Solubilisation of preservatives by non-ionic agents

SIR,—Evans (1964) has recently reported a method for the solubilisation and inactivation of preservatives by non-ionic agents in which he has titrated *p*-hydroxybenzoic acid (100 ml 0·01 or 0·03M) with sodium hydroxide (0·1N) and showed that the pH is displaced to higher values in the presence of octylphenol/8·5 moles ethylene oxide. He assumed solubilisation of the acid in the detergent micelles and calculated a partition coefficient for the distribution of the acid between the detergent and water. Without giving details of the calculation, Evans indicated how the partition coefficient could be used to calculate the distribution of acid between detergent and water at various pH values.

We have evolved independently a similar potentiometric method in which displacements of the pH of titration curves of sodium benzoate with hydrochloric acid towards higher values in the presence of a non-ionic surface-active agent (cetomacrogol) were shown to be characteristic of acids which were solubilised in the micelles (Donbrow & Rhodes, 1963a). These pH displacements were interpreted using distribution theory, and the distribution coefficient

$$K_D \text{ or } [HA_m]/[HA_w] \quad .. \quad .. \quad .. \quad .. \quad .. \quad (1)$$

was calculated from the equation:

$$\text{antilog } \Delta \text{ pH} = K_D.V_m/V_w + 1 \quad .. \quad .. \quad .. \quad .. \quad (2)$$

in which V_m, V_w are the volumes of the micellar and aqueous phases and Δ pH is the difference in pH between the titrations in the presence and absence of the surfactant. Phase volumes (estimated from density measurements) were used in this formula to enable comparison to be made with literature K_D values of benzoic acid in organic solvents, from which it appeared that the micelles were behaving as polar rather than non-polar organic solvents, which was taken as evidence that solubilisation was occurring in the "palisade" layer rather than in the micellar core (Donbrow & Rhodes, 1963b). The same formula is applicable for the calculation of the partition coefficient per unit weight of phase by substituting phase weights for phase volumes. Attention was also drawn to the significance of the partition coefficient in pharmaceutical formulation, since its value governs the relationship between the total amount of drug in a surfactant solution (the "capacity" of the system) and the concentration, or activity, in the aqueous phase. The phenomenon was further shown to be a general one, occurring with a variety of acids, amines, or phenol and a variety of non-ionic and ionic surface-active agents (Donbrow & Rhodes, 1963; 1965; Rhodes, 1964). Our method differs from that of Evans in some important respects that involve fundamental points of theory and interpretation to which we would like to draw attention.

We have throughout our work titrated the sodium salt of the acid with hydrochloric acid (or the hydrochloride of the base with sodium hydroxide) in order to keep the ionic strength relatively constant. The Henderson equation may be applied to the titrations in the form (Donbrow & Rhodes, 1963b):

$$\text{pH} = \text{p}K_a + \log[A^-]/[HA_w] + \log f_{\pm} \quad .. \quad .. \quad .. \quad (3)$$

where $\text{p}K_a$ is the thermodynamic dissociation constant exponent, $[A^-]$ is the concentration of the ionised (salt) form of the acid, $[HA_w]$ is the concentration of the unionised "free" acid (i.e. the acid not bound by the surfactant), and $f_{\pm}$ is the appropriate activity coefficient correction. Since the total free acid in the system, HA_t, is known from the percent neutralisation, the amount of bound or micellar acid, HA_m, is calculated by difference:

$$HA_m = HA_t - HA_w \quad .. \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where HA_w is the amount of unbound unionised acid in the aqueous phase. It is evident that the errors in $[HA_w]$ and $[HA_m]$ introduced by the use of uncorrected data do not cancel out, hence the partition coefficient will not be independent of the activity coefficient.

There are two methods of dealing with the salt effects: either the thermodynamic dissociation constant, pK_a, may be used together with the appropriate activity coefficient, if known, or a comparative method may be used. With the comparative method, it is convenient to define an apparent dissociation constant exponent pK'_c by the equation:

$$pK'_c = pK_a + \log f_{\pm} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (5)$$

Its value may be determined from a "blank" titration in which a solution containing the same concentration of the salt of the acid is titrated under identical conditions (except for the absence of surfactant) as in the "surfactant" titration. If the acid is back-titrated from the salt form, as in our procedure, the ionic strength of the solution and hence the value of $\log f_{\pm}$ will vary only to a small extent, provided the volume of titrant added is small compared with the total volume of the system, and the pK'_c term will be virtually constant (Albert & Sergeant, 1962). Change of anion does not seem to be of importance for 1:1 electrolytes of relative short chain-length. The comparative method has the advantage of not requiring the estimation of an activity coefficient, and is preferable for establishing the operative distribution coefficient in a formulated product, provided the comparative titrations can be made at a concentration and under conditions simulating those in the formulated product. Obvious limitations occur when the acid is too insoluble in water for a comparable "blank" titration to be made. For insoluble acids, we have used the thermodynamic constant and estimated the activity coefficient.

Evans has titrated free acid to salt throughout his work; thus the ionic strength varies continuously in individual titrations and the variation through the neutralisation range may be large. Moreover, there will be large differences in ionic strength at corresponding points in titrations in which the initial concentration of acid is not the same, as in his work at 0·01 and 0·03M, so that comparisons made at arbitrarily chosen points are invalid. The effect of ionic strength on the activity coefficients and pH values observed may be predicted by means of the Deybe–Hückel equation and it would appear that near the end-point of the 0·03M titration, for example, the pH value may differ by 0·05 to 0·1 units from the value at a low ionic strength. In addition, changes in salt concentration affect micellar properties and distribution coefficients of "semi-" polar solutes. Evans's method of calculation is not given, but since he quotes a single dissociation constant of constant value (K_c $2{\cdot}95 \times 10^{-5}$) without reference to correction for ionic strength, it would appear that no correction was applied, though pH values were recorded to $\pm 0{\cdot}01$ units. This procedure can lead to errors in partition coefficient values and aqueous phase concentrations of unionised acid, particularly if the method is applied to formulation of preservatives in the presence of concentrations of salts. Unfortunately, Evans has not presented his results in a way that permits recalculation from his data, and though his partition coefficients are of qualitative interest, they are not in good agreement with the values calculated from cloud point data, and are probably insufficiently accurate for bactericidal or pharmacodynamic studies.

Evans states that, with the exception of some work by McBain "all previously reported solubilisation data have been obtained by examination of systems containing excess insoluble phases." This is not correct, for in addition to our

own publications on the potentiometric method, Kostenbauder and his collaborators have successfully applied equilibrium dialysis to a number of unsaturated surfactant systems (Patel & Kostenbauder, 1958; Pisano & Kostenbauder, 1959; Miyawaki, Patel & Kostenbauder, 1959; Deluca & Kostenbauder, 1960; Hurwitz, Deluca & Kostenbauder, 1963; Patel & Foss, 1964).

Evans has interpreted his results as we had in the earlier publications in terms of partition between an aqueous and a micellar phase. It is often more convenient to treat aqueous solutions of amphiphilic colloids, such as non-ionic surfactants, as uni-phase systems (Kruyt, 1952; Martin, 1960). The potentiometric evidence does not support the use of a two-phase model. Evans found that the presence of surfactant did not affect the activity of either hydrochloric or acetic acids. If a surfactant solution was a two-phase system one would expect the activity of these acids to be increased by the presence of surfactant by reason of the reduction of the volume of the aqueous phase. Such "concentration" effects would lead to a pH reduction of about 0·1 units in the stronger surfactant solutions, which should have been detectable.

School of Pharmacy,
Hebrew University,
Jerusalem, P.O.B. 517, Israel.

M. DONBROW

School of Pharmacy,
Purdue University,
Lafayette, Ind., U.S.A.

C. T. RHODES

February 23, 1965

References

Albert, A. & Sergeant, E. P. (1962). *Ionization Constants of Acids and Bases.* Methuen, London.

Deluca, P. P. & Kostenbauder, H. (1960). *J. Amer. pharm. Ass., Sci. Ed.*, **49**, 430–436.

Donbrow, M. & Rhodes, C. T. (1963a). *J. Pharm. Pharmacol.*, **15**, 233–238.

Donbrow, M. & Rhodes, C. T. (1963b). *F.I.P. Conference*, Münster, Sept., 1963. 23rd Internationaler Kongress der Pharmazeutischen Wissenschaften, Münster (Westfalen), Govi-Verlag GMBH, Pharmazeutischer Verlag, Frankfurt/Main, 1964.

Donbrow, M. & Rhodes, C. T. (1965). *J. chem. Soc.*, in the press.

Evans, W. P. (1964). *J. Pharm. Pharmacol.*, **16**, 323–331.

Hurwitz, A. R., Deluca, P. P. & Kostenbauder, H. (1963). *J. pharm. Sci.*, **52**, 893–897.

Kruyt (1952). *Colloid Science*, Elsevier Publishing Co., New York.

Martin, A. N. (1960). *Physical Pharmacy* Kimpton, London.

Miyawaki, G. M., Patel, N. K. & Kostenbauder, H. (1959). *J. Amer. pharm. Ass., Sci. Ed.*, **48**, 315–318.

Patel, N. K. & Kostenbauder, H. (1958). *Ibid.*, **47**, 289–294.

Patel, N. K. & Foss, N. E. (1964). *J. pharm. Sci.*, **53**, 94–97.

Pisano, F. D. & Kostenbauder, H. (1959). *J. Amer. pharm. Ass., Sci. Ed.*, **48**, 310–314.

Rhodes, C. T. (1964). Ph.D. Thesis, University of London.