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Prediction of the solubility of griseofulvin in glycerides and other solvents of relatively low polarity from simple regular solution theory

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Summary

Regular solution theory is applied to literature values of the solubility of griseofulvin in hydrocarbons and in other solvents of relatively low polarity. The solubility parameter of griseofulvin is calculated as 10.2 ± 0.2 $cal^{1/2} \cdot cm^{-3/2}$ at 25°C. The relatively high solubilities of griseofulvin in polar, non-hydrogen-bonded solvents are interpreted in terms of dipolar or hydrogen-bonding interactions between solute and solvent, whereas the sub-ideal solubilities in alcohols and water are attributed to solvent self-association. The solubilities of griseofulvin in the glycerides are predicted from regular solution theory in its simplest form, assuming that London dispersion forces are the most important interactions in solution. The solubility parameter of each solvent is calculated from its refractive index. The predicted values agree well with the experimental values of solubility in the triglycerides and diglycerides, except when the hydrocarbon component is so high that the solvent is behaving effectively as a hydrocarbon. The solubilities of griseofulvin in the monoglycerides are about one-fifth of the predicted values, and this is attributed to appreciable solvent self-association by hydrogen-bonding.

Introduction

The solubility is one of the most important fundamental physical properties of a drug since it usually controls dissolution rate and bioavailability and is a significant

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factor in formulation. Regular solution theory has proved particularly successful in predicting the solubility of solutes of relatively low polarity in solvents of similar polarity (Hildebrand and Scott, 1950; Hildebrand et al., 1970). The prediction of the solubility of more polar solute–solvent combinations is more difficult on account of the influence of specific interactions (Fung and Higuchi, 1971; Anderson et al., 1980). Since drug molecules often comprise a variety of polar functional groups, each of which is capable of interacting with the solvent molecules, the solubility behaviour of drugs is often complicated.

The present report shows how regular solution theory in its simple form may be applied to predict the solubility of the drug, griseofulvin (Fig. 1), in lipid solvents and examines some of the limitations of the approach. It will be seen, for example, that part of the success of the predictions may be attributed to the exclusion or minimization of specific hydrogen-bonding interactions. The absence of proton-donating groups in the drug molecule facilitates this approach.

Griseofulvin (Fig. 1) contains 6 proton-accepting oxygen atoms, comprising 2 keto groups and 4 ether groups. Since these groups are capable of forming hydrogen bonds with the proton-donating groups, such as the hydroxyl groups of phenols (Higuchi et al., 1969) and the carboxyl group of fatty acids (Grant and Abougela, 1982), the solubility behaviour of griseofulvin in these solvents is much higher than in hydrocarbon solvents, on account of the specific solute–solvent interactions, and is more difficult to predict.

Solution theory

When considering ideal and regular solutions, the standard state of unit activity of the solute (and the solvent) is most conveniently defined as the pure liquid at the temperature of interest. For a crystalline drug, such as griseofulvin, this standard state is a hypothetical supercooled state corresponding to an oil. The activity of the pure solute, a_2, is related to the mole fraction solubility of the solute, x_2, as follows

$$a_2 = x_2\gamma_2 \tag{1}$$

where γ_2 is the activity coefficient of the solute. Hildebrand and Scott (1950) derived the following accurate expression for the activity of the pure solid solute at a given temperature:

$$\ln a_2 = \frac{-\Delta H_m^f}{R} \cdot \frac{T_m - T}{TT_m} + \frac{\Delta C_p}{R} \cdot \frac{T_m - T}{T} - \frac{\Delta C_p}{R} \cdot \ln \frac{T_m}{T} \tag{2}$$

where R is the gas constant (8.3144 $J \cdot K^{-1} \cdot mol^{-1}$), T is the absolute temperature,

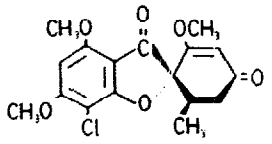

Fig. 1. Structure of the griseofulvin molecule (from Windholz et al., 1976).

ΔH_m^f is the enthalpy of fusion of the solid solute at its melting point, T_m, and ΔC_p is the difference in heat capacity of the solid and that of the supercooled liquid. ΔC_p is usually assumed to be independent of temperature, which is normally an excellent approximation.

The molar Gibbs free energy of solution of the solid solute in the solvent with respect to the standard state defined above is given by

$$\Delta G_2^\theta = -RT \ln x_2 \tag{3}$$

In the case of an ideal solution, $\gamma_2 = 1$, so that Eqn. 1 becomes $a_2 = x_2$ (ideal). Eqn. 3 then affords the ideal free energy of solution, thus:

$$\Delta G_2^\theta(\text{ideal}) = -RT \ln a_2 \tag{4}$$

For non-ideal solutions the excess free energy, of the solute, ΔG_2^E is defined by

$$\Delta G_2^E = \Delta G_2^\theta - \Delta G_2^\theta(\text{ideal}) = RT \ln \frac{a_2}{x_2} = RT \ln \gamma_2 \tag{5}$$

The simplest type of non-ideal solution is a regular solution.

Regular solution theory in its simplest form assumes: (a) that the entropy of mixing of the solute with the solvent is the same as for an ideal solution; and (b) that the intermolecular interactions involved are simply London dispersion forces, such that the solute–solvent interaction energy is given by the geometric mean of the solute–solute and solvent–solvent interaction energies (Hildebrand and Scott, 1950; Hildebrand et al., 1970). These assumptions lead to the following expression for excess free energy and the activity coefficient of the solute:

$$\Delta G_2^E(\text{regular}) = RT \ln[a_2/x_2(\text{regular})] = RT \ln \gamma_2(\text{regular}) = V_2\phi_1^2(\delta_2 - \delta_1)^2 \tag{6}$$

where V_2 is the molar volume of the solute, ϕ_1 is the volume fraction of the solvent and δ_1 and δ_2 are the solubility parameters of the solvent and solute, respectively. The solubility parameter is equal to the square root of the cohesive energy density, thus:

$$\delta = (\Delta U^v/V)^{1/2} \tag{7}$$

where ΔU^v is the internal energy of vaporization and V is molar volume. The solubility or solubility parameter of the solute in a regular solution may be calculated by substituting known values into Eqn. 6.

Materials and Methods

Materials

The sample of griseofulvin contained not less than 99% of the drug; its analysis has been reported by Grant and Abougela (1982). The sources of the glycerides are

as follows. B.D.H. Chemicals, Poole, Dorset, U.K., supplied glycerol, glycerol diacetate and glycerol triricinoleate. Croda Chemicals Ltd., Leek, Staffs., U.K., supplied glyceryl monolaurate, glyceryl monostearate (N/E), glyceryl monoleate, glyceryl dioleate, glyceryl trioleate and glyceryl monoricinoleate. Leek Chemicals, Leek, Staffs., U.K., supplied glyceryl distearate. Sigma Chemicals (London) U.K., supplied glyceryl triacetate, glyceryl tributyrate, glyceryl tricaproate, glyceryl tricaprylate, glyceryl trilaurate, glyceryl trimyristate, glyceryl tripalmitate and glyceryl tristearate.

Solubility determination at various temperatures

The solubility of griseofulvin in each of the glycerides was determined at 5 different temperatures by a synthetic method described by Grant and Abougela (1983). The mole fraction solubilities were interpolated or extrapolated to one of the reference temperatures, 373.15K (100°C) or 403.15 K (130°C), by means of the following integrated form of the van't Hoff equation.

$$\ln x_2 = -\frac{\Delta H_2^\theta}{R} \cdot \frac{1}{T} + \text{constant} \qquad (8)$$

Here ΔH_2^θ is the apparent differential molar enthalpy of solution which is assumed to be independent of temperature over the ranges employed (e.g. 102.5–108°C, 120.5–169°C, 161–191°C). High correlation coefficients (> 0.995) were obtained in the van 't Hoff plots. The particular choices of reference temperature ensured that all but two of the quoted standard solubilities, presented in Table 2, could be evaluated by an extrapolation of less than 15K (23K for glyceryl tristearate and 27K for glyceryl trioleate).

Ideal solubility of griseofulvin

From differential scanning calorimetric measurements on griseofulvin (Grant and Abougela, 1982), the enthalpy of fusion at the melting point ($T_m = 495.15$K) is 39.39 kJ · mol^{-1}, while ΔC_p, the difference between the heat capacity of the solid and that of the supercooled liquid, is 20.03 J · K^{-1} · mol^{-1} between 373.15K and T_m. From these data the following values were calculated at various reference temperatures by means of Eqns. 2 and 4: $10^3 x_2$(ideal) = 2.60 at 298.15K, 48.70 at 373.15K, 119.0 at 403.15K; ΔG_2^θ(ideal) kJ · mol^{-1} = 14.76 at 298.15K, 9.376 at 373.15K, 7.126 at 403.15K.

Results and Discussion

Determination of the solubility parameter of griseofulvin

Direct experimental determination of the solubility parameter, δ_2, of griseofulvin from Eqn. 7, from vapour pressure data (Hoy, 1970) or from the boiling point using the Hildebrand rule (Hildebrand and Scott, 1950) is extremely difficult, because griseofulvin has negligible vapour pressure and decomposes above its melting point.

Consequently, δ_2 was calculated from published solubilities of griseofulvin in various solvents of known solubility parameter, δ_1, using the method described by Hildebrand and Scott (1950) and by Shinoda (1978) and exemplified by iodine.

From published solubilities of griseofulvin at 298.15K (Sekiguchi et al., 1964, 1976; Elworthy and Lipscomb, 1968; Cook, 1978; Townley, 1979) x_2 values were calculated (Table 1) and ΔG_2^θ was evaluated from Eqn. 3. Fig. 2 shows plots of ΔG_2^θ against δ_1 evaluated from published tables (Burrell, 1968; Hoy, 1970; Barton, 1975). The vertical and horizontal lines show the limits of variation of literature values of ΔG_2^θ and δ_1, respectively. The published solubilities of griseofulvin in heptane differ widely (Elworthy and Lipscomb, 1968; Townley, 1979) as do reported values of the solubility parameter of propylene glycol. Nevertheless with increasing δ_1 of solvents of relatively low δ_1 ($\leqslant 12$ cal$^{1/2}\cdot$cm$^{-3/2}$), the solubility tends to increase and ΔG_2^θ to decrease.

Fig. 2 shows that the solubility of griseofulvin is abnormally low, and ΔG_2^θ abnormally high, in the alcohols, methanol, ethanol and propylene glycol and in water (not plotted, $\Delta G_2^\theta = 37.09$ kJ$\cdot$mol^{-1}, $\delta_1 = 23.4$–23.5 cal$^{1/2}\cdot$cm$^{3/2}$) and also in

TABLE 1

ESTIMATES OF THE SOLUBILITY PARAMETER, δ_2, OF GRISEOFULVIN FROM ITS MOLE FRACTION SOLUBILITY, x_2, IN VARIOUS SOLVENTS (OF MOLAR VOLUME, V_1, DIPOLE MOMENT, μ, AND SOLUBILITY PARAMETER, δ_1) AT 298.15K

Solvent	V_1 [a] (cm$^3\cdot$mol^{-1})	μ [a] (D)	$x_2\times10^6$	δ_1 (cal$^{1/2}\cdot$cm$^{-3/2}$)	δ_2 (cal$^{1/2}\cdot$cm$^{-3/2}$)
2,2,4-Trimethyl-pentane	166.1	0	1.564 [b]	6.9 [f]	10.31
				6.86 [g]	10.35
n-Hexane	131.6	0.085	19.4 [c]	7.3 [f]	10.07
				7.27 [g]	10.10
n-Heptane	147.5	0.0	1.493 [d]	7.4 [f]	10.96
				7.5 [g]	10.86
			125.4 [e]	7.4 [f]	9.70
				7.5 [g]	9.60
Diethyl ether	104.8	1.15	208.0 [e]	7.4 [f]	9.54
				7.53 [g]	9.41
Carbon tetrachloride	97.1	0	550.8 [e]	8.6 [f]	10.13
				8.55 [g]	10.18
Toluene	106.9	0.31	133.3 [c]	8.9 [f]	11.11
				8.93 [g]	11.08
Mean value of δ_2 (cal$^{1/2}\cdot$cm$^{-3/2}$)					10.24
Standard error of the mean [h] (cal$^{1/2}\cdot$cm$^{-3/2}$)					±0.15

[a] From Riddick and Bunger (1970).
[b] From Mehdizadeh and Grant (1982).
[c] From Cook (1978).
[d] From Elworthy and Lipscomb (1968).
[e] From Townley (1979).
[f] From Burrell (1968) and Barton (1975).
[g] From Hoy (1970).
[h] Assuming a normal (Gaussian distribution), if appropriate.

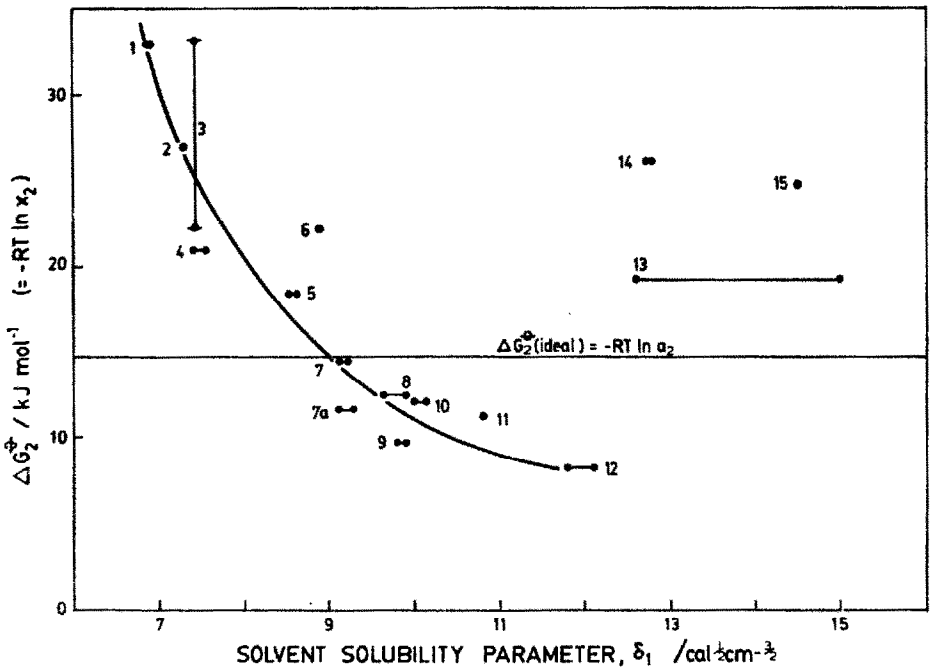

Fig. 2. Influence of the solubility parameter of the solvent, δ_1, on the standard molar Gibbs free energy of solution, ΔG_2, of griseofulvin, based on the mole fraction solubility, x_2, at 298.15K. Solvents: 2,2,4-trimethylpentane (1), *n*-hexane (2), *n*-heptane (3), diethyl ether (4), carbon tetrachloride (5), toluene (6), benzene (7), chloroform (7a), acetone (8), dichloroethane (9), dioxane (10) dimethylacetamide (11), dimethylformamide (12), propylene glycol (13), ethanol (14), and methanol (15).

formamide (not plotted, $\Delta G_2^{\theta} = 26.06$ kJ · mol^{-1}, $\delta_1 = 17.9$–19.2 cal$^{1/2}$ · cm$^{-3/2}$). Since these solvents undergo considerable self-association, the most likely explanation for their poor solvency for griseofulvin is the solvophobic interaction, or the hydrophobic interaction in the case of water (Ben-Naim, 1980; Tanford, 1980). It is clearly inappropriate to apply regular solution theory in its original, simple form to these solvents.

The solubility of griseofulvin is greater than the ideal value (i.e. $\Delta G_2^{\theta} < \Delta G_2^{\theta}$(ideal) in Fig. 2 and ΔG_2^{E} is negative) in acetone, chloroform, dichlorethane, dimethylacetamide and dimethylformamide, which possess appreciable dipole moments (1.15–3.86 D; Riddick and Bunger, 1970). The solubility also exceeds the ideal value in benzene ($\mu = 0$) and dioxane ($\mu = 0.45$ D) which are capable of forming solid solvates with griseofulvin (Sekiguchi et al., 1976), suggesting a significant degree of drug–solvent interaction. Solubilities greater than the ideal also occur in acetic acid ($\Delta G_2^{\theta} = 12.15$ kJ · mol^{-1}; Mehdizadeh and Grant, 1982) which, like chloroform, acts as a hydrogen bond donor to the griseofulvin acceptor molecule (Higuchi et al., 1969; Grant and Abougela, 1982) and also forms a stoichiometric solid solvate with the drug (Sekiguchi et al., 1964; Abougela and Grant, 1979; Grant and Abougela, 1981). None of these 'greater than ideal' solubilities can be accounted for by regular solution theory in its original, simple form. Some deviations from the theory may be attributed to dipole–dipole forces, dipole-induced dipole interactions, charge-trans-

fer complexation and hydrogen-bonding between the solute and the solvent. Attempts have been made to accommodate these types of interactions by introducing multicomponent solubility parameters as extensions to the original Hildebrand theory (for refs., see Barton, 1975; Karger et al., 1976).

Non-hydrogen bonding solvents which have small or zero dipole moments and which give solubilities less than the ideal value ($\Delta G_2^{\theta} > \Delta G_2^{\theta}$(ideal)) are most likely to obey regular solution theory in its original, simple form. Such solvents fall on or near the curve on the left of Fig. 2, have $\delta_1 < 9$ cal$^{1/2} \cdot$ cm$^{-3/2}$ and include hydrocarbons and carbon tetrachloride. Accordingly, δ_2 was calculated from a_2 for solid griseofulvin at 298.15K and from x_2 in each solvent of known δ_1 using Eqn. 6. In order to obtain the calculated values of δ_2 shown in Table 1, V_2 and ϕ_1 also required evaluation.

The molar volume (= molecular weight/density) of pure liquid griseofulvin, V_2, at 25°C is not available in the literature and was therefore calculated from group contribution data (Exner, 1967; Rheineck and Lin, 1968). From Exner's (1967) tabulations at 20°C, $V_2 = 374.5$ cm$^3 \cdot$ mol^{-1} was calculated. Assuming that the coefficient of expansion of liquid griseofulvin is the mean of that of a gas and a solid (c.f. Bauer and Lewin, 1959), then $V_2 = 378.8$ cm$^3 \cdot$ mol^{-1} at 25°C. From the group tabulations of Rheineck and Lin (1968) at 25°C, $V_2 = 361.6$ cm$^3 \cdot$ mol^{-1} was calculated. The mean value at 25°C, $V_2 = 370$ cm$^3 \cdot$ mol^{-1}, was used throughout the present work. The volume fraction of the solvent, ϕ_1, was calculated from x_2, V_2 and the density of the solvent (Riddick and Bunger, 1970), but as it differed from unity only in the 3rd–6th decimal place, it could be taken as 1.00 with very little error.

From the above data, namely, a_2, V_2, R and T throughout, and x_2, δ_1 and ϕ_1 for each solvent, the solubility parameter of griseofulvin, δ_2, was calculated and its values, presented in Table 1, show good agreement. The mean value of δ_2, 10.24 cal$^{1/2} \cdot$ cm$^{-3/2}$, was used in subsequent calculations.

Calculation of the solubility parameters of the glycerides and solubility prediction

The glycerides have high boiling points and, as a corollary, low vapour pressures. Consequently, estimates of the solubility parameter from the energy of vaporization, ΔU^v, at 25°C (Eqn. 7) using vapour pressure data (Hoy, 1970) or using the Hildebrand rule (Hildebrand and Scott, 1950) are either hindered by lack of experimental data or are subject to large errors, especially in the case of the higher homologues. The following argument attempts to justify and describe the preferred method used here to calculate the solubility parameters of the glyceride solvents.

The crystal structures of the longer chain triglycerides, such as glyceryl trilaurate (see Chapman, 1962), show that each molecule assumes an h-shaped tuning-fork conformation. The central and one of the two extreme acyl chains are oriented along the same axis. Two neighbouring triglyceride molecules pack in such a way that the third remaining acyl group in each molecule lies along the same axis parallel with the first. The resulting arrangement strongly resembles that of a long chain hydrocarbon, such that the presence of the glyceryl triester group at the centre of each molecule exerts only a small perturbing effect. Thus, the crystallization behaviour of the triglycerides resembles that of the long chain paraffins. Although the liquid state

is more disordered than the solid state, such that other conformations are also present, the conformation found in the crystal, being of lowest energy, is likely to persist, on average, even in the liquid state. The significance of this is that the dipoles of the ester groups, which are in close proximity in the centre of the triglyceride molecule, are likely to be subject to a mutual cancellation. As a result, the triglycerides will not be as polar as the mono-esters, such as ethyl acetate ($\mu = 1.88$ D, Riddick and Bunger, 1970), which are regarded as moderately polar solvents. Consequently, triglycerides like other liquids, are often regarded as models for non-polar biological molecules and are classed with the hydrocarbons as 'lipophilic' and 'hydrophobic' molecules.

In view of their low polarity, the triglycerides will be considered to interact with griseofulvin essentially by London dispersion forces, ignoring dipole–dipole and dipole-induced dipole interactions. This assumption is probably a good approximation and enables regular solution theory to be applied in its simplest form. Several workers (Scatchard, 1949; Sewell, 1966; Lawson and Ingham, 1969; Keller et al., 1971; Karger et al., 1976) have shown, either theoretically or experimentally when London dispersion forces are operating alone, that the solubility parameter, δ, is proportional to the Lorentz-Lorenz function, χ, thus

$$\delta = k \cdot \chi \tag{9}$$

where

$$\chi = \frac{n_D^2 - 1}{n_D^2 + 2} \tag{10}$$

and where n_D is the refractive index of the liquid to light of wavelength 590 nm, and k is a constant. Sewell (1966) derived the value $k = 30.3$ cal$^{1/2} \cdot$ cm$^{-3/2}$, whereas Keller et al. (1971) and Karger et al. (1976), considering a larger number of compounds, reported that $k = 30.7$ cal$^{1/2} \cdot$ cm$^{-3/2}$ provided that $\chi \leqslant 0.28$ ($n_D \leqslant 1.472$, $\delta < 8.6$ cal$^{1/2} \cdot$ cm$^{-3/2}$). We have confirmed the latter value of k from linear plots of $(\Delta U^v/V)^{1/2} = \delta$ (see Eqn. 7) against χ for hydrocarbons (paraffins, olefins and aromatics) and their halogenated derivatives of $\mu \leqslant 0.3$ D at 25°C using the data provided by Riddick and Bunger (1970). When, however, $\chi > 0.28$, Keller et al. (1971) and Karger et al. (1976) have shown empirically that

$$\delta(\text{cal}^{1/2} \cdot \text{cm}^{-3/2}) = -2.24 + 53\chi - 58\chi^2 + 22\chi^3 \tag{11}$$

These authors have emphasized that the solubility parameter, calculated by applying Eqns. 9 and 11 to polar compounds and to substances which can participate in hydrogen-bonding, may be termed the 'dispersive or dispersion component' of the multicomponent solubility parameter.

Thus, in the present work the solubility parameters of the glycerides were calculated from the refractive index, n_D, at 590 nm and at 20–25°C by means of Eqns. 9 or 11 and are listed in Table 2. The value of n_D was usually provided by

TABLE 2

COMPARISON OF EXPERIMENTAL AND PREDICTED (REGULAR SOLUTION) VALUES OF THE EXCESS MOLAR FREE ENERGY, ΔG_2^E, AND MOLE FRACTION SOLUBILITY, x_2, OF GRISEOFULVIN IN VARIOUS GLYCERIDE SOLVENTS AT 373.15K and 403.15K

Solvent	n_D^{20-25} [a]	δ ($cal^{1/2} \cdot cm^{-3/2}$)	Temperature T (K)	Predicted		Experimental	
				ΔG_2^E ($kJ \cdot mol^{-1}$)	$x_2 \times 10^3$	ΔG_2^E ($kJ \cdot mol^{-1}$)	$x_2 \times 10^3$
Triacetin	1.4304	7.93	373.15	8.28	3.4	8.59	3.1
Tributyrin	1.4359	8.02	373.15	7.66	4.1	6.30	6.4
Tricaproin	1.4427	8.13	373.15	6.93	5.2	8.21	3.5
Tricaprylin	1.4482	8.21	373.15	6.37	6.3	6.49	6.0
Trilaurin	1.4582	8.37	403.15	5.42	24	6.66	16
Trimyristin	1.4625	8.44	403.15	5.03	27	8.36	9.8
Tripalmitin	1.4633	8.45	403.15	4.96	27	8.55	9.3
Tristearin	1.4631	8.45	403.15	4.98	27	8.95	8.2
Triolein	1.4676	8.52	403.15	4.59	30	12.20	3.1
Triricinolein	1.4698	8.56	403.15	4.41	32	7.93	11
Diacetin	1.4395	8.08	373.15	7.27	4.7	7.14	4.9
Distearin	1.4643	8.47	403.15	4.87	28	6.04	20
Diolein	1.4728	8.55	403.15	4.46	31	5.89	21
Monolaurin	1.4769	8.60	373.15	4.18	13	9.00	2.7
Monostearin	1.4763	8.59	403.15	4.22	34	9.91	6.2
Monoolein	1.4653	8.48	403.15	4.79	29	9.90	6.2
Mono-ricinolein	1.4889	8.75	403.15	3.44	43	10.0	6.0
Dodecane	1.4216	7.79	403.15	9.33	7.4	see trilaurin	
Tetradecane	1.4290	7.91	403.15	8.44	9.6	see trimyristin	
Hexadecane	1.4345	8.00	403.15	7.81	12	see tripalmitin	
Octadecane	1.4390	8.07	403.15	7.32	13	see tristearin	
cis-Octa-9-decene	1.4470	8.20	403.15	6.49	17	see triolein	
cis-Octa-9-decen-1-ol	1.4606	8.41	403.15	5.20	25	see triricinolein	
Glycerol	1.4730	8.55	403.15	4.44	32	3.54	0.37

[a] From Weast (1982).

Weast (1982), but if available at a temperature other than at 20°C or 25°C, it was converted to the value at 25°C by means of the empirical Eykman (1896) equation, which is

$$\frac{n_D^2 - 1}{n_D + 0.4} \cdot \frac{1}{d} = C \tag{12}$$

where d is the density of the liquid at the temperature to which n_D refers and C is a

constant. For a given liquid, C is found to be remarkably invariant over a wide range of temperatures and pressures (for refs., see Riddick and Bunger, 1970). Usually d was available at the same temperature as n_D, so that C could be readily calculated. However, the value of d is required at 20–25°C to enable n_D at this temperature to be calculated from C. If d was not available in the literature, it was calculated from the molar volume derived from group contributions (Exner, 1967), having first ascertained that the calculated values agree with the experimental values for other glycerides within 1%.

The solubility parameter, δ_2, of the solute griseofulvin, and that of each solvent, δ_1, were determined at 298.15K whereas the solubility data in the glycerides were interpolated or extrapolated to 373.15K or 403.15K, the chosen reference temperatures. However, further extrapolation of the solubilities down to 298.15K might cause errors. Fortunately, $V_2\phi_1^2(\delta_1 - \delta_2)^2$, which is equal to ΔG_2^E(regular) according to Eqn. 6, is almost independent of temperature, because a given change of temperature causes similar changes in both δ_1 and δ_2 (Barton, 1975). Consequently, the predicted value of ΔG_2^E for griseofulvin as the solute in each glyceride as the solvent at 373.15K or 403.15K (Table 2) was taken to be the value of $V_2\phi_1^2(\delta_1 - \delta_2)^2$ calculated at 298.15K. Insertion of this value and a_2 into Eqn. 5 enabled x_2 to be predicted (Table 2) at the reference temperature of interest.

Comparison of the predicted and experimental solubilities in the glycerides

The predicted values of ΔG_2^E and x_2 are compared in Table 2 with the corresponding values determined experimentally. In solubility predictions discrepancies of 2.3 kJ · mol^{-1} in ΔG or by a factor of 0.5–2.0 in solubility are usually considered to be relatively small (Yalkowsky and Valvani, 1980; Amidon and Williams, 1982), while discrepancies of 5.4 kJ · mol^{-1} in ΔG or by a factor of 0.2–5.0 in solubility are not uncommon examples in a set which otherwise demonstrates satisfactory predictions overall. Table 2 shows that theory gives good predictions (within a factor of 1.5) for the solubility of griseofulvin in the lower triglycerides (triacetin to trilaurin) and in the diglycerides (e.g. diacetin and distearin). The estimated ideal solubilities of griseofulvin at 373.15K and 403.15K are $10^3 x_2 = 48.7$ and 119, respectively, which are greater than the experimental values by factors which often exceed 10.

The predicted solubility (Table 2) increases with increasing solubility parameter, polarizability or refractive index of the solvent (as expected if $\delta_1 < \delta_2$) and these quantities all increase on ascending the homologous series of the triglycerides or diglycerides as solvents. The experimental solubilities do not, however, follow this trend. In the higher triglycerides (above trilaurin), for example, the predicted solubilities exceed the measured values by factors of about 3. This may be attributed to the disturbing influence of the longer hydrocarbon chain on the polarizability of the solvent. The triester grouping is the most polarizable part of the triglyceride molecule on account of its non-bonded and Π electrons (Le Fèvre, 1965). This is reflected in the relatively high molar refractivity of the ester group (Vogel, 1948). The presence of the poorly polarizable hydrocarbon chain may reduce the strength of the short range London dispersion forces with griseofulvin. This supposition suggests that the solubility parameter of each of the higher triglycerides may be

approximately equal to that of the corresponding hydrocarbon residue, which may or may not have attached functional groups. The solubility parameter of each of the corresponding (unsubstituted or substituted) hydrocarbons, listed at the foot of Table 2, has been calculated from the refractive index (Weast, 1982), as before. The solubility of griseofulvin in each of the higher triglycerides is very close to that predicted from the solubility parameter of the (unsubstituted or substituted) hydrocarbon, in agreement with the above supposition. However, this casts further doubt on the utility of regular solution theory for predicting solubility in polarizable systems or on the methods used to estimate solubility parameters.

The higher diglycerides, distearin and diolein, conform more closely to regular solution theory than do the higher triglycerides, e.g. tristearin and triolein (Table 2). Following the above argument, the presence of only two hydrocarbon chains in each diglyceride molecule may be insufficient to mask completely the influence of the polarizable ester groups, while the hydroxyl group may enable the neighbouring ester groups to exert their polarizable effects by limited solvent–solvent hydrogen bonding. The low molar ratio of hydroxyl to methylene groups in the diglycerides probably ensures that solvophobic interactions cause relatively small deviations from regular behaviour, whereas the higher ratio in the lower aliphatic alcohols, such as methanol and ethanol, gives rise to significant solvophobic interactions (Tanford, 1980) which reduce the solubility of griseofulvin (Fig. 2).

The solubility of griseofulvin in the monoglycerides (Table 2) is only about 1/5 of that predicted from simple regular solution theory. Presumably, the presence of two hydroxyl groups per solvent molecule causes pronounced self-association of the solvent molecules by hydrogen bonding, and this reduces the solubility by the solvophobic effect, as in the lower aliphatic alcohols, mentioned above. Evidently, griseofulvin is not a strong enough proton acceptor to undergo sufficiently powerful interactions with the hydroxyl groups to overcome this effect. In support of this explanation, the solubility of griseofulvin in glycerol (Table 2) is much smaller (ΔG_2^E larger) than predicted by simple regular solution theory. Independent evidence indicates that the presence of 2 or 3 hydroxyl groups in the molecules of ethylene glycol or glycerol, respectively, effectively reduces the solubility of other non-polar substances, thereby showing a solvophobic effect which approaches that of water (Sinanoglu and Abdulnur, 1965; Tanford, 1980).

The similar magnitude of the experimental and predicted solubilities of griseofulvin in the triglycerides and diglycerides suggests that simple regular solution theory provides a rough estimate of solubility. This in turn suggests that London dispersion forces are the dominant intermolecular interactions, despite the fact that the griseofulvin molecule (Fig. 1) contains 4 ether groups, 2 keto groups and a benzenoid chloro-substituent, all of which confer polarity. The 'lone-pair' and 'non-bonded' electrons in these polar groups, however, will undergo conjugation with the Π molecular orbitals of the aromatic ring of the olefinic group. The resulting mesomeric effects will change the dipole moment of the groups (Minkin et al., 1970; Exner, 1975) perhaps in a direction such as to weaken the dipole–dipole (Keesom) and dipole-induced dipole (Debye) interactions with the solvent molecules. The London dispersion force, however, does not involve permanent dipole moments but increases

with increasing polarizability or refractive index, both of which increase with increasing delocalization of the electrons. Intermolecular interactions have been discussed by Kihara (1976).

The results suggest that simple regular solution theory may provide a useful but rough estimate of the solubility of poorly water-soluble (so-called lipophilic) drugs in solvents of low polarity, such as lipids. In such cases, the solubility parameter of the solvent may be calculated from the refractive index, which is a readily accessible quantity. Experiment does not, however, conform to the theory in detail. For example, in polar, self-associated or interactive solvents obvious deviations may be expected. Emphasis on the points of discrepancy may serve to stimulate further research in this somewhat neglected area.

References

Abougela, I.K.A. and Grant, D.J.W., Fatty acid solvates of griseofulvin. J. Pharm. Pharmacol., 31 Suppl. (1979) 49P.

Amidon, G.L. and Williams, N.A., A solubility equation for non-electrolytes in water. Int. J. Pharm., 11 (1982) 249–256.

Anderson, B.D., Rytting, J.H. and Higuchi, T., Solubility of polar organic solutes in nonaqueous systems: role of specific interactions. J. Pharm. Sci., 69 (1980) 676–680.

Bauer, N. and Lewin, S.Z., Determination of density. In Weissberger, A. (Ed.), Physical Methods of Organic Chemistry, 3rd Edn., Techniques of Organic Chemistry, Vol. 1, Pt. 1, Interscience Publishers, New York, 1959, pp. 131–190.

Barton, A.F.M., Solubility parameters. Chem. Rev., 75 (1975) 731–753.

Ben-Naim, A., Hydrophobic Interactions, Plenum Press, New York, 1980.

Burrell, H., Solubility parameter values. In Brandrup, J. and Immergut, E.H. (Eds.), Polymer Handbook, John Wiley and Sons, New York, 1968, pp. IV.337–IV.359.

Chapman, D., The polymorphism of glycerides. Chem. Rev., 62 (1962) 433–456.

Cook, D.T., A Study of the Wetting Properties of a Hydrophobic Powder, Ph.D. Thesis, University of Nottingham, U.K., 1978, p. 49.

Elworthy, P.H. and Lipscomb, F.J., A note on the solubility of griseofulvin. J. Pharm. Pharmacol., 20 (1968) 790–792.

Exner, O., Additive physical properties. II. Molar volume as an additive property. Czech. Chem. Commun., 32 (1967) 1–23.

Exner, O., Dipole Moments in Organic Chemistry, Georg Thieme, Stuttgart, 1975, p. 108.

Eykman, J.F., Recherches réfractométriques (suite). Rec. Trav. Chim. Pays-Bas, 14 (1895) 185–202.

Fung, H.-L. and Higuchi, T., Molecular interactions and solubility of polar nonelectrolytes in nonpolar solvents. J. Pharm. Sci., 60 (1971) 1782–1783.

Grant, D.J.W. and Abougela, I.K.A., The fatty acid solvates of griseofulvin-desolvation data. J. Pharm. Pharmacol., 33 (1981) 619–620.

Grant, D.J.W. and Abougela, I.K.A., Solubility behaviour of griseofulvin in fatty acids. J. Pharm. Pharmacol., 34 (1982) 766–770.

Grant, D.J.W. and Abougela, I.K.A., A synthetic method for determining the solubility of solids in viscous liquids. Int. J. Pharm., 16 (1983) 11–21.

Higuchi, T., Richards, J.H., Davis, S.S., Kamada, A., Hou, J.P., Nakano, M., Nakano, N.I. and Pitman, I.H., Solvency and hydrogen bonding interactions in nonaqueous systems. J. Pharm. Sci., 58 (1969) 661–671.

Hildebrand, J.H. and Scott, R.L., The Solubility of Non-electrolytes, 3rd Edn., Reinhold Publishing, 1950, Dover Publications, New York, 1964, pp. 13, 274, 427.

Hildebrand, J.H., Prausnitz, J.M. and Scott, R.L., Regular and Related Solutions, Van Nostrand Reinhold, New York, 1970.

Hoy, K.L., New values of the solubility parameters from vapor pressure data. J. Paint Technol., 42 (1970) 76–118.

Karger, B.L., Snyder, L.R. and Eon, C., An expanded solubility parameter treatment for classification and use of chromatographic solvents and adsorbants. Parameters for dispersion, dipole and hydrogen bonding interactions. J. Chromatogr., 125 (1976) 71–88.

Keller, R.A., Karger, B.L. and Snyder, L.R., Use of the solubility parameter in predicting chromatographic retention and eluotropic strength. In Stock, R. (Ed.), Gas Chromatography—1970—Institute of Petroleum, London, 1971, pp. 125–140.

Kihara, T., Intermolecular Forces, translated by S. Ichimaru, John Wiley and Sons, Chichester, NY, 1976.

Lawson, D.D. and Ingham, J.D., Estimation of solubility parameters from refractive index data. Nature (Lond.), 223 (1969) 614–615.

Le Fèvre, R.J.W., Molecular refractivity and polarizability. Adv. Phys. Org. Chem., 3 (1965) 1–90.

Mehdizadeh, M. and Grant, D.J.W., unpublished observations (1982).

Minkin, V.I., Ospov, O.A. and Zhdanov, Y.A., Dipole Moments in Organic Chemistry, translated and edited by B.L. Hazzard and W.E. Vaughan, Plenum Press, New York, 1970, p. 204.

Rheineck, A.E. and Lin, K.F., Solubility parameter values based on group contributions. J. Paint Technol., 40 (1968) 611–616.

Riddick, J.B. and Bunger, W.B. In Weissberger (Ed.), Organic Solvents, Physical Properties and Methods of Purification, 3rd Edn., Techniques in Chemistry, Vol. II, Wiley-Interscience, New York, 1970, pp. 27–28, 70 et seq.

Scatchard, G., Equilibrium in non-electrolyte mixtures. Chem. Rev., 44 (1949) 7–35.

Sekiguchi, K., Ito, K., Owada, E. and Ueno, K., Studies on the method of size reduction of medicinal compounds. II. Size reduction of griseofulvin by solvation and desolvation method using chloroform. Chem. Pharm. Bull. (Tokyo), 12 (1964) 1192–1197.

Sekiguchi, K., Shirotani, K., Kanke, M., Furukawa, M. and Iwatsuru, M., Studies on methods of particle size reduction of medicinal compounds. VI. Solvate formation of griseofulvin with benzene and dioxane. Chem. Pharm. Bull. (Tokyo), 24 (1976) 1621–1630.

Sewell, J.H., A study of the cohesive forces, refractive indices and glass transition temperature data of polymers. Royal Aircraft Establishment, Technical Report No. 66185. Ministry of Aviation, Farnborough, Hampshire, U.K., 1966.

Shinoda, K., Principles of Solution and Solubility, translated by Becker, P., Marcel Dekker, New York, 1978, p. 67.

Sinanoglu, O. and Abdulnur, S., Effect of water and other solvents on the structure of biopolymers. Fed. Proc., 24 (1965) S.12–S.23.

Tanford, C., The Hydrophobic Effect: Formation of Micelles and Biological Membranes, 2nd Edn., John Wiley and Sons, New York, 1980, pp. 11–13.

Townley, E.R., Griseofulvin. In K. Florey (Ed.), Analytical Profiles of Drug Substances, Vol. 8, Academic Press, New York, 1979, pp. 219–249.

Vogel, A.I., Physical properties and chemical constitution. XXIII. Miscellaneous compounds. J. Chem. Soc., (1948) 1833–1855.

Weast, R.C., CRC Handbook of Chemistry and Physics, 63rd Edn., CRC Press, Boca Raton, FL, 1982, C313–C314.

Windholz, M., Budavari, S., Stroumtsos, L.Y. and Fertig, M.N. (Eds.), The Merck Index, 9th Edn., Merck and Co., Rahway, NJ, 1976, p. 590.

Yalkowsky, S.H. and Valvani, S., Solubility and partitioning I: Solubility of non-electrolytes in water. J. Pharm. Sci., 69 (1980) 912–922.