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Partition coefficients of salicylic acid between water and the micelles of some non-ionic surfactants

J. H. COLLETT AND R. WITHINGTON

Department of Pharmacy, University of Manchester, Manchester M13 9PL, U.K.

Partition coefficients of ionized and unionized salicylic acid molecules between water and the micelles of several non-ionic surfactants have been determined. Those of unionized molecules decreased with decreasing length of the surfactant alkyl chain and with increasing length of the surfactant polyoxyethylene chain. Ionized salicylic acid partitioned to a significant extent only into those surfactants having more than approximately 44 oxyethylene units in their hydrophile. The findings are discussed in terms of their biopharmaceutical significance.

Surfactants have been shown to be capable of modifying the rate of absorption of drugs across biological membranes. Whether an increase or a decrease is obtained is determined by the relative magnitudes of a number of opposing effects. These effects include increased dissolution rate of drugs from solid dosage forms, reduced availability of the drug by complexation with, or solubilization by, surfactants, changes in the mobility and viscosity of the gastrointestinal contents, and modification of the permeability of biological membranes to the drug (Gibaldi & Feldman, 1970). Where drug-surfactant interactions make a significant contribution to the overall effect of the surfactant on drug absorption, knowledge of the extent of the interaction in terms of unionized drug molecules would be of value.

With the aim of describing more fully the process of drug absorption from surfactant solutions a study of the interactions of the ionized and unionized molecules of salicylic acid with non-ionic surfactants has been undertaken and is reported here.

Non-ionic surfactants are the most widely used group of surfactants in formulation technology. The most commonly encountered are the polyoxyethylene sorbitan monoesters (polysorbates). A series of these having the same number of oxyethylene units in their hydrophile was selected so that the effect of the nature of the hydrophobe on their interaction with salicylic acid could be determined. A complementary series of polyoxyethylene stearates in which the length of the polyoxyethylene chain is different for each member has enabled the effect of this part of the molecule to be determined.

MATERIALS AND METHODS

Materials

The surfactants used were: polyoxyethylene (20)* sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan mono-oleate (polysorbates 20, 40, 60 and 80 respectively); polyoxyethylene (30) monostearate, polyoxyethylene (40) monostearate, polyoxyethylene (50) monostearate and polyoxyethylene (100) monostearate (myrjs 51, 52, 53 and 59 respectively). Surfactants were supplied by Honeywill-

* The number in brackets denotes the nominal number of oxyethylene units per molecule.

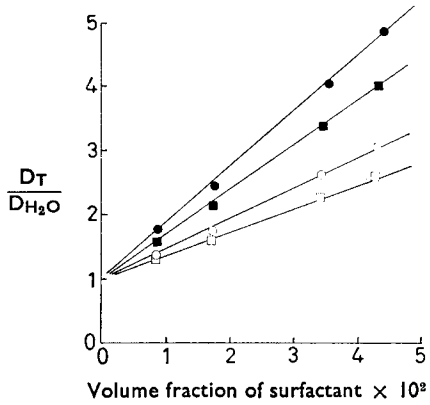

FIG. 1. Plot of D_T/D_{H_2O} against surfactant concentration at pH 2·0. D_T is the solubility of salicylic acid in surfactant solutions and D_{H_2O} is the solubility of salicylic acid in water. ●, polysorbate 80; ■, polysorbate 20; ○, myrj 53; □, myrj 59.

Atlas Ltd., Carshalton, Surrey, U.K. The surfactants were characterized by their mass spectra and proton magnetic resonance (pmr) spectra (Crooks, Collett & Withington; unpublished observations, 1972). The numbers of oxyethylene units per molecule of myrj 51, 52, 53 and 59 were found to be 30·3, 44·7, 59·8 and 89·1 respectively. Analytical reagent grade salicylic acid was used throughout.

Methods

Solubility determinations. Excess (2·0 g) of salicylic acid was added to 30 ml volumes of surfactant solutions contained in 50 ml Quickfit Ehrlenmeyer flasks. The flasks were shaken for 48 h in a water bath (25° ± 0·1°; 120 strokes/min; stroke length of 3·0 cm). The time required for equilibration (48 h) was established by a repetitive sampling technique. After equilibration, samples were filtered through 0·45 μm Millipore filters held in Swinney filter adapters, and diluted appropriately. The diluted samples were assayed for salicylic acid by ultraviolet absorption spectroscopy at 298 nm. The presence of surfactants did not interfere with the assay.

pH maintenance. During the preparation of surfactant-salicylic acid solutions sufficient 1·0N HCl or 1·0N NaOH was added to provide the pH required. At 24 and 48 h after commencement of the equilibration period the pH of the solutions was adjusted, if necessary, by the addition of 1·0N acid or alkali. Additions were made under the control of a pH stat (Radiometer, Copenhagen). During pH adjustments solutions were stirred in a water jacketed vessel, thermostated at 25° ± 0·1°. The effect of added electrolyte on the solubility of salicylic acid was found to be negligible over the range of ionic strengths obtained in the course of pH adjustments.

Density determinations. The apparent densities of the surfactants in 1·0 and 5·0% w/v aqueous solutions at 25° were determined using a 25 ml Nicol pyknometer.

RESULTS AND DISCUSSION

The effect of surfactant concentration on the solubility of salicylic acid at pH 2·0 is illustrated in Fig. 1. The solubility of salicylic acid is expressed as the ratio of its solubility, D_T, in surfactant solutions to its solubility, D_{H_2O}, in water. In all cases increases in the concentration of surfactant increase the solubility ratio which reflects an increase in the solubility of salicylic acid. The linearity of the relation between

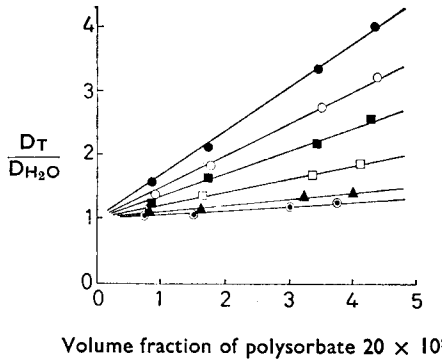

FIG. 2. Plot of D_T/D_{H_2O} against polysorbate 20 concentration at various pH values. ●, pH 2·0; ○, pH 2·6; ■, pH 3·0; □, pH 3·45; ▲, pH 3·6; ⊙, pH 3·82.

surfactant concentration and salicylic acid solubility is typical of solubilization of the solute within surfactant micelles. Increases in the length of the hydrophobe of the polysorbates are seen to increase the ability of the surfactants to solubilize salicylic acid. On the other hand, increases in the length of the polyoxyethylene chain reduce the solubilizing capacity of the myrj surfactants. Similar relations between solubilizing capacity and surfactant structure were found for the solubilization of barbiturate homologues by these same surfactants (Ismail, Wafik Gouda & Motawi, 1970; Wafik Gouda, Ismail & Motawi, 1970).

The effect of pH on the solubilization of salicylic acid by polysorbate 20 is shown in Fig. 2. Increases in pH reduce the slope of solubility ratio versus surfactant concentration plots. Similar results were obtained with all the other surfactants examined. The pKa of salicylic acid is approximately 3·0 and it therefore exists predominantly in the ionized form at pH 3·8. At pH 2·0 it is mainly unionized. The high solubilizing capacity of polysorbate 20 at pH values where salicylic acid is mainly unionized suggests that this form of the acid is solubilized to a greater extent than the ionized form.

The contributions of ionized and unionized molecules to the total amount of drug solubilized can be quantified (Rippie, Lamb & Romig, 1964). By considering solubilization to be a partition phenomenon, partition coefficients of ionized and unionized drug molecules between water and surfactant micelles can be obtained. The slopes of the lines of Fig. 2 are plotted in Fig. 3 versus the percentage of unionized salicylic acid

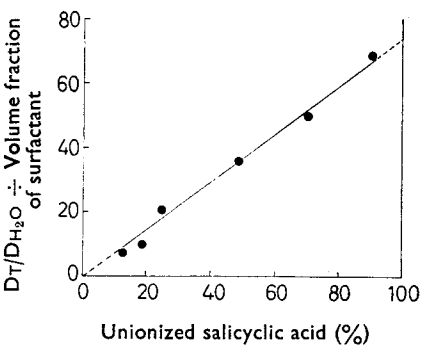

FIG. 3. Plots of $D_T/D_{H_2O} \div$ volume fraction of surfactant (from Fig. 2) against the percentage of unionized salicylic acid present at each pH.

Table 1. *The partition coefficients of salicylic acid between water and surfactant micelles at* 25°.

	Polysorbates				Myrjs			
	20	40	60	80	51	52	53	59
No. of oxyethylene units	19·5[a]	19·8[a]	19·6[a]	18·0[a]	30·3	44·7	59·8	89·1
No. of alkyl carbon atoms	11	15	17	17[b]	17	17	17	17
Partition coefficient of ionized molecules	0	0	0	0	0·7	2·8	2·7	4·1
Partition coefficient of unionized molecules	74·9	83·4	85·8	99·6	70·3	67·6	53·6	41·1

[a] Crooks & others, unpublished 1972.
[b] Includes –C=C– linkage.

present at each pH. The intercept on the ordinate at 0% unionized acid is the partition coefficient of the ionized acid molecules between water and surfactant micelles; at 100% unionized acid, the intercept is the partition coefficient for the unionized molecules.

Partition coefficients for ionized and unionized salicylic acid molecules between water and micelles of each of the surfactants studied are presented in Table 1. The partition coefficient of unionized molecules increases with increasing length of the hydrophobe (polysorbates) but decreases as the length of the polyoxyethylene chain increases (myrjs). Ionized salicylic acid molecules partitioned significantly only into micelles of those surfactants having more than about 44 oxyethylene units in their hydrophile. Polyoxyethylene chains are hydrated in aqueous solution, the degree of hydration depending on the length of the chain (Becher, 1961). It is thought here that polyoxyethylene chains of about 44 units in length are sufficiently hydrated to provide a polar environment in which ionized salicylic acid molecules may become solubilized.

The solubilization of unionized salicylic acid by the surfactants examined will reduce the concentration of drug that is available for absorption from solutions containing the surfactants. The concentration of unionized molecules is a factor in determining the rate of passive diffusion of salicylic acid across biological membranes. The presence of surfactants will therefore tend to reduce the rate of absorption and a contribution to the overall effect of surfactants on drug absorption will be made.

Studies (Whitworth & Yantis, 1967) using frogs have shown that polysorbate 60 at concentrations greater than 1·0% reduces the absorption of salicylic acid. In similar experiments (Levy, Miller & Reuning, 1966) found the absorption of secobarbitone in goldfish to be reduced by 0·02 to 2·0% of polysorbate 80. In both cases the conclusion was that solubilization of the drug reduced its effective concentration and produced a lowered rate of absorption. Our results support this conclusion.

Further work is aimed at studying the effect of surfactants on drug absorption in model systems and at determining the magnitude of the contribution of drug-surfactant interactions to the overall effect of surfactants on drug absorption.

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