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Some effects of urea on drug dissolution

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Solubilities and dissolution rates of salicylic acid have been determined in urea solutions at different pH values. Solubilities increased with pH and urea concentration; a solubilization mechanism was considered to be operating. The solubilization effect of urea was greatest on the non-ionized moieties of the solute. Dissolution rates of salicylic acid increased with pH and urea concentration. The increase in dissolution rate paralleled increases in solubility. The role of solubilizing effect in the enhancement of dissolution rate by urea is discussed.

The dispersion of a poorly water soluble drug in a water soluble inert carrier is reported to result in an enhancement of drug dissolution rate (Chiou & Riegelman, 1971). This enhancement has been attributed to the state of fine subdivision of crystalline particles throughout the carrier. Other workers maintained that the phenomenon was caused by solid solution formation.

The general experimental approach to assessing the role of carriers has been to measure dissolution rates from fused mixtures of drug and carrier. Despite several reports of the solubilizing effects of carriers such as urea, there has been little interest in the measurement of dissolution into solutions of carriers. From the results of such a study Nogami, Nagai & Ito (1966) suggested that urea influenced dissolution by an unspecified reaction in the drug diffusion layer.

The purpose of this investigation is to evaluate the importance of solubilization in the enhancement by urea of the dissolution of salicylic acid. Solubilities and dissolution of salicylic acid in solutions of urea at different pH will be determined and relations between these parameters investigated.

MATERIALS AND METHODS

Materials

Non-disintegrating discs of salicylic acid A.R. (BDH) were prepared by compression at a pressure of 300 kg m^{-2} in an Apex type A14 hydraulic press.

Solutions of urea, S.L.R. (Fisons) were prepared in single distilled water at controlled pH in the following concentrations: 0·5, 1·0, 2·0, 3·0 M.

Methods

The procedure for solubility determinations has been described (Collett, Rees & Dickinson, 1972). Solubilities of salicylic acid in urea were determined at pH 1·0 to 3·5.

The rotating disc apparatus for dissolution rate measurements, and the method of automatic pH control has been described (Rees & Collett, 1974). This method of pH control takes account of the suggestions of Lindstrom & Giaquinto (1970) for the control of salt effects in aqueous solutions of urea.

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Samples of salicylic acid solution from solubility and from dissolution experiments were passed through Millipore filters (0·45 μm pore size) before spectrophotometric determinations at 302·5 nm. Urea did not interfere with the assay.

RESULTS AND DISCUSSION

Equilibrium solubility data indicate that urea interacts with salicylic acid. This interaction is manifested as a linear increase in drug solubility as the concentration of urea in solution is increased. Table 1 shows solubilities of salicylic acid in graded concentrations of urea at controlled pH.

An indication of the type of reaction occurring between a solute and solvent can be obtained from values of the free energy of transfer of a solute from one solvent to another. When a drug dissolves in aqueous urea solution it effectively distributes itself between the water and urea solution phase. The free energy of transfer (ΔG_t) can be calculated from:

$$\Delta G_t = RT \ln \frac{N}{N_o}$$

when N is the mole fraction of drug in urea solution and N_o the mole fraction in water. Small negative values from -11 to -485 cal mol^{-1} were obtained, observations in agreement with Wetlaufer, Malik & others (1964). When two solutes interact in solution by a complexation mechanism values of 2–5 kcal mol^{-1} (8–20 kJ mol^{-1}) would be expected. It may be concluded that urea salicylic acid complexes are not formed. Urea salicylic acid interaction parameters cannot be estimated with certainty since the methods of analysing solubility data in this system are more sensitive than the experimental procedures (Feldman & Gibaldi, 1967).

Slopes of ratios of drug solubility in water D_{H_2O} and different concentrations of urea D_T at each pH value were calculated and found to be a linear function of salicylic acid unionized. The relative increase in solubility due to the presence of urea decreases as the pH of the solutions increase.

The solubilities of salicylic acid increase with an increase in urea concentration. This effect is an example of "salting in" and an equation describing this phenomenon has been reported (Setschenow, 1889), and modified by Lindstrom & Giaquinto, 1970,

$$\log \frac{S_o}{S} = kC$$

where S_o and S are molar solubilities of salicylic acid in water and in solutions containing C mol litre^{-1} of urea respectively. The constant, k, is an empirical factor characteristic of the species in solution and is negative for salting in. It can be seen from Table 1 that salting in coefficients decrease with increase in pH.

Table 1. *Equilibrium solubilities of salicylic acid (mg ml^{-1}) at 37° in urea solutions.*

pH	Concentrations of urea (mol litre^{-1})					k(×10)
	0	0·5	1·0	2·0	3·0	
1·0	2·57	3·06	3·56	4·33	5·15	−1·20
2·0	3·11	3·39	3·90	4·98	6·03	−1·00
2·5	3·83	4·40	4·98	6·13	7·27	−0·87
3·0	6·19	7·36	8·18	9·20	10·79	−0·64
3·5	15·62	16·84	18·23	19·79	22·01	−0·45

Solubility phenomena can often be described in terms of the effects of solute on water structure, although Lindstrom (1970) has described the necessity for care in using this approach. It has been suggested that water is an equilibrium mixture of distinguishable species designated as "bulky" and "dense" (Frank & Franks, 1968). The same workers believe that urea added to water dissolves only in the "dense" unstructured water thus altering the equilibrium between "dense" and "bulky" water and thereby acting as an indirect structure-breaker. In order to re-establish equilibrium the "bulky" water would break down giving an environment more suitable to solution of solute molecules. In the present system an equilibrium may be expected between water associated with hydronium ions and free water. Increasing concentrations of urea would remove water bound to hydronium ions thus increasing the amount of water available to salicylic acid. This type of model can be used to account for the changes in solubility ratio D_T/D_{H_2O} and the decrease in k with pH. Solubilities in water or weak organic acids such as salicylic acid and benzoic acid are mainly controlled by the presence of polar groups on the aromatic rings but is influenced by the hydrophobic surface of the molecule. In the case of salicylic acid at different pH values the hydrophobic surface decreases with increasing pH, resulting in an increased solubility in water. The presence of urea in aqueous solution makes more water available for dissolution of hydrophobic moieties thus urea should have a greater effect on the solubility of the more hydrophobic moiety present at low pH accounting for the decrease in solubility ratio with increasing pH.

Measurement of the dissolution rates of drugs into urea solutions is an approach which has not been widely reported in this type of work. Nogami & others (1966) reported that the dissolution of salicylic acid in urea solutions gave a non-linear concentration time curve. They stated that this phenomenon was caused by a slow reaction taking place in the diffusion layer causing a delay in the transfer of solutes to the bulk solution. The pH at which the dissolution experiments were carried out was not mentioned but the authors considered the fraction of drug ionized to be low and unimportant. If inadequate pH control is exercised then the pH of the dissolution medium will be subjected to two competing influences as the drug itself dissolves. Firstly an acidic drug will tend to lower the pH of the medium as the concentration of dissolved drug increases. Secondly, urea is known to increase the pH of solutions (Bull, Bresse & others, 1964), due to the presence of traces of ammonium cyanate.

In the present work the pH of the dissolution medium was monitored and maintained constant by the pH-stat assembly. Dissolution rate constants were calculated from the slopes of concentration of drug in dissolution media as a function of time. Table 2 gives dissolution rate constants of salicylic acid in urea solutions at different pH. A linear relation exists at each pH between the dissolution rate constant of drug and urea concentration. Dissolution rates paralleled solubilities in that the dissolution

Table 2. *Dissolution rate constants* ($mg\ ml^{-1}\ min^{-1}$) $\times$ 10^3 *of salicylic acid at 37° in urea solutions.*

pH	Concentration of urea (mol litre^{-1})				
	0	0·5	1·0	2·0	3·0
1·0	5·40	5·73	6·44	8·58	1·020
2·0	6·68	6·98	8·14	9·97	12·36
2·5	7·24	8·18	9·79	11·44	13·54
3·0	7·95	9·26	10·18	12·98	14·34

rate of salicylic acid increased as the pH increased from 1 to 3·0. Furthermore slopes of ratios of dissolution rate in urea and water at each pH were a linear function of fraction of salicylic acid unionized. It can be seen that increases in solubility due to the presence of urea roughly parallel increases in drug dissolution rate when urea is present in the dissolution medium. Under sink conditions dissolution rate is proportional to drug solubility. In the present experimental situation it is unlikely that urea will promote effects such as solid solution formation and particle size reduction, thus, it would appear that one controlling influence of drug dissolution rate into urea solution is the solubilization effect of urea on the drug.

Since urea and salicylic acid are each present in fused mixtures used for dissolution studies it may be assumed that both components would be present in a diffusion layer and that solubilization by urea increases the solubility of drug in the diffusion layer. One criticism of this interpretation could be that solubility is an equilibrium function whereas dissolution is a kinetic phenomenon. However there is no suggestion that these findings could be extrapolated to the influence of urea on the rate of achieving equilibrium solubility, *i.e.* under "non-sink conditions". Within these limitations it may be concluded that solubilization is an important factor controlling dissolution of drug from drug urea mixtures.

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