation development is to provide a controlled release profile. To examine this possibility, the

cholestyramine resinate of mefenamic acid was encapsulated within a hardened gelatin-acacia microcapsule. The release profile of this is shown in Figure 7 and reveals that an increase in the half life for drug release from 3.5 min with cholestyramine resinate to 30 min with the encapsulated material is obtainable.

As noted earlier with the arylpropionic acids resinates, the cholestyramine complexes release drug rapidly. This is also noted with the mefenamic acid profile in Figure 7. It is of interest to compare this release rate with that from a normal dissolution of solid mefenamic acid. A dispersion of mefenamic acid in lactose was subjected to dissolution and gave the profile which is also recorded in Figure 7. This corresponds to a half life for the dissolution of 22 min and demonstrates that the cholestyramine resinate ($t_{\frac{1}{2}}$ 3.5 min) provides a significantly greater rate of liberation of mefenamic acid into solution than the solid system. Ion exchange resins may thus may prove to be a viable means to overcome poor dissolution behaviour of weakly ionic compounds.

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