Effect of non-ionic surfactants on the dissolution and solubility of hydrocortisone

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For drugs of low water solubility dissolution may be a rate limiting step in the process of absorption into the body, so that practices which increase dissolution rate are often adopted, e.g. fine subdivision. Where a drug surface is not readily wetted by aqueous fluids dissolution rates have been increased by lowering surface tension (e.g. Solvang & Finholt, 1970; Moran, Gillard & Roland, 1971; Braun & Parrott, 1972; Wan, 1972; Martis, Hall & Thakkar, 1972; Short, Sharkey & Rhodes, 1972; Rees & Collett, 1974). Where surfactant is present in concentrations above the critical micelle concentration (cmc) dissolution may also be favoured by the increased solubility resulting from micellar solubilization.

Materials. Hydrocortisone, micronized (Farbwerke Hoechst A.G., Frankfurt (Main), Germany, Batch 85L389); Polysorbate 80, (Koch-Light Labs. Ltd, Bucks., England, Batch 52581); Solulan 16 and Solulan 25 (American Cholesterol Products Inc., U.S.A., Batch 38F-4279 and 108F-4381 respectively) were used as received without further purification.

Methods. For dissolution rate determination hydrocortisone was stirred at 100 rev min^{-1} in 500 ml medium (0·1 M HCl containing surfactant) maintained at 37° in a double-walled beaker. At zero time 300 mg of the powder was placed on the surface of the liquid. Samples of liquid were removed via a filter at suitable time intervals until the liquid became $\frac{1}{4}$ to $\frac{1}{3}$ saturated with hydrocortisone which was assayed spectrophotometrically. As both peak wavelength and molar absorptivity values changed with changing surfactant concentration, it was necessary to prepare a standard curve for each surfactant concentration. Plots of amount of hydrocortisone dissolved versus time were essentially linear over the concentration range studied, enabling slopes to be used for comparison of initial dissolution rates, which were calculated using forced zero regression analysis. Correlation coefficients were always greater than 0·965.

Solubility of hydrocortisone was measured by placing an excess with the appropriate solvent in a shaker waterbath at 37°. Samples were assayed at intervals until the concentration became constant.

Values of the cmc of surfactants in 0·1 M HCl were obtained from surface tension measurements (Wilhelmy plate and du Nuoy Tensiometer (Cambridge Instrument Co., England) having beam extended 10 cm as pointer to be brought to same reference mark after bringing the liquid surface to a constant level).

Initial dissolution rates are given in Fig. 1. The following cmc values at 37° in 0·1 M HCl were obtained:

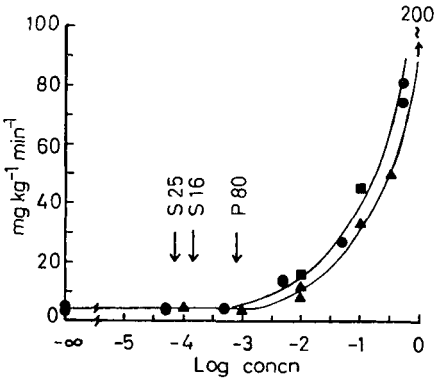

FIG. 1. Effect of various non-ionic surfactants (log concn (% w/w)) on the initial dissolution rates (mg kg^{-1} min) of hydrocortisone powder at 37°. ● Solulan 25, ■ Solulan 16, ▲ Polysorbate 80. ↓ cmc.

Polysorbate 80, $8{\cdot}20 \times 10^{-4}$; Solulan 25, $7{\cdot}15 \times 10^{-5}$ and Solulan 16, $1{\cdot}36 \times 10^{-4}$ (all in % w/w).

For polysorbate 80 and Solulan 25 when present at concentrations below the cmc the initial dissolution rate did not differ significantly from the value in 0·1 M HCl alone. This was true for solutions with surface tensions well below that for 0·1 M HCl. Visual observation showed that most of the hydrocortisone tended to float, was poorly wetted and dispersed which probably accounts for the differences in dissolution rates in the absence of surfactants. At surfactant concentrations appreciably greater than the cmc the hydrocortisone was well wetted and disposed which would account for the better reproducibility dissolution rates. Above the cmc the initial dissolution rate increases (Fig. 1). The increasing dissolution rate as surfactant concentration increased above the cmc was accompanied by an in-

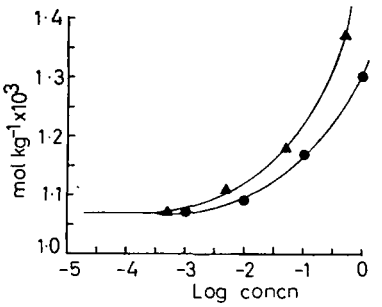

FIG. 2. Effect of various non-ionic surfactants (log concn (% w/w)) on the solubility of hydrocortisone (mol $kg^{-1} \times 10^3$) powder at 37°. ▲ Solulan 25, ● Polysorbate 80.

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creased wetting and dispersion of the powder such that at the highest concentrations used the powder was dispersed to a semi-colloidal state. Short & others (1972), studying similar systems found a pronounced maximum dissolution rate near to the cmc while we did not observe a maximum.

Solubilities of hydrocortisone are shown in Fig. 2. Solulan 16 and 25 are ethoxylated lacohol fractions of lanolin containing respectively 16 and 25 moles of ethylene oxide. Mulley (1964) has shown that altering the ethylene oxide chain number does not alter the general shape of solubility curves hence the solubility of hydrocortisone was determined in Solulan 25 only. Similarly there are only two data points for Solulan 16 dissolution (Fig. 1). As these fit the Solulan 25 line, any further points could be expected to follow the trend. The rate of increase of solubility relative to solubility in 0·1 M HCl is much less than for relative rate of increase of initial dissolution rate. This indicates that changing solubility is unlikely to be a major factor in increased dissolution rates in these systems. The main factor thus appears to be increased dispersion and wetting of the powder. That wetting and dispersion occur appreciably only above the cmc is unexpected. However, on the basis of cmc values, assumptions about the molecular weight of surfactants and of the particle size of hydrocortisone, it is possible to calculate the approximate surface area of the particles and the approximate surface area of surfactant molecules at the cmc. Comparison shows that even if all surfactant molecules were adsorbed they would cover less than 1% of the surface of the hydrocortisone particles. Thus concentrations of surfactant well above the cmc are required to permit sufficient to be adsorbed onto the hydrocortisone particles to give adequate wetting. Solulans, which have a ring structure similar to hydrocortisone, might be expected to be adsorbed more strongly on hydrocortisone than polysorbate. The observed measurements do not indicate any significant difference.

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Electron-microscope studies of the effect of subinhibitory concentrations of phenylethanol and polysorbate 80 on *Pseudomonas aeruginosa* 'sensitive' and 'resilient' to benzalkonium chloride

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The effect of benzalkonium chloride and disodium edetate on the morphology of the cell envelope of *Pseudomonas aeruginosa* has been examined by Richards & Cavill (1976). Evidence was obtained, about the mode of action of the two chemicals used singly and in combination, which further explained their effectiveness in combination against *P. aeruginosa*.

Phenylethanol and polysorbate 80, when used in combination with benzalkonium chloride, also show enhanced activity against *P. aeruginosa* (Richards & McBride, 1972; Brown & Richards, 1964a; Richards, 1975). The current investigation was to further elucidate the action of phenylethanol and polysorbate 80 on the cell envelope of *P. aeruginosa* using similar techniques to those used with benzalkonium and edetate disodium.

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The test organism was *P. aeruginosa* NCTC 6750 and the liquid and solid culture media were nutrient broth No. 2 and Oxoid nutrient agar (Oxoid) respectively. The 2-phenylethanol was a BDH laboratory reagent, the polysorbate 80 was from Hopkin and Williams and benzalkonium chloride (alkyl dimethyl benzylammonium chloride C_{14} 50%, C_{12} 40%, C_{16} 10%) from Rhom and Haas.

Cultures were maintained as described by Brown & Richards (1964b) and incubation was at 37°.

Benzalkonium 'sensitive' cells were prepared from the agar stab stock cultures by inoculating into broth and incubating for 16 h before using as an inoculum.