International Journal of Pharmaceutics, 87 (1992) 31–36

IJP 02830

Investigation of the bioavailability of codeine from a cation-exchange sulphonic acid 2. Evaluation of release kinetics of codeine from the resinate and uptake of Na^+ from the solution

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(Received 9 December 1991)
(Accepted 2 March 1992)

Key words: Ion exchange; Sustained-release kinetics; Codeine resinate; Diffusivity; Mass law; Kinetics

Summary

The rate of release of codeine from a cation-exchange resin at varying codeine resinate and NaCl concentrations was investigated. The kinetics of exchange between Na^+ and codeine were also studied. Determination of codeine was performed by UV spectrophotometry. For the determination of Na^+, a radioactive tracer (^{22}Na) and a radioactive tracer technique were employed. The kinetics of both products were followed as a function of time and evaluated on the basis of different equations: Boyd's equation, that of Viswanathan and the mass law. The release kinetics of codeine could be described with the three equations. The same diffusivities were evaluated with the equations of Boyd and Viswanathan. Using the mass law, the graphs for both codeine and Na^+ were composed of two straight lines, suggesting two binding sites on the resinate and two release rate processes: rapid release during the initial period, followed by a decreasing release rate, the rate being influenced by the amount of codeine and the concentration of NaCl. The mass law appeared to be most suitable to detect the two processes of release. The results confirm the existence of two binding sites, as determined via the analysis of release rate data under equilibrium conditions.

Introduction

In the preceding paper (Plaizier-Vercammen, 1992), the effect of a number of parameters on the exchange of codeine from a sulphonic acid exchange resin was studied, using equilibrium values. Two different sites for Na^+ were noted.

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The release of drug from a resinate particle can be controlled in different manners: pore diffusion resistance or particle diffusion control, film diffusion and chemical exchange. Several equations have been proposed in the literature. However, in most studies on ion-exchange resins, the release was only investigated in the case of the resinate-bound compound, ion uptake from solutions being ignored (Borodkin et al., 1971; Khouw et al., 1978).

In this study, the release rate kinetics of both Na^+ and codeine were investigated, with the purpose of gaining more insight into the release rate

pattern and of confirming the existence of two binding sites on the resinate as suggested in the previous investigation (Plaizier-Vercammen, 1992).

Materials and Methods

Codeine resinate (Certa, Belgium) is composed of codeine bound on the cation exchange sulphonic acid resin Resicat ABM Na-042. The diameter of the beads is 250 μm. The cation exchange ion used was sodium chloride (Merck, Darmstadt), containing radioactive NaCl (^{22}Na) (NEN, U.K.) as tracer. A radioactive stock solution of 1.68×10^6 Bq/10.5 ml was employed.

Kinetics of Na^+ uptake from solution onto codeine resinate

A solution composed of 40 ml of 0.001 M NaCl and 1 ml ^{22}Na stock solution was continuously stirred and pumped. Codeine resinate was added and the radioactivity measured every 20 s. The dead time was 40 s.

Release rate of codeine

Drug release experiments were performed in a dissolution apparatus of the flow-through type, as used by others (Gyselinck et al., 1981). For the release of codeine, a known amount of codeine resinate was added to 40 ml of NaCl solution (containing $^{22}Na^+$ as tracer) and the free codeine concentration monitored continuously using a UV spectrophotometer connected to a recorder. The concentration of Na^+ was 0.1 and 1 M, the amount of codeine resinate being 0.16 and 0.25 g, respectively.

Mathematical Approaches to Drug Release from Resinates

The release of drug from a resinate can be described according to different equations:

Particle diffusion

The precise expression for particle diffusion as rate-controlling step was given by Boyd et al. (1947) and later simplified by Reichenberg (1953):

$$Bt = 2\pi - \pi^2 F/3 - 2\pi(1 - \pi F/3)^{1/2}. \quad (1)$$

and

$$B = 4\pi^2 D/d^2 \quad (2)$$

where B is an intermediate variable (min^{-1}), F denotes the fractional dissolution value (defined by H_t/H_∞ with H_t and H_∞ representing the amount of drug released at time t and ∞, respectively), t is time (min), D denotes diffusivity (mm^2/min) and d is the diameter (mm) of the resin particles. In a standard table, the Bt values were listed at different values of F (at different times). By plotting Bt vs time a straight line should be obtained, the slope yielding the B value and hence the diffusivity can be calculated.

Although the method is cumbersome, it has been used by various authors (Chaudry and Saunders, 1956; Gyselinck et al., 1982; Schacht et al., 1982).

Equation of Viswanathan

Bhaskar et al. (1986) showed that an alternative and simpler expression, the Viswanathan equation, can be used:

$$-ln(1 - F) = 1.59\left(\frac{6}{d}\right)^{1.3} \cdot D^{0.65} \cdot t^{0.65} \quad (3)$$

Using Eqn 3, particle diffusion can be examined when linearity is noted between $-\ln(1 - F)$ and $t^{0.65}$.

The diffusivity is then given by:

$$D = \frac{d^2}{36}(slope/1.59)^{1/0.65} \quad (4)$$

As stated by Bhaskar et al. (1986), the method is simple, and Eqns 3 and 4 are applicable for all drug-resin complexes.

Kinetics according to the mass law

Kinetics can also be described as a chemical phenomenon (Boyd et al., 1947). For the case of

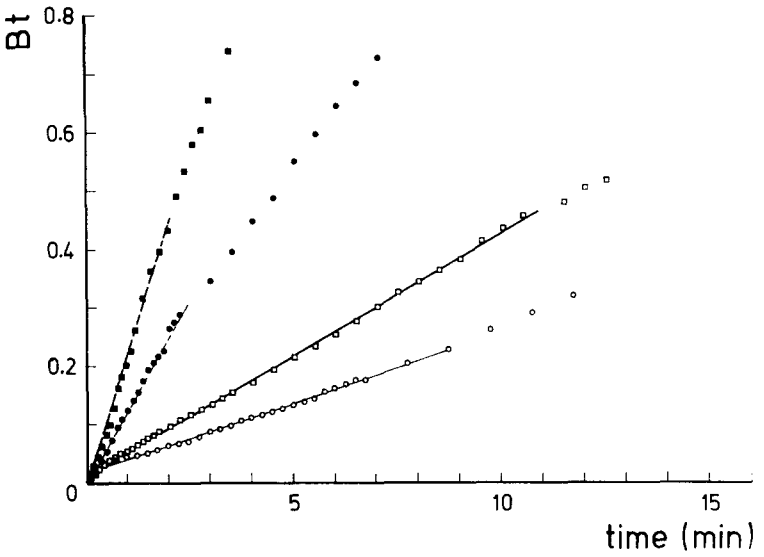

Fig. 1. *Bt* plot of the release of codeine as a function of time: (○) 0.16 g codeine resinate in 0.1 M NaCl; (□) 0.25 g codeine resinate in 0.1 M NaCl; (●) 0.16 g codeine resinate in 1 M NaCl; (■) 0.25 g codeine resinate in 1 M NaCl.

two monovalent ions, the mass law applies to the exchange when written as

$$A^+ + BR \text{---} B^+ + AR \qquad (5)$$

where A^+ and B^+ are the exchanging monovalent cations and where R refers to the insoluble resinate.

When the concentrations of A^+ and B^+ in solution are maintained constant, it can be shown that Eqn 6 may be derived

$$\ln(1 - F) = -k \cdot t \qquad (6)$$

Eqn 6 predicts an exponential decay of the quantity $(1 - F)$. If several mass action rate processes

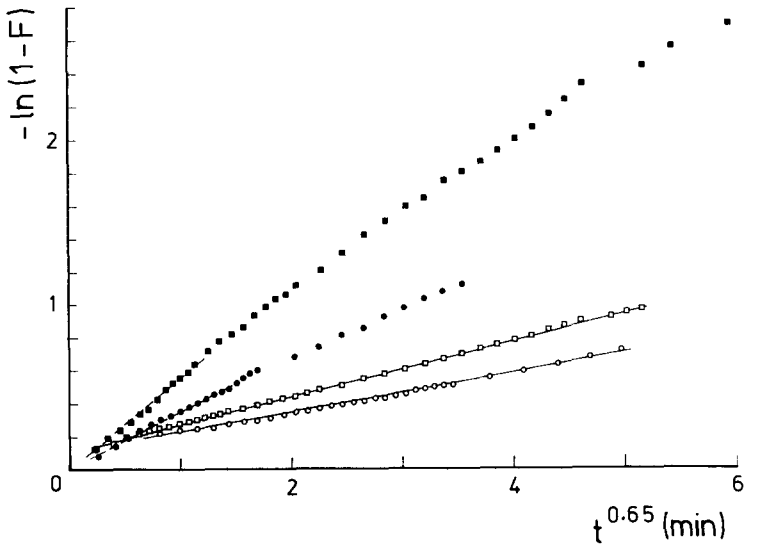

Fig. 2. Plot of the release of codeine according to the method of Viswanathan. Symbols as in Fig. 1.

TABLE 1

Diffusivities calculated from the linear portions of the graphs

Codeine-resinate (g)	NaCl concentration (M)	Equation of Boyd D (mm^2/min)	Correlation coefficient (r)	Equation of Viswanathan D (mm^2/min)	Correlation coefficient (r)
0.16	0.1	0.000038	0.996	0.000033	0.995
0.25	0.1	0.000053	0.999	0.000055	0.999
0.16	1.0	0.00022	0.997	0.00023	0.996
0.25	1.0	0.00025	0.997	0.00027	0.998

occur independently, the individual rate constants may be obtained by analyzing a $\ln(1-F)$-time plot in the same manner as for the decay of a mixture of radioactive species (Boyd et al., 1947) or as a biphasic sigma-minus plot (Koch, 1984).

Results and Discussion

The amount of codeine determined in the resinate was 13.8%.

Release of codeine from the resinate

On calculating the Bt values and plotting them as a function of time (Fig. 1), straight lines were obtained with the 0.1 M NaCl solutions over almost the entire region of measurements. With the 1 M NaCl solutions, only a small initial linear region was observed. The release rate is a function of the amount of resinate and the ionic strength.

The results obtained using the equation of Viswanathan plotted according to Eqn 3 are represented in Fig. 2. The same observations as before could be made: almost overall linearity was attained with the 0.1 N NaCl concentration and partial linearity in the case of 1 M NaCl, suggesting that the diffusion of ions is controlled by a particle diffusion process (Borodkin et al., 1971). Using the slopes of the linear portions of the graphs plotted according to Eqns 1 and 3, the diffusivities were calculated according to Eqns 2 and 4, respectively, and have been listed in Table 1. The diffusivity values determined via the two

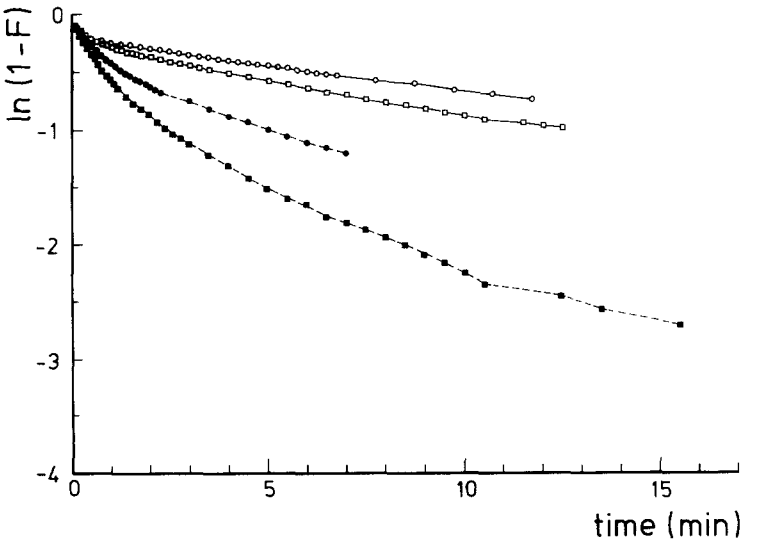

Fig. 3. Release rate of codeine according to the mass law. Symbols as in Fig. 1.

TABLE 2

Kinetic constants of the release rate of codeine calculated according to the mass law

Codeine resinate (g)	NaCl concentration (M)	Constant A	a = slope	Constant B	b = slope
0.16	0.1	–	–	–	−0.042
0.25	0.1	0.200	−2.80	0.760	−0.059
0.16	1.0	0.659	−4.09	0.666	−0.113
0.25	1.0	0.514	−1.42	0.454	−0.145

equations are quite close to each other. For the initial linear region, the kinetics can be described well by both equations.

When plotting the results according to the mass law (Eqn 6), the deviation from linearity is most pronounced in the case of the 1 M NaCl solution (Fig. 3). The graphs can be described by two rate processes. The individual rate constants were obtained using the method reviewed by Koch (1984). The values are presented in Table 2. Bimodal relationships of this type were noted previously during studies on the release of several drugs from Amberlite XAD (Khouw et al., 1978) and with dihydrocodeine bound on a sulphonic acid divinylbenzene-copolymerisate (Mühlenbruch et al., 1982). However, in those investigations, no explanations were given for this biphasic behaviour.

Release rate of Na^+ disappearance from the solution and bound on the resinate

The exchange kinetics of Na^+ were investigated. The amount of Na^+ removed from the solution decreased as a function of time. The attainment of equilibrium took 30 min. The equilibrium values obtained after 30 min were taken into account.

A first-order kinetic reaction was examined, as given in Eqn 7.

$$\ln \frac{(A - A_\infty)}{(A_0 - A_\infty)} = -k \cdot t \qquad (7)$$

where A is the number of radioactivity counts at time t, A_0 denotes the number of counts at time $t = 0$ and A_∞ is the number of counts at equilibrium. The same deviations were noted as with codeine.

In addition, the data could also best be interpreted according to a first-order process with two kinetic reactions. A straight line was fitted through the linear part (tail) of the curve; from this curve, the slope (b) and intercept (ln B) were determined, and B calculated. With these values Eqn 8 could then be constructed:

$$\text{Number of counts} = 1965e^{-0.000584t} + 11136e^{-0.0262t} \qquad (8)$$

From Eqn 8, it can be concluded that about 15% of Na^+ bound very rapidly onto the resin and about 85% slowly, suggesting the presence of two binding sites. The first reaction had thereby reached completion within 5 min.

This result is in agreement with the existence of two binding sites on the resinate, as noted in the previous study (Plaizier-Vercammen, 1992).

Conclusion

The rate of release of codeine can be described satisfactorily by the three equations proposed. Good agreement was found between the diffusivities calculated on the basis of the equations of Boyd and Viswanathan. However, the mass law appears to be the most suitable for the case where two kinetic processes occur. This study suggests that for Na^+, as well as for codeine, two binding sites exist on the resinate. The release rate of codeine from the resinate is a function of the amount of resinate and the ionic strength.

References

Bhaskar, R., Murthy, R.S.R., Miglani, B.D. and Viswanathan, K., Novel method to evaluate diffusion controlled release of drug from resinate. *Int. J. Pharm.*, 28 (1986) 59–66.

Borodkin, S. and Sundberg, S.P., Polycarboxylic acid ion-exchange resin adsorbates for taste coverage in chewable tablets. *J. Pharm. Sci.*, 60 (1971) 1523–1527.

Boyd, G.E., Adamson, A.W. and Myers L.S., The exchange adsorption of ions from aqueous solutions by organic zeolites II. Kinetics. *J. Am. Chem. Soc.*, 69 (1947) 2836–2848.

Chaudry, N.C. and Saunders, L., Sustained release of drugs from ion exchange resins. *J. Pharm. Pharmacol.*, 8 (1956) 975–986.

Gyselinck, P., Van Severen, R., Braeckman, P. and Schacht, E., Drug-polymer combinations. 1: The preparation of sustained release drugs by combination with ion exchange resins. *Pharmazie*, 36 (1981) 769–772.

Gyselinck P., Steyaert H., Van Severen R. and Braeckman P., Drug-polymer combinations. 2: Evaluation of some mathematic approaches to drug release from resinates. *Pharmazie*, 37 (1982) 190–192.

Khouw, V., Giles, H.G. and Sellers, E.M., Binding of drugs to ion-exchange resins in simulated gastric fluid. *J. Pharm. Sci.*, 67 (1978) 1329–1330.

Koch, H.P., Die Technik der Dissolutionsbestimmung (Teil 2). *Pharm. Acta Helv.*, 59 (1984) 130–139.

Mühlenbruch, B., Strauss, H. and Glaubitz, H., Untersuchungen zur Bioverfügbarkeit von Resinaten als perorale Depot-Arzneimittel 1. Mitteilung: Pharmazeutische Verfügbarkeit von Dihydrocodein-Resinaten. *Pharmazie*, 37 (1982) 200–203.

Plaizier-Vercammen, J.A., Investigation of the bioavailability of codeine from a cation ion-exchange sulfonic acid. 1: Effect of parameters. *Int. J. Pharm.*, 85 (1992) 45–50.

Reichenberg, D., Properties of ion-exchange resins in relation to their structure. III: Kinetics of exchange. *J. Am. Chem. Soc.*, 75 (1953) 589–597.

Schacht, E., Goethals, E., Gyselinck, P. and Thienpont, D., Polymer drug combinations. VI: Sustained release of bevamisole from ion exchange resins. *J. Pharm. Belg.*, 37 (1982) 183–188.