IJP 02766

Investigation of the bioavailability of codeine from a cation ion-exchange sulfonic acid 1. Effect of parameters

J.A. Plaizier-Vercammen

Vrije Universiteit Brussel, Faculty of Medicine and Pharmacy, Pharmaceutical Technology, Laarbeeklaan 103, Brussels (Belgium)

(Received 9 November 1991)
(Accepted 20 January 1992)

Key words: Ion exchange; Sustained release; Codeine resinate

Summary

The effect of a number of parameters on the ion exchange of Na^+ and codeine was investigated by following a radioactive tracer technique. The parameters were the Na^+ concentration, ionic strength, pH, temperature and solvent mixtures. The influence of these parameters was found to be very different for Na^+, as compared with codeine. The solubility of codeine played an important role in binding. Determination of the distribution constants, number of milliequivalents and Scatchard plots suggests that two different binding sites exist for Na^+. Moreover, no detectable stoichiometric exchange between Na^+ and codeine was observed.

Introduction

The use of ion-exchange resins occupies an important place in the development of sustained release preparations due to their readily controllable properties, e.g., particle shape, and lack of toxicity. Moreover, the rate of release is regular, which has been attributed to the nearly constant ionic strength of the gastric and intestinal juices (Becker and Swift, 1959), the rate constant for absorption being less variable for resinated compounds (Hinsvak et al., 1973). Strongly acidic ion-exchange resins, like sulphonic acid, are very suitable for the design of preparations with prolonged action, since they provide a more moderate release than the carboxylic acid resins (Chaudry and Saunders, 1956).

Codeine resinate is prescribed not only in the form of capsules but also in suspensions through the addition of suspending agents, e.g., sodium benzoate. The adjuvants in such suspensions tend to lead to the release of codeine from the resin. It was the purpose of this work to investigate the influence of a number of parameters on the release of codeine from the cation resin in solution.

Materials and Methods

Codeine resinate (Certa, Belgium) is composed of codeine bound on the cation exchange sulphonic acid resin, Resicat AMB Na-042. The

Correspondence to: J.A. Plaizier-Vercammen, Vrije Universiteit Brussel, Faculty of Medicine and Pharmacy, Pharmaceutical Technology, Laarbeeklaan 103, Brussels, Belgium.

diameter of the beads is 250 μm. The amount of codeine bound on the resinate is 13.8%. Sodium chloride (Merck, Darmstadt, Germany) was used as received. Radiolabelled NaCl (^{22}NaCl; NEN, U.K.) was used as tracer for the test solutions. A stock solution of 1.68×10^6 Bq/10.5 ml was used throughout.

Effect of sodium concentration and ionic strength on the exchange of Na^+ and codeine

A series of Na^+ concentrations (from 10^{-4} to 1 M) were prepared, containing 0.1 ml radioactive Na^+ from the stock solution of tracer. To 25 ml solution, 0.1 g codeine resinate was added and the mixture stirred. At equilibrium, 4 ml of the filtered and free resinate solution was counted for 1 min to determine free Na^+. Free codeine was determined by UV spectrophotometry at a wavelength of 286.5 nm.

Effect of pH on ion exchange

Solutions containing different amounts of NaCl and HCl, with ionic strength adjusted to $\mu = 0.1$, were prepared. To 25 ml solution, 0.1 ml of $^{22}Na^+$ was added and then 0.1 g codeine resinate. At equilibrium, the concentration of free codeine and Na^+ was determined.

Effect of temperature on ion exchange

The same procedure as that above was followed, using a 0.05 M NaCl solution and maintaining the solutions at different temperatures.

Influence of solvent on ion exchange

Solutions containing 0.05 M Na^+ were prepared in solvent mixtures of ethanol/water. To 25-ml portions of the solutions, the radioactive tracer and codeine resinate were added. At equilibrium, the concentration of Na^+ and codeine was determined.

Solubility of codeine at different temperatures and solvent mixtures

Saturated solutions of codeine in 0.05 M NaCl and solvent mixtures were prepared and stirred at the temperatures of determination. On attaining equilibrium, the supernatant was analyzed by UV spectrophotometry for codeine.

Results and Discussion

Time to reach equilibrium

In an initial experiment, the time to reach equilibrium was determined: radioactive counts were followed as a function of time. The number of counts gradually diminished; equilibrium was attained after 22 min. For all the other experiments, a 1 h interval was allowed to pass before measuring. The same period of time to attain equilibrium was reported by others (Borodkin and Junker, 1970).

Effect of Na^+ concentration and ionic strength on the exchange of Na^+ and codeine

Equilibrium values are often expressed as distribution coefficients (K_d values) (Helfferich, 1962) or Langmuir isotherms (Helfferich, 1962; Khouw et al., 1978). The numbers of milliequivalents (meq.) (Helfferich, 1962) of codeine and Na^+ simultaneously exchanged were also determined.

The K_d coefficients are represented in Fig. 1. For both codeine and Na^+, S-shaped isotherms were noted. The K_d values diminished as a function of Na^+ concentration. At the same time, the percentage of codeine bound increased as a function of decreasing Na^+ concentration. An increase in K_d value with dilution of the solution is generally observed with ion-exchange resins, and has been attributed to saturation of the resin at

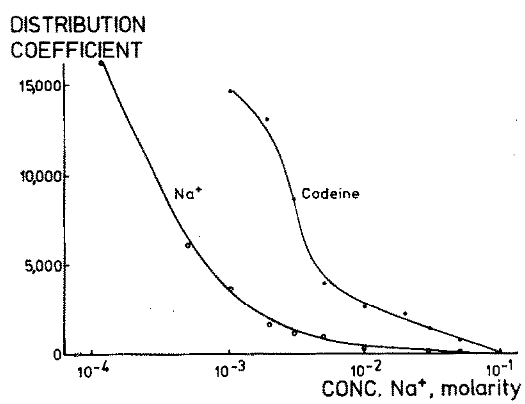

Fig. 1. Distribution coefficients for Na^+ and codeine as a function of the concentration of Na^+.

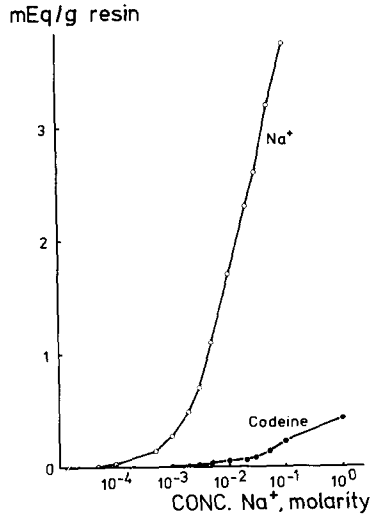

Fig. 2. Milliequivalents of Na^+ and codeine exchanged as a function of Na^+ concentration.

relatively low concentration, resulting in a curve which deviates from linearity (Helfferich, 1962).

The number of meq./g resinate was calculated for codeine and Na^+ and is plotted in Fig. 2. The values obtained differed markedly, being much higher for Na^+ than for codeine. The number of meq. Na^+/g resin in a 0.1 M NaCl solution approximates the binding capacity of the resin: for the dry resin employed, a binding capacity of 4.7 meq. was determined. The amount of codeine bound on the resin was found to be only 460 μeq. The exchange between codeine and Na^+ is not a stoichiometric reaction, suggesting that more sites or another type of site are/is available for Na^+ than for codeine.

Binding on ion-exchange resin was also examined by constructing Langmuir isotherms. A curved isotherm was obtained. Determination of the binding constants was difficult. The theory of complex formation was then employed in attempting to resolve the problem, since this theory appeared more suitable for interpreting our results.

This theory (Edsall and Wyman, 1958; Steinhardt and Reynolds, 1969), normally used in the analysis of the binding of ligand or small molecules onto macromolecules, can be applied: the conditions for complex formation, i.e., reversibility and the presence of binding sites on the macromolecule, are also fulfilled with ion-exchange resins (Paterson, 1970). The similarity of the equations describing binding on solids and complex formation on macromolecules has been discussed (Klotz, 1953) and the expressions are more suitable for the determination of more than one class of sites (Plaizier-Vercammen and De Nève, 1980). By treating the data according to the theory of complex formation and constructing Scatchard plots (Scatchard, 1949), the existence of more than one binding site can be clearly illustrated (Klotz and Hunston, 1971). The results are depicted in Fig. 3, in which r/F is plotted as a function of r, where r denotes the amount of bound codeine/g resin and F is the free codeine concentration. The curved part of the plot is indicative of two different sites with two association constants (Karush, 1950). Graphical representation of two classes of binding sites was discussed previously by Klotz and Hunston (1971). The intercept on the x-axis represents the sum of two binding sites (n_1 and n_2), and the intercept on the y-axis corresponds to the sum of the association constants multiplied by the number of sites. Individual values for n_1, n_2, k_1 and k_2 cannot directly deviate from the graph.

From Fig. 3, the intercept on the y- and x-axes was determined. Values of $n_1 + n_2 = 0.173$ and $n_1k_1 + n_2k_2 = 880$ were obtained. A computer fitting program was used and the results analyzed. With the best fit (represented in Fig. 3), values of $k_1 = 55\,700$ mol^{-1}, $n_1 = 0.0154$ mol/g resin or 0.387 meq./g resin, $k_2 = 118$ mol^{-1} and $n_2 = 0.158$ mol/g resin or 3.96 meq./g resin were obtained. The sum of meq. represents practically the total binding capacity of the resin. The num-

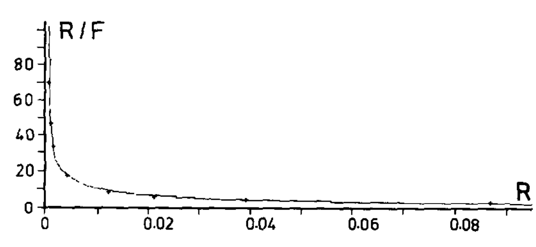

Fig. 3. Scatchard isotherm for Na^+.

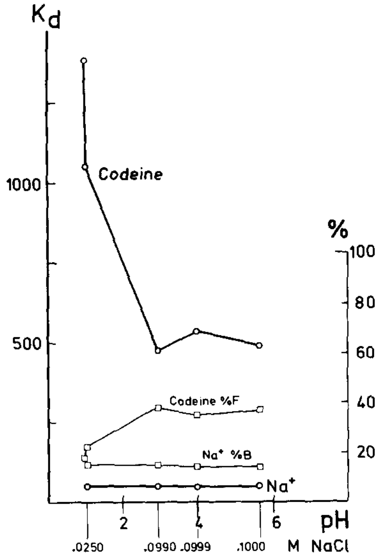

Fig. 4. Effect of pH on ion exchange of codeine and Na^+.

ber of meq. codeine on 1 g resin is 0.461 meq., corresponding to n_1.

These results suggest that binding occurred on two levels, the greater association constant being coupled with the exchange of codeine, and the lower association constant with other multiple sites.

Effect of pH on ion exchange

The results for Na^+ and codeine released as a function of pH are represented in Fig. 4. The K_d values for Na^+ or percentage bound Na^+ remained unchanged with increasing Na^+ concentration, which was attributed to the constant ionic strength of the solutions. A K_d value of 51 was noted in the 0.025 M Na^+ solution.

Hydrogen ions, present in the solutions on varying the pH, could also take part in binding, thus occupying sites for Na^+. For polystyrene sulfonic acid resins, the adsorption strength follows the lyotropic series of Hofmeister (Inczédy, 1966), Na^+ being bound more strongly on the resin than H^+. The pH as such has no effect on the exchange of Na^+.

The K_d values for codeine or the percentage of free codeine were not constant. High K_d values were noted at low hydrogen ion concentration (up to 0.025 M), remaining nearly constant in NaCl concentrations from about 0.1 M.

Codeine is bound as a cation on sulfonic acid. A priori, the pH can influence the charge on the codeine. However, at the highest pH value tested, i.e., pH 5.65, codeine with a $pK_a = 8.2$ is practically totally in the acid form.

It should be borne in mind that two models can be considered: a physical model (distribution) and a chemical model (ion-exchange) (Paterson, 1970).

These reactions can be written as follows:
(a) Physical:

$$K_d = \frac{Na^+_{resin}}{Na^+_{solution}} \qquad K_d = \frac{H^+_{resin}}{H^+_{solution}}$$

(b) Chemical:

$$\text{R-cod}^+ + Na^+ \leftrightarrow \text{R-Na}^+ + \text{cod}^+$$

$$\text{R-cod}^+ + H^+ \leftrightarrow \text{R-H}^+ + \text{cod}^+$$

$$\text{Cod}^+ \leftrightarrow \text{cod} + H^+$$

with

$$K_a = \frac{[\text{cod}][H^+]}{[\text{cod}^+]} \quad (K_a\text{: dissociation constant})$$

or

$$[\text{cod}^+] = \frac{[\text{cod}][H^+]}{K_a}$$

and

$$k_1 = \frac{[\text{R-Na}^+][\text{cod}^+]}{[Na^+][\text{R-cod}^+]} \quad (k_1\text{: association constant})$$

or

$$k_1 = \frac{[\text{R-Na}^+][\text{cod}][H^+]}{[Na^+][\text{R-cod}^+]K_a}$$

According to the physical model, K_d is a constant at fixed ionic strength. This is what we found for Na^+. However, the association constant is a func-

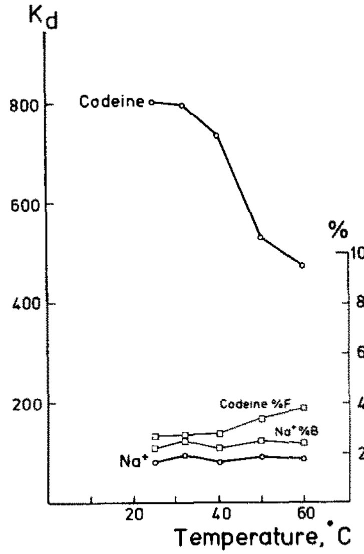

Fig. 5. Effect of temperature on ion exchange of codeine and Na^+.

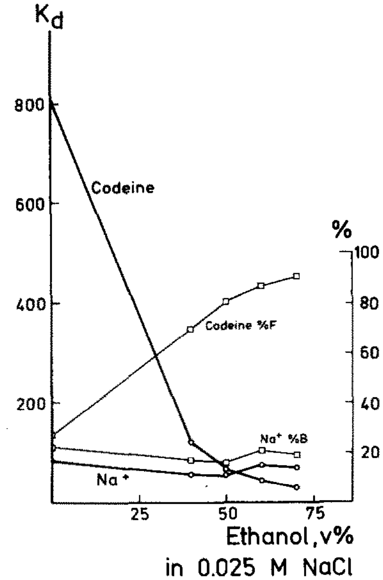

Fig. 6. Effect of solvent mixtures on ion exchange of codeine and Na^+.

tion of the dissociation constant (K_a) and the pH. These effects will be negligible at the pH values tested. Therefore, the results suggest that independent binding sites exist for Na^+ and codeine.

Effect of temperature on ion-exchange

The effect of temperature on the release of Na^+ and codeine, shown in Fig. 5, is expressed as the K_d values and percent released (codeine) or bound (Na^+). For Na^+, binding was practically unchanged from 25 up to 60°C. For codeine, however, the K_d values diminished and the percent free codeine increased somewhat with rising temperature.

Temperature can also exert an influence on the resin as well as on the bound ion: for the resin, swelling (Helfferich, 1962) can occur, while for the binding ion, the solubility can be modified.

Effect of solvent mixtures on ion exchange

As noted from Fig. 6 the K_d values determined for Na^+ and the percent Na^+ bound are nearly constant in the different solvent mixtures with constant ionic strength. However, the K_d values for codeine diminished considerably. The percent free codeine increased as a function of

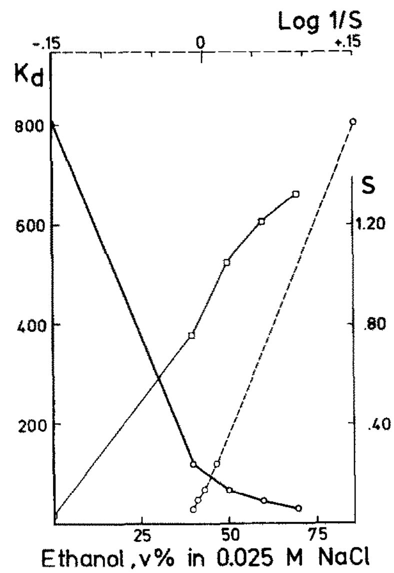

Fig. 7. Relationship between the solubility of codeine and distribution constants with varying solvent mixtures. (○——○) K_d codeine vs amount ethanol; (○- - - - -○) K_d codeine vs log $1/S$; (□——□) solubility codeine vs amount alcohol.

increasing amount of alcohol in solution. The behaviour of both ions is the same as that noted for varying temperature. Here also, the solubility of codeine can be changed.

Relationship of solubility of codeine and distribution constants with varying solvent mixtures and temperature

The solubility of codeine was determined and compared with the K_d values in the solvent mixtures: K_d decreased and the solubility of codeine increased as a function of the amount of alcohol. As shown in Fig. 7, a linear relationship is demonstrated by plotting K_d as a function of log $1/S$, i.e. binding of codeine onto the resin is related inversely to its solubility in the solvent mixtures. Thus, the solvent played an important role. When the K_d values and log $1/S$ were compared as a function of increasing temperature, binding of codeine onto the resin decreased and, concomitantly, the solubility increased. However, a direct linear relationship between K_d or log K_d and $1/S$ of log $1/S$ was not detected. Nevertheless, we can conclude that the temperature exerts a strong negative influence on the binding of codeine onto the resin.

Conclusion

When codeine resinate is used in suspensions, care should be taken to avoid addition of salts, dissociated products, or alcoholic solvents and to prevent change in the pH. These adjuvants influence the amount of bound codeine and at the same time alter the sustained release action of the resinate.

References

Becker, B.A. and Swift, J.G., Effective reduction of the acute toxicity of certain pharmacologic agents by use of synthetic ion-exchange resins. *Toxicology*, 1 (1959) 42–54.

Borodkin, S. and Yunker, M.H., Interaction of amine drugs with a polycarboxylic acid ion-exchange resin. *J. Pharm. Sci.*, 59 (1970) 481–486.

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

Edsall, J.T. and Wyman, J., Some aspects of molecular interactions. *Biophysical Chemistry*, Academic Press, New York, 1958, Vol. 1, pp. 591–662.

Helfferich, F., *Ion Exchange*, McGraw-Hill, New York, 1962, pp. 125–132.

Hinsvark, O.N., Truant, A.P., Jenden, D.J. and Steinborn, J.A., The oral bioavailability and pharmacokinetics of soluble and resin-bound forms of amphetamine and phentermine in man. *J. Pharm. Biopharm.*, 1 (1973) 319–328.

Inczédy, J., *Analytical Applications of Ion Exchangers*, Pergamon, Oxford, 1966, p. 27.

Karush, F., Heterogeneity of the binding sites of bovine serum albumin. *J. Am. Chem. Soc.*, 72 (1950) 2705–2713.

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

Klotz, I.M., Protein interactions. In Neurath H. and Bailey K. (Eds), *The Proteins*, Vol. 1, part B, Academic Press, New York, 1953, pp. 727–806.

Klotz I.M. and Hunston D.L., Properties of graphical representations of multiple classes of binding sites. *Biochemistry*, 10 (1971) 3065–3069.

Paterson, R., *An Introduction to Ion Exchange*, Heyden, London, 1970, pp. 1–46.

Plaizier-Vercammen, J.A. and De Nève, R.E., Interaction of povidone with aromatic compounds. I: Evaluation of complex formation by factorial analysis. *J. Pharm. Sci.*, 69 (1980) 1403–1408.

Scatchard, G., The attractions of proteins for small molecules and ions. *Ann. N.Y. Acad. Sci.*, 51 (1949) 660–672.

Steinhardt, J. and Reynolds, J.A., *Multiple Equilibria in Proteins*, Academic Press, New York, 1969, pp. 10–25.