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# The solubility of sulphadiazine in water–dimethylformamide mixtures

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Precise measurements of the solubility of sulphadiazine in water, dimethylformamide (DMF), and a range of mixtures of these solvents have been made at 20°, 30°, and 40°. The solubility of sulphadiazine in the mixtures increases with their DMF content. The partial molar heats and entropies of solution decrease with increasing DMF concentration.

THE influence of particle size on the efficiency of absorption of certain drugs has been described in many publications. The uptake of sulphadiazine has been shown to be dependent on its particle size (Rheinhold, Phillips & Flippen, 1945). This drug was therefore considered suitable for investigations on methods capable of producing drugs in fine particle form.

The production of small sized crystals of various drugs, by a continuous process involving pumping a solution of the drug into a second miscible liquid in which the drug is insoluble, is being investigated. To study the fundamentals of this process of precipitation it was necessary to determine precise solubilities of the drug. These are reported here for the system sulphadiazine–water–dimethylformamide (DMF).

## Experimental

### MATERIALS

Sulphadiazine (B.P. quality) was twice recrystallized from an ethanol–DMF mixture (3 : 1 by volume) and dried over phosphorus pentoxide. M.p. 255° (Roblin, Williams & others, 1940, give 255–6°). Assay by the Pharmacopoeial method gave 100·0% purity calculated with reference to the material dried at 105°. Dimethylformamide (May & Baker Ltd.) was distilled under reduced pressure and gave $n_{25}^{D} = 1{\cdot}4283$ ($n_{25}^{D} = 1{\cdot}4294$ Dawson, Golben & others, 1952 and $n_{25}^{D} = 1{\cdot}4269$ Ruhoff & Reid, 1937).

### SOLUBILITY DETERMINATIONS

Solvent mixtures were prepared by weight. Solutions were presaturated by shaking with powdered sulphadiazine for 24 hr, and transferred to the solubility apparatus, which was of the percolation type, and a modification of that used by Davies & Griffiths (1953). The percolator was thermostated at the required temperature ±0·05°. The solution was recycled in the apparatus until saturated (in general 7–14 days). Use of porosity 5/3 sintered glass filters gave the same results as porosity 4 filters.

The concentration of sulphadiazine in solution was determined by one of three methods: (a) concentration greater than 1·5%, by evaporation of solvent and drying to constant weight; (b) concentration 0·02 to 1·5%, samples were diluted to give a 70% DMF solvent mixture and assayed

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spectrophotometrically measuring the extinction at 270 mμ; (c) concentration less than 0·02%, samples were diluted with water and assayed as in (b). In all spectrophotometric assays suitable calibration lines were prepared. Each solubility determination was duplicated and each solution assayed in duplicate.

Zimmerman (1952) emphasizes the need to verify the stability of the system during the equilibration period. There is evidence that DMF is stable under the experimental conditions used (Lang, 1960). There are no published quantitative studies on the stability of sulphadiazine solutions. Each solubility apparatus was painted black to protect the solutions from light. No change was detected in the ultraviolet absorption curve of sulphadiazine in water and 50% DMF water solutions when the solutions were heated at 40° for 14 days. The pH of all solutions lay in the range 5 to 6 and any difference in solubility over the pH range was within experimental error.

*Density*. The density of solutions was determined in a 10 ml pycnometer.

## Results and discussion

Fig. 1 shows that the solubility of sulphadiazine increases in a non-linear manner as the DMF concentration is increased. The solubility behaviour

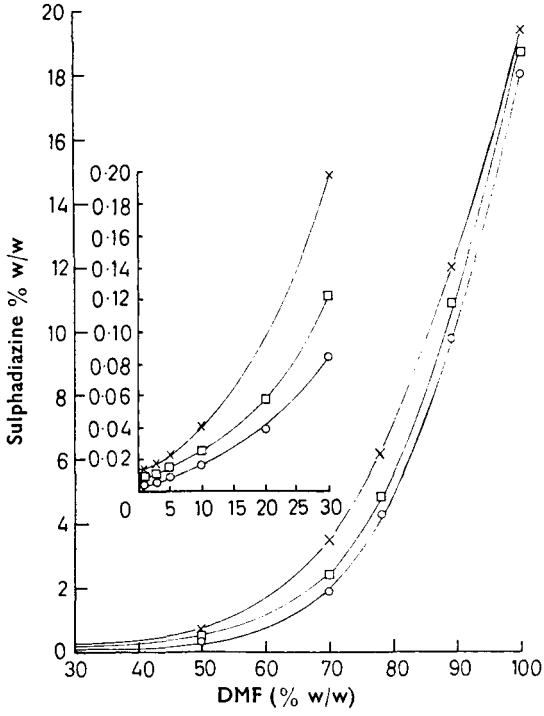


FIG. 1. Solubilities of sulphadiazine in water–DMF mixtures. Insert: solubilities at low DMF concentrations. ○——○ 20°, □——□ 30°, ×——× 40°.

TABLE 1. THE SOLUBILITY OF SULPHADIAZINE IN WATER–DMF MIXTURES

| % w/w DMF in solvents | Sulphadiazine % w/w saturated solution | | | Mole fraction, $N^s$, sulphadiazine in solution | | |
|---|---|---|---|---|---|---|
| | 20° | 30° | 40° | 20° | 30° | 40° |
| 0·0 | 0·00454 | 0·00760 | 0·0129 | $3{\cdot}27 \times 10^{-6}$ | $5{\cdot}47 \times 10^{-6}$ | $9{\cdot}29 \times 10^{-6}$ |
| 0·5 | 0·00490 | 0·00828 | 0·0138 | $3{\cdot}54 \times 10^{-6}$ | $5{\cdot}92 \times 10^{-6}$ | $9{\cdot}97 \times 10^{-6}$ |
| 1·0 | 0·00520 | 0·00881 | 0·0147 | $3{\cdot}78 \times 10^{-6}$ | $6{\cdot}39 \times 10^{-6}$ | $1{\cdot}07 \times 10^{-5}$ |
| 2·0 | 0·00598 | 0·00987 | 0·0166 | $4{\cdot}37 \times 10^{-6}$ | $7{\cdot}21 \times 10^{-6}$ | $1{\cdot}21 \times 10^{-5}$ |
| 3·0 | 0·00679 | 0·0111 | 0·0187 | $5{\cdot}00 \times 10^{-6}$ | $8{\cdot}18 \times 10^{-6}$ | $1{\cdot}38 \times 10^{-5}$ |
| 5·0 | 0·00861 | 0·0141 | 0·0233 | $6{\cdot}44 \times 10^{-6}$ | $1{\cdot}06 \times 10^{-5}$ | $1{\cdot}74 \times 10^{-5}$ |
| 10·0 | 0·0170 | 0·0252 | 0·0410 | $1{\cdot}33 \times 10^{-5}$ | $1{\cdot}97 \times 10^{-5}$ | $3{\cdot}19 \times 10^{-5}$ |
| 20·0 | 0·0395 | 0·0579 | 0·0968 | $3{\cdot}35 \times 10^{-5}$ | $4{\cdot}87 \times 10^{-5}$ | $8{\cdot}21 \times 10^{-5}$ |
| 30·0 | 0·0850 | 0·123 | 0·188 | $7{\cdot}91 \times 10^{-5}$ | $1{\cdot}14 \times 10^{-4}$ | $1{\cdot}75 \times 10^{-4}$ |
| 50·0 | 0·352 | 0·502 | 0·758 | $4{\cdot}08 \times 10^{-4}$ | $5{\cdot}84 \times 10^{-4}$ | $8{\cdot}81 \times 10^{-4}$ |
| 70·0 | 1·90 | 2·40 | 3·50 | $2{\cdot}94 \times 10^{-3}$ | $3{\cdot}73 \times 10^{-3}$ | $5{\cdot}50 \times 10^{-3}$ |
| 78·0 | 4·28 | 4·85 | 6·20 | $7{\cdot}75 \times 10^{-3}$ | $8{\cdot}84 \times 10^{-3}$ | $1{\cdot}14 \times 10^{-2}$ |
| 89·0 | 9·80 | 10·9 | 12·0 | $2{\cdot}32 \times 10^{-2}$ | $2{\cdot}60 \times 10^{-2}$ | $2{\cdot}90 \times 10^{-2}$ |
| 100·0 | 18·0 | 18·7 | 19·4 | $6{\cdot}02 \times 10^{-2}$ | $6{\cdot}29 \times 10^{-2}$ | $6{\cdot}57 \times 10^{-2}$ |

appears to be complex. Liquid water is known to be highly structured due to the formation of intermolecular hydrogen bonds (Robinson & Stokes, 1959). There is also a substantial interaction between water and DMF which must affect the structuring of the former considerably. Evidence for the formation of hydrates of the form $HCONMe_2(H_2O)_n$ where n = 2 to 4 is available (Blankenship & Clampitt, 1950; Geller, 1961). Either solvent component may interact with the sulphadiazine. The ability of a number of amides to increase the solubility of a third substance in water is well documented by Higuchi & Connors (1965), and these authors endeavour to relate solute-solvent-cosolvent interactions on a molecular basis to the total solubility.

Here we test the validity of equations for calculating solubilities, $n^s$, from those in the pure solvents, $n_1^s$ and $n_2^s$. The first method of calculation uses a simple mole fraction equation

$$n^s = n_1^s N_1 + n_2^s N_2 \qquad (1)$$

where $N_1$ and $N_2$ are the mole fractions of the two solvents.

A molar volume mixture rule in which

$$n^s = n_1^s V_1^* + n_2^s V_2^*$$

can be used, where $V_1^* = \dfrac{N_1 V_1}{N_1 V_1 + N_2 V_2}$ and $V_2^* = \dfrac{N_2 V_2}{N_1 V_1 + N_2 V_2}$ (2)

$V_1$ and $V_2$ being the molar volumes of the two components. Substitution of molar volumes by partial molar volumes in equation (2) gives a third method of calculation (Fleming, 1954). The densities used in the calculation of partial molar volumes are given in Table 2.

In Fig. 2 the calculated solubilities from the equations given above are shown. There is a large divergence between the experimental results and the calculated solubilities indicating that the basis of calculation of the solubility in water–DMF mixtures from values for the pure separate solvents is not correct. The addition of DMF does not increase the solubility of the sulphadiazine as much as might be expected from the solubility in pure

TABLE 2. THE DENSITY OF WATER–DMF MIXTURES

| % w/w DMF | Density | | |
|---|---|---|---|
| | $d_4^{20}$ | $d_4^{30}$ | $d_4^{40}$ |
| 0·000 | 0·9982 | 0·9957 | 0·9922 |
| 9·746 | 0·9978 | 0·9944 | 0·9902 |
| 19·591 | 0·9985 | 0·9941 | 0·9889 |
| 29·321 | 0·9996 | 0·9940 | 0·9879 |
| 49·978 | 0·9999 | 0·9922 | 0·9841 |
| 70·045 | 0·9911 | 0·9821 | 0·9728 |
| 78·929 | 0·9823 | 0·9731 | 0·9636 |
| 82·876 | 0·9773 | 0·9681 | 0·9586 |
| 89·322 | 0·9677 | 0·9583 | 0·9487 |
| 95·582 | 0·9570 | 0·9477 | 0·9381 |
| 100·000 | 0·9490 | 0·9395 | 0·9299 |

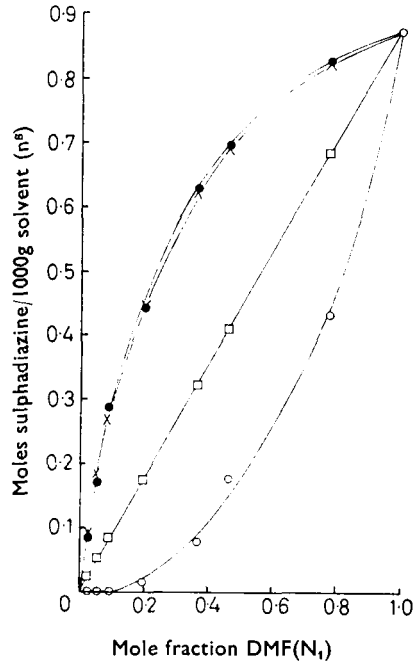


FIG. 2. Calculated and experimental solubility curves for sulphadiazine in water–DMF mixtures at 20°. ○——○ experimental. □——□ calculated from equation 1. ×——× equation 2. ●——● equation 2 using partial molar volumes. See text.

DMF. This may well be due to the interaction of water and DMF. The complex (or complexes) formed between the two solvents has a poorer solvent power for sulphadiazine than the ideal case (mole fraction line in Fig. 2). It seems possible that a complicated series of equilibria between water and DMF are in operation, as well as possible associations between the complexed solvents and the solute.

## THERMODYNAMICS OF SOLUBILITY

The Clausius–Clapeyron equation was used to calculate partial molar heats ($\Delta\bar{H}$) of solutions, and the partial molar entropies obtained from

$\Delta\bar{S} = \Delta\bar{H}/T$, since $\Delta\bar{G} = 0$ at the saturated, equilibrium condition. Activity coefficients have been neglected in these calculations, although error arising from this assumption may become significant in solutions containing a high proportion of DMF, where the solubility is substantial. The results are summarized in Table 3.

TABLE 3. THE PARTIAL MOLAR HEATS AND ENTROPIES OF SOLUTION, $\Delta\bar{H}$ AND $\Delta\bar{S}$, FOR SULPHADIAZINE IN WATER–DMF MIXTURES

| % w/w DMF in solvent | $\Delta\bar{H}$ k cal mole | | $\Delta\bar{S}$ cal/mole degree | |
|---|---|---|---|---|
| | 25 | 35° | 25° | 35° |
| 0·0 | 9·1 | 9·9 | 30·5 | 32·4 |
| 0·5 | 9·3 | 9·5 | 31·5 | 31·0 |
| 1·0 | 9·2 | 9·7 | 31·0 | 31·4 |
| 2·0 | 8·9 | 9·7 | 29·9 | 31·6 |
| 3·0 | 8·7 | 9·8 | 29·3 | 31·8 |
| 5·0 | 8·7 | 9·5 | 29·2 | 30·8 |
| 10·0 | 7·1 | 9·1 | 23·7 | 29·7 |
| 20·0 | 6·6 | 9·8 | 22·3 | 31·8 |
| 30·0 | 6·4 | 8·1 | 21·6 | 26·2 |
| 50·0 | 6·4 | 7·7 | 21·6 | 25·2 |
| 70·0 | 4·2 | 7·3 | 14·1 | 23·8 |
| 78·0 | 2·3 | 4·8 | 7·7 | 15·6 |
| 89·0 | 2·0 | 2·1 | 6·7 | 6·7 |
| 100·0 | 0·75 | 0·82 | 2·5 | 2·7 |

The principal trends in the thermodynamic properties are the decrease of both $\Delta\bar{H}$ and $\Delta\bar{S}$ as the DMF content is increased and the slightly larger values obtained at 35° compared with 25°. The heat of solution will be made up of three main parts: the heat necessary to break the bonds in the crystal lattice $\Delta H^{l}$, the heat of dilution $\Delta H^{d}$ and any heat changes arising from solvent–solute interactions. Since the heat change involved in disrupting the crystal lattice will be independent of DMF concentration, the decrease in $\Delta\bar{H}$ seems likely to be due to changes in heat of dilution or heat of interaction with DMF concentration.

Water structuring around sulphadiazine molecules will probably be replaced by hydrogen bonding between DMF and sulphadiazine as the concentration of the latter solvent is increased from zero. The concurrent formation of DMF–water complexes may lead to interaction of the complex with the sulphadiazine. It is impossible to decide, on the basis of the present data, whether heat of dilution effects, or those due to heat of interaction, or both, are responsible for the decrease of $\Delta\bar{H}$ with increase of DMF concentration.

The increase of $\Delta\bar{H}$ with temperature may represent reduced solute–solvent and DMF–water interaction at the higher temperature.

The entropy changes ($\Delta\bar{S}$), as expected, imply a far greater disorder of sulphadiazine molecules in solution than in the crystal. Also, the more concentrated solutions, with respect to sulphadiazine, present at high DMF concentrations, represent a state closer to that in the crystal than the very dilute solutions present at high concentrations of water. Consequently $\Delta\bar{S}$ for the high concentrations of water is high, while for solutions rich in DMF it is low.

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