Letter to the Editor

Solution Properties of Two Fluoroquinolone Antibacterials

It is necessary to comment on the results and interpretation of a recent publication by Yu, Zipp and Davidson on the solution properties of two fluoroquinolone antibacterials (1). The main difficulty with this paper is that the thermodynamic basis for the interpretation of its solubility-temperature dependence data has been glossed over and obscured. This has led to the startling proposition that the change in heat (enthalpy) for fusion of a solid (ΔH_m) may be obtained from the temperature dependence of its solubility in non-ideal aqueous solutions. This letter will attempt to address the fallacy leading to this proposition, as well as some other issues.

Thermodynamics of Solubility-Temperature Dependence Phenomena. There is a tacit and unwarranted assumption that aqueous solutions of these zwitterionic electrolytes (see below) are thermodynamically ideal. Given that their estimated intrinsic solubilities in water are very small (e.g., 0.037 and 0.27 mg/mL at 6°C for ciprofloxacin and norfloxacin, respectively), they must exhibit grossly positive deviations from Raoult's law, and thus very large departures from ideality.

The real problem is that the false assumption of ideality leads to the further assumption that equations (7) and (8), and also equations (9) and (10) are equivalent. They are not. The enthalpy term in equations (8) and (10) for non-ideal solutions such as those in the present paper are the apparent enthalpies of solution (2), not enthalpies of fusion as is true for equations (7) and (9). They are not even the standard enthalpies for solution, as has been made clear by Hollenbeck (3). Both Denbigh (4), and Higuchi and Grant (5) make it clear that the enthalpy terms in equations (7) and (8), and in equations (9) and (10), can only be equated when the solutions are ideal. Equations (7) and (9) are derived from equation (6) as indicated, whereas equations (8) and (10) are derived by integration of the van't Hoff reaction isotherm. The derivations are described in detail for solubilities by Prankerd and McKeown (2) and for rate constants by Prankerd (6). The estimation of thermodynamic functions from solubility-temperature dependence measurements is a far more complex issue (7) than is indicated here (1).

It should be clear that aqueous solubility (in ln mole fraction units) is not a linear function of either 1/T (integrated van't Hoff equation) or lnT (Hildebrand equation) (5). The speculation that better estimates of the heat of fusion may be obtained by use of non-linear solubility-temperature dependence relationships is unfounded. That the application of the Hildebrand equation in the study of Yu et al (1) gave an estimated enthalpy change from the solubility-temperature dependence for ciprofloxacin which was close to its measured enthalpy of fusion is simply a fortunate coincidence. It might be possible to use the approach described in the paper under discussion (1) if the solubility-temperature dependence of ideal solutions could be examined. Such an approach could be useful in the case of substances that degrade rapidly on melting, as may be the case with ciprofloxacin (see below). However, given the extreme rarity of such solutions, especially for those of pharmaceutical interest, this is unlikely.

It should be noted that equation (6) has the wrong sign for the second term in the bracket. Correct presentations of this equation are found in most of the solubility literature (5,7–9), while other texts have typographical errors for this equation (10,11).

There is no doubt that solubility-temperature dependence studies, even in non-ideal aqueous solutions, have considerable predictive value in the pharmaceutical sciences. However, it is imperative that the thermodynamic quantities derived from such studies be correctly identified.

Treatment of Solubility-pH Dependence. The macroscopic pKa values obtained from this (1) and other studies cited should indicate that the species in solution for each compound at its solubility-pH minimum is most likely to be its zwitterionic form. This is made clear by the cited study of Ross and Riley, in which the ratio of zwitterion to neutral species was 444 for ciprofloxacin and 118 for norfloxacin (12). This alters the form of the activity coefficients needed to correctly estimate the pKa values. Furthermore, the specific interactions between these charged species and solvent molecules (directed charge-dipole interactions) re-emphasizes the non-ideality of the aqueous solutions that have been studied.

The authors (1) have used Davies' modification of the Debye-Hückel equation to estimate the activity coefficients for each of the dissolved ionic species. Davies' modification was originally developed to estimate activity coefficients for multivalent inorganic cations. When applied to organic anions, e.g., for the ionization of p-nitrophenol at several different ionic strengths (13), the linear constant for ionic strength (I) in Davies' modification had to be increased by 100% to better fit the experimental data. Acid-base equilibrium studies on other organic acids, e.g., phenylbutazone (14) and 5,5-disubstituted barbituric acid derivatives (15), indicated that the value for this constant could be in error by up to an order of magnitude. Furthermore, it is debatable whether Davies' modification as given (1) can reliably estimate activity coefficients at ionic strengths as high as I = 0.3 M. Peck and Benet are in agreement with this assessment (16), as they used a more precise modification of the Debye-Hückel equation to estimate activity coefficients, yet even this modification was considered of doubtful accuracy at I > 0.15M. In the very careful work on the ionization of p-nitrophenol in four different buffers (13), the Davies' modification did not give consistent results for any of the buffer solutions at ionic strengths above I = 0.1 M, even after alteration of the linear term in I. This may account for some of the deviations between literature pKa values for the quinolones and those reported by Yu *et al* (1).

It is better to perform experimental measurements (e.g., potentiometric titrations, spectrophotometric titrations or solubility-pH dependence) at several values for the ionic

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strength, calculate an apparent pKa value for each ionic strength, then fit the apparent values to a linear relationship in I and obtain the thermodynamic pKa value by extrapolation to zero ionic strength. This is essentially the Guggenheim modification of the Debye-Hückel equation (17).

Accuracy of Measured Heats of Fusion. The DSC curves from which the reported heats of fusion were obtained include some unacknowledged sources of potential error. In the norfloxacin curve, there is a small endotherm prior to the main melting endotherm. This endotherm may be due to impurities or to another polymorphic form. The ciprofloxacin curve shows a rapid decrease in heat flux, presumably due to exothermic degradation, immediately after the melting endotherm. The melting endotherms for both curves exhibit a significant degree of premelting, also due to impurities in the samples. No indications were given for the purity of the two compounds studied. The heat of fusion values for both compounds could be compromised by these sources of error.

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