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# COMMUNICATIONS

## Some effects of surfactant structure on the solubilization of salicylic acid

Several workers have used solubility data to determine the distribution of partially polar solubilizates between micellar and aqueous phases of surfactant solutions (Elworthy, Florence & McFarlane, 1968). Others have considered the location of solubilizate molecules within the surfactant micelles. Mukerjee (1971) related the distribution of substituted benzoic acids between the hydrophobic core and the hydrophilic matrix of polyoxyethylene micelles to solubilizate structure. This report describes the influence of surfactant structure on the solubilization and distribution of salicylic acid in micelles of some structurally related non-ionic surfactants.

Two series of surfactants with graded differences in structure were chosen. Polyoxyethylene (20) sorbitan monolaurate, monopalmitate and monostearate (polysorbates 20, 40 and 60 respectively) have the same hydrophile and different hydrophobe. Polyoxyethylene (30), (40), (50) and (100) monostearate (Myrjs 51, 52, 53 and 59 respectively) have the same hydrophobe and different hydrophile. The characterization of these surfactants is reported elsewhere (Crooks, Collett & Withington, 1974). Equilibrium solubilities and densities of salicylic acid in aqueous solutions containing different concentrations of surfactants at controlled pH were measured using procedures described previously (Collett & Withington, 1972).

The influence of alkyl chain length of the surfactant on the solubilizing capacity of surfactants was investigated using the polysorbates. Solubilizing capacity was compared on the basis of molar ratios of solubilizate to solubilizer (McBain & Hutchinson, 1955). Molar ratios shown in Table 1 were calculated from plots of salicylic acid solubility as a function of surfactant concentration. Increases in the length of the alkyl chain of polysorbates increased the molar ratio of solubilizate to solubilizer. When expressed as moles of salicylic acid per $CH_2$ group of the alkyl chain there is only a slight change with increasing alkyl chain length suggesting that solubilized salicylic acid is closely associated with the alkyl chains in the micellar core. Increases in the length of the hydrophobic group of both ionic and nonionic surfactants are generally considered (Mulley, 1964) to increase the size of their micelles thus enabling more solubilizate to be accommodated. These observations are in agreement with this explanation and with the findings of other workers (Thakkar & Hall, 1967; Ismail, Gouda & Motawi, 1970).

The influence of oxyethylene chain length on surfactant solubilizing capacity was

Table 1. *The effect of alkyl chain length of polysorbates and polyoxyethylene chain length of Myrjs on the solubilization of salicylic acid (SA).*

| Polysorbate | $CH_2$ groups/ alkyl chain | Molar ratio SA: surfactant | SA: mol/$CH_2$ | Myrj | No. of $OCH_2$ units | Molar ratio SA: surfactant | SA: mol/$OCH_2$ |
|---|---|---|---|---|---|---|---|
| 20 | 10 | 0·98 | 0·098 | 51 | 30·3 | 1·32 | 0·042 |
| 40 | 14 | 1·19 | 0·085 | 52 | 44·7 | 1·77 | 0·040 |
| 60 | 16 | 1·30 | 0·081 | 53 | 59·8 | 1·88 | 0·032 |
| | | | | 59 | 89·0 | 1·92 | 0·022 |

Table 2. *Ratios of amounts of salicylic acid in the mantle and core of Myrj and polysorbate micelles at different pH.*

| pH | Myrj | | | | Polysorbate | | |
|---|---|---|---|---|---|---|---|
| | No. of oxyethylene units in hydrophile | | | | No. of $CH_2$ groups in the alkyl chain | | |
| | 30·3 | 44·7 | 59·8 | 89·0 | 10 | 14 | 16 |
| 2·0 | 0·64 | 0·94 | 1·25 | 1·86 | 3·80 | 2·72 | 2·34 |
| 2·5 | 0·60 | 0·89 | 1·19 | 1·77 | 2·91 | 2·10 | 1·82 |
| 3·0 | 0·55 | 0·81 | 1·08 | 1·61 | 2·35 | 1·68 | 1·47 |
| 3·3 | 0·43 | 0·63 | 0·84 | 1·25 | 1·94 | 1·39 | 1·21 |
| 3·6 | 0·38 | 0·57 | 0·76 | 1·13 | 0·90 | 0·73 | 0·64 |

investigated using the Myrjs. Molar ratios of solubilizate to solubilizer and the number of molecules of solubilizate per oxyethylene unit are shown in Table 1. As the number of oxyethylene units in the hydrophile is increased the molar ratio of salicylic acid to surfactant increases. At longer oxyethylene chain lengths the extent of this increase is diminished, in agreement with the findings of Gouda, Ismail & Motawi (1970). When solubilization is expressed as moles of salicylic acid per oxyethylene unit there is a decrease in solubilization as the chain length is increased. It would appear that salicylic acid solubilized by the Myrj surfactant is less closely associated with the polyoxyethylene chain than with the alkyl chain of polysorbates. It could be inferred that solubilized salicylic acid molecules are situated predominantly in the hydrocarbon core of both polysorbate and Myrj micelles. Solubilization of some salicylic acid within the polyoxyethylene chains near the hydrocarbon core of the micelle would account for the increased solubilization as the chain length of short Myrj surfactants is increased. If the solubilizate is not present in the outer regions of the hydrophile then further increases in chain length would have little effect on salicylic acid solubilization.

Further information on the distribution of solubilizate between the core and mantle of non-ionic surfactants can be obtained using the analysis of solubility data described by Mukerjee (1971). In the case of the Myrj series, the number of equivalents of solubilizate per equivalent of ethylene oxide and of alkyl group can be obtained from slopes and intercept values of plots of equivalents of solubilizate solubilized per equivalent of ethylene oxide as a function of stearate: ethylene oxide mole ratio. For polysorbates the ordinates and abscissae are equivalents solubilized per alkyl group and ethylene oxide stearate mole ratio respectively. These slope and intercept values have been used to calculate the distribution of the salicylic acid between core and mantle; the values are presented in Table 2. The ratio of amount in the mantle to that in the core increases with increasing polyoxyethylene chain length for the Myrj but for any one chain length decreases as pH increases. If the salicylic acid were associated with the hydrophilic mantle then it would be expected that the amount in the mantle would increase as the fraction ionized increased with pH. In the case of the polysorbates, the amount in the core increases with length of the alkyl chain and for any one chain length with increasing pH, further evidence of close association between the solubilizate and hydrophobic core.

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# The concept of dissolution efficiency

The recent interest in drug availability has resulted in a proliferation of *in vitro* dissolution testing, now standard for many dosage forms. The usual method of evaluation is the comparison of the time taken for given proportions of the active drug to be released into solution and figures such as the $^{t}20$, $^{t}50$ and $^{t}90\%$ times are often quoted. Alternatively the fraction of drug in solution after a given time is used for comparison, i.e. 60% release in 30 min.

A further parameter suitable for the evaluation of *in vitro* dissolution has been suggested by Khan & Rhodes (1972), who introduced the idea of Dissolution Efficiency. This is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. The simplest case, dissolution of a tableted drug, is shown in Fig. 1 where,

$$\text{Dissolution Efficiency (D.E.)} = \frac{\int_0^t y.dt}{y_{100}.t} \cdot 100\%$$

Before mentioning the advantages of this concept, the following points should be appreciated:

1. The Dissolution Efficiency can have a range of values depending on the time intervals chosen. This should preferably be greater than the $^{t}90\%$ of the formulation to ensure that most of the dissolution pattern is taken into account, although this is not always convenient with slowly released drugs. In any case, constant time intervals should be chosen for comparison. For example the index $D.E.^{30}$ would relate to the dissolution of drug from a particular formulation after 30 min and could only be compared with the $D.E.^{30}$ of other formulations.

2. With formulations in capsules, there are two schools of thought on whether or not the lag time should be included in the calculation (Fig. 2). If a comparison of various capsule fills is desired then assuming there is no interaction between capsule contents and gelatin shell, the lag time could be excluded as in (a) Fig. 2. However, if a final product is being tested, i.e. production or storage test samples, the lag time would be included as in (b) Fig. 2.

3. It is essential to establish that the total content of drug in the formulation is available for release and is not insolubilized by interaction with, or adsorption by, formulation aids. This is also the case with other methods of treating *in vitro* dissolution results.