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A synthetic method for determining the solubility of solids in viscous liquids

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Summary

Measurement of the solubility of a solid in a viscous liquid at a predetermined temperature using an analytical method poses problems on account of the difficulty of removing excess of the suspended solid from the viscous solution at constant temperature. As an alternative, a simple synthetic method is proposed involving measurement of the temperature at which a stirred solute–solvent mixture of predetermined composition just forms a homogeneous solution. By means of this the equilibrium solubility temperature can be quickly bracketted to 1°C. From the solubility–temperature data thus obtained, ΔG, ΔH and ΔS for the solution process may be readily calculated. Furthermore, physicochemical interactions between a solid drug and a molten excipient may be studied at regions of composition in which other thermal methods of analysis may not be suitable.

Introduction

Preformulation studies frequently require knowledge of the solubility of a solid drug at a given temperature in a viscous liquid excipient, such as a molten suppository base, a viscous suspending agent or the molten vehicle of a solid dispersion system. In some cases a complete solubility–temperature profile of a drug in a viscous solvent system may be required. Under the above circumstances the

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usual analytical methods of measuring the solubility of the solid in the liquid solvent (Mader et al., 1959) may present problems owing to the difficulty of separating the excess of undissolved solid solute from the viscous saturated solution at constant temperature prior to analysis of the solution. Processes of filtration and centrifugation may be excessively slow and laborious and may consequently be subject to temperature changes which will alter the measured concentration at saturation.

Under the circumstances outlined above we propose a synthetic method (SM) of solubility measurement in which preselected compositions of the solute–solvent system are prepared and the temperature is measured at which the mixture just forms a homogeneous solution. This approach has been outlined in certain elementary physical chemistry texts (Goddard and James, 1967; Wallwork and Grant, 1977) and has been used extensively to determine the mutual solubility of liquid mixtures (Gordon and Scott, 1952; Mader et al., 1959). The synthetic method has, however, been little used in the pharmaceutical sciences despite its advantages in the situations outlined above. In the present report we describe our adaptation of the method for pharmaceutical systems and compare it with other, better known thermal methods of analysis, such as differential thermal analysis (DTA) and thermal microscopy (TM). We also show how the method lends itself to the determination of the thermodynamic quantities of solution of the solute in the solvent.

Apparent independent melting of the drug and the excipient, when examined at one or two compositions by a thermal method of analysis, is frequently encountered in preformulation studies. This behaviour is often assumed to indicate the absence of

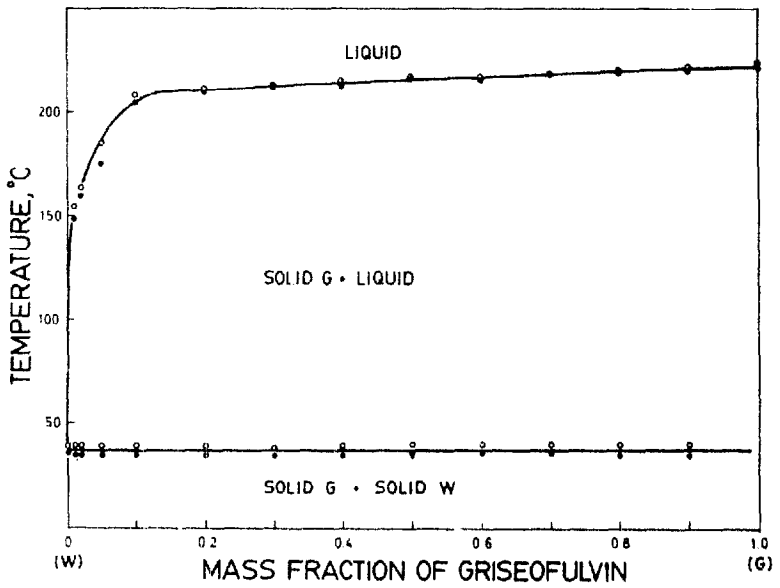

Fig. 1. Phase equilibrium diagram of ground physical mixtures of griseofulvin (G) and Witepsol E75 (W) determined by thermal microscopy: melting point or solidus (●); freezing point or liquidus (○). Differential thermal analysis failed to detect phase changes at mass fractions of G below 0.10 but confirmed the thermal microscopic data at mass fractions of G above 0.10. The thermal behaviour corresponds to a monotectic system.

interactions, but may actually reflect a monotectic system, for which Fig. 1 represents a typical phase diagram, determined by TM or DTA. The monotectic system was originally reported for silicon–tin melts (Bowden, 1938), but our studies have shown that it applies to the following drug–excipient mixtures: griseofulvin with polyethylene glycol 2000 (Kaur et al., 1980), and with glyceryl monostearate, Witepsol E75 (fatty suppository base), polyoxyethylene 40 stearate (Myrj 52), polyoxyethylene 23 lauryl ether (Brij 35), polyoxyethylene 20 sorbitan tristearate (Tween 65), sorbitan monostearate (Span 60), and stearic acid; ketoprofen or metronidazole with various triglycerides (Liversidge and Grant, 1982) and with *n*-eicosane; glyceryl monostearate with Witepsol E75 (fatty suppository base); and adipic acid with various fatty acids C_6–C_{14} (Fairbrother and Grant, 1980); binary mixtures of monoacid triglycerides of sufficiently different chain length (Liversidge and Grant, 1981).

The monotectic system (Fig. 1) can be regarded as a eutectic system with one arm missing, so that the lower melting substance at its freezing point replaces the eutectic point. Thus, the lower melting substance appears to melt independently of the presence of the higher melting substance. Monotectic systems arise when the binding forces (U) between the molecules of the lower melting component (the solvent, 1) and those of the higher melting component (the solute, 2) in the liquid state (l) are such that $U^l_{1,2} = U^l_{2,2} > U^l_{1,1}$, while in the solid state (s) the solute–solvent interaction is negligible, i.e. $U^s_{2,2}$ and $U^s_{1,1} \gg U^s_{1,2} = 0$ (Vasil'ev, 1964). The inability of the drug and the excipient to form a common crystal lattice is a general rule on account of differences in molecular shape and size and accounts for the rarity of true solid solutions (i.e. mix-crystals) in pharmaceutical systems.

The rising curve to the left of Fig. 1 corresponds to the solubility curve of the higher melting substance (usually the drug) in the liquid (which comprises the lower melting substance, usually the excipient). This part of the diagram, which corresponds to a solid dispersion system or suppository containing a small amount of drug dispersed in a much larger amount of lower melting excipient, may often represent the composition region for the fastest release of drug from these dosage forms. This rising curve may therefore be of potential importance, but its detection as a liquidus endotherm in DTA may be difficult at low levels of drugs, in which case the present method of determining the solubility curve is recommended.

Materials and Methods

Materials

Griseofulvin was a gift from ICI (Pharmaceuticals), Macclesfield, Cheshire, U.K. and consisted of angular crystals of specific surface area 308 $m^2 \cdot kg^{-1}$ and of volumetric median diameter 57.7 μm. The sample gave a single, sharp peak in DTA at the m.p. 222–224°C, which was confirmed by TM, and was stated by the manufacturers to contain at least 99% griseofulvin.

Witepsol E75 (batch no. W75 321, triglyceride suppository base) and Imwitor 900 (batch no. 340541, glyceryl monostearate, Eur. P. Vol. III) were gifts from Dyamit-

Nobel, Troisdorf, F.R.G. Glycerol monostearate self-emulsifying (S/E, batch no. MP 802-1891, containing 5% sodium stearate) was a gift from Croda Chemicals, Leek, Staffordshire, U.K. The following materials were gifts from Honeywill-Atlas: Span 60 (sorbitan monostearate, batch no. B. 404); Tween 65 (polyoxyethylene 20 sorbitan tristearate, batch no. BA-0932); Brij 35 (polyoxyethylene 23 lauryl ether, batch no. B.5373/81/84). Stearic acid (99%, batch no. 2207750) was purchased from B.D.H. Chemicals, Poole, Dorset, U.K.

Synthetic method (SM) of solubility determination

The solubility of a drug, such as griseofulvin, in each of the viscous liquid excipients was determined at a variety of temperatures using the following synthetic method (SM) in which each of various mass fractions, w_2, of griseofulvin (e.g. 0.01–0.05) just become soluble in the solvent. Fig. 2 shows the simple apparatus. The solvent (7–10 g) is placed in a large boiling tube surrounded by a paraffin bath. The paraffin bath is heated by an electrical hotplate under which a magnetic stirrer is fitted. Magnetic followers in the paraffin bath and boiling tube enable the paraffin and the solvent to be stirred simultaneously to maintain thermal equilibrium. If the solvent or solute is susceptible to aerial oxidation, this is prevented by passing nitrogen gas well above the surface of the liquid. Under these conditions evaporation

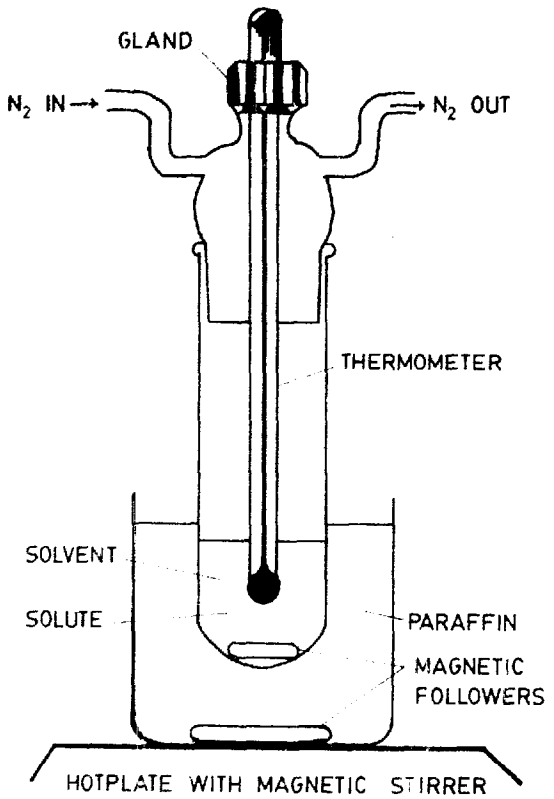

Fig. 2. Diagram of the apparatus used for the synthetic method for determining the solubility of drugs in viscous liquids.

of the solvent is negligible. A small amount of solute (about 1% w/w) is added to the solvent with stirring. While heating at a constant rate of 0.5–1.0°C/min, the temperature is noted at which the last crystal of drug just dissolves in the molten excipient. This temperature corresponds to the liquidus (i.e. freezing point) for the composition of the entire contents of the tube. After further accurate addition of a small amount of drug followed by further slow heating, the liquidus temperature is again determined. The liquidus temperatures recorded are each within 0.5–1°C of the true equilibrium temperature for the entire contents of the tube on account of the following observations: (a) the temperature is increased very slowly; (b) agitation is very rapid; (c) the temperatures are reproducible to within 0.5–1.0°C; (d) linear plots of log (solubility) against either the reciprocal or the logarithm of the absolute temperature are obtained as shown in Fig. 3. The correlation coefficient of each of these plots is invariably better than ± 0.995 and often better than ± 0.9995, provided that the solubility does not exceed about 5% (w/w).

In order to facilitate observation of the last few remaining crystals, the solution may be illuminated by a microscope lamp placed behind the glass assembly and the solution viewed with a lens placed in front. These are not shown in Fig. 2. Paraffin tends to discolour during repeated heating, thereby obscuring accurate observation and allowing any untoward decomposition to pass undetected. This may be obviated by using a clear silicone oil instead of paraffin.

Differential thermal analysis (DTA)

Differential thermal analysis (DTA) was carried out in a Stanton-Redcroft model 671 Thermal Analyzer coupled to a two-channel potentiometric recorder (Servoscribe 2S, Smiths Industries). Samples of mass 5–15 mg were heated at 2–10°C/min using alumina as the reference material and static air as the gas phase. The instrument was calibrated using benzoic acid, thermochemical grade (B.D.H. Chemicals). For each DTA peak (first-order or enthalpic transition), tangents at the steepest slope of the curve were drawn on each side of the summit. The onset of the transition (melting point or solidus) was taken to be the temperature corresponding to the point of intersection of the low temperature tangent and the base line. The culmination of the transition (freezing point or liquidus) was taken to be the temperature corresponding to the point of intersection of both tangents. For each transition both temperatures are presented in Fig. 1 and Table 1.

Thermal microscopy (TM)

For thermal microscopy (TM), also known as hot-stage microscopy, a fraction of 1 mg of sample was placed between a microscope slide and a cover-slip in a Kofler hot-stage microscope (Reichert, Austria) fitted with polarizers, and the temperature was increased at a rate of 1–5°C/min. The temperature was noted at which crystals of the solute (the drug) appeared to begin to melt or dissolve in the molten excipient and again at which melting or dissolution of the solute was complete. For each process of melting or dissolution, both temperatures are presented in Fig. 1 and Table 1, and agree more or less closely with the temperatures of the corresponding transition obtained from DTA.

Sample preparation for DTA and TM

The mixtures of drug and excipient used for these techniques were either physical mixtures of the two components, which had been ground together in an agate pestle and mortar, or cooled, ground melts which had previously been heated to 60°C and maintained at that temperature for 10 min, cooled to 20°C and again ground. Samples prepared by these two different techniques showed essentially the same behaviour in DTA and TM.

Results and Discussion

Table 1 compares the solubility temperatures determined by the synthetic method (SM) with the liquidus temperatures determined by TM and DTA for various compositions of griseofulvin with various viscous excipients. DTA was usually too insensitive to detect the liquidus of the solute when present at a mass concentration less than 10% (w/w). Furthermore, neither DTA nor SM were able to give a precise value of the liquidus temperature. Instead these techniques showed dissolution or melting of griseofulvin over a range of temperature. This may be attributed to poor solid–liquid equilibration in DTA and TM on account of the absence of agitation in these essentially static techniques. In most cases the equilibrium solubility temperature determined by SM was within the range of the liquidus temperatures determined by TM or DTA. When the TM or DTA temperature range was above the SM temperature, griseofulvin was probably dissolving more slowly in the viscous excipient in TM or DTA than in SM. The reverse situation, which occurred at the lowest griseofulvin concentrations, i.e. 1 and 2% w/w, also suggests that DTA behaviour is unrepresentative, since good linear correlations of the van 't Hoff plots were always obtained as exemplified by Fig. 3a. With TM, there is an added danger that the sample being examined is so small that it is unrepresentative.

The influence of the absolute temperature, T, on the solubility, often expressed as mole fraction, x_2^{sat}, is frequently represented by the van 't Hoff (1886) equation, thus:

$$\frac{d\ln x_2^{sat}}{dT} = \frac{\Delta H_2}{RT^2} \tag{1}$$

$$\text{i.e. } \ln x_2^{sat} = -\frac{\Delta H_2}{R} \cdot \frac{1}{T} + \text{constant} \tag{2}$$

or in terms of the following equation due to Hildebrand (1952) and described by Hildebrand et al. (1970):

$$\frac{d\ln x_2^{sat}}{d\ln T} = \frac{\Delta S_2}{R} \tag{3}$$

$$\text{i.e. } \ln x_2^{sat} = \frac{\Delta S_2}{R} \cdot \ln T + \text{constant}' \tag{4}$$

TABLE 1

COMPARISON BETWEEN THE SYNTHETIC METHOD (SM) AND THE THERMAL MICROSCOPIC METHOD (TM) FOR THE DETERMINATION OF SOLUBILITY TEMPERATURES (i.e. LIQUIDUS TEMPERATURES) OF GRISEOFULVIN IN VARIOUS VISCOUS EXCIPIENTS

Mass percent (% w/w) of griseofulvin	Correlation coefficient [a] for SM	Solubility temperature [b] (°C) by SM	Liquidus temperature (°C) by TM [c]
Solvent = glyceryl monostearate (Imwitor 900, m.p. [d] = 58–60°C)			
1		140	130–134, 125–130
2		151.5	–, 142–150
3	$r = -0.9950$	160	155–158, –
4		165	–, –
5		170	168–171, 170–181
Solvent = glyceryl monostearate self-emulsifying (S/E, m.p. [d] = 55–58°C)			
1		145	127–134, 125–130
2		160	160–166, 142–150
3	$r = -0.9999$	170	–, –
4		177	–, –
5		183	176–183, 170–181
Solvent = Witepsol E75 (m.p. [d] = 36–39°C)			
1		147	148–154
2		162.5	159–163
3	$r = -0.9993$	171.5	–
4		177.5	–
5		184.5	175–185
Solvent = sorbitan monostearate (Span 60, m.p. [d] = 56–63°C)			
1		126	–
2		131	–
3	$r = -0.9980$	134	–
4		136.5	–
5		139	158–165 [e]
Solvent = polyoxyethylene 20 sorbitan tristearate (Tween 65, m.p. [d] = 28–38°C)			
1		120	–
2		129	76–84
3	$r = -0.9988$	133	–
4		137	–
5		140	142–148
Solvent = polyoxyethylene 23 lauryl ether (Brij 35, m.p. [d] = 41–44°C)			
1		94.5	–
2		98	–
3	$r = -0.9956$	101	130–149.5
4		103	–
5		105	158–167.5
Solvent = stearic acid (m.p. [d] = 70–72°C)			
1		120	–
2		136	134–140
3	$r = -0.9999$	146	–
4		153	–
5		159	172–180

[a] Correlation coefficient for 5 data points in van 't Hoff (1886) plots of ln(molal solubility) against 1/(absolute temperature) (e.g. Fig. 3a).

[b] The stated solubility temperatures are the mean of 3 measurements differing by not more than 1°C and are quoted to the nearest 0.5°C.

[c] DTA was usually too insensitive to detect the liquidus of the solute when present at less than 10% (w/w).

[d] Melting points of the neat solvents were determined by TM and confirmed by DTA.

[e] DTA afforded the liquidus temperatures 152–167°C in this case.

ΔH_2 and ΔS_2 are, respectively, the apparent differential enthalpy and entropy of solution and are assumed to be independent of temperature, which may not be true over a temperature range of 20–30°C. Furthermore, since mole fraction has taken the place of the activity, a_2, of the solute in the above equations, the calculated enthalpy or entropy may not be the actual value, because each includes a function which characterizes the extent of deviation from ideal behaviour as represented by variations in activity coefficient, $\gamma_2 = a_2/x_2$ (Hollenbeck, 1980). Ideal behaviour in this sense is represented either by Raoult's law, corresponding to $a_2 = x_2$, or by Henry's law, corresponding to a proportional relationship between a_2 and x_2. The latter condition is likely to be valid for $x_2^{sat} \leqslant 0.05$, in the case of solute–solvent combinations of low solubility, but may extend to $x_2^{sat} \leqslant 0.2$ for more soluble combinations which approximate more closely to ideal behaviour.

Solubilities determined by the proposed synthetic method at various temperatures in fact conform closely to both Eqns. 1 and 3, since plots of $\ln x_2^{sat}$ against either $1/T$ (eqn. 2) or $\ln T$ (eqn. 4) are linear with good correlations (r better than ± 0.995). This is exemplified by the solubility of griseofulvin (0–5% w/w) in various lipoidal materials, such as fatty acids (Grant and Abougela, 1982), glycerides, neat polymers (e.g. polyoxyethylenes), neat surfactants (e.g. polyoxyethylene esters, polyoxyethylene ethers, polyoxyethylene sorbitan esters, sorbitan esters) and by metronidazole (0–0.5% w/w) or ketoprofen (0–15% w/w) in various mono-acid triglycerides (Liversidge and Grant, 1982). These examples encompass a wide range of concentrations and equilibrium temperatures (40–180°C).

Many pharmaceutical excipients are polymers or mixtures of substances of differing molecular weight. Under these circumstances the molecular weight of the solvent is very large or uncertain, so that mole fraction has little meaning. It is then preferable to express solubility as a molality, m_2^{sat}, as in Fig. 3. Under these circumstances x_2^{sat} in Eqns. 1–4 may be replaced by m_2^{sat} with little error since, for

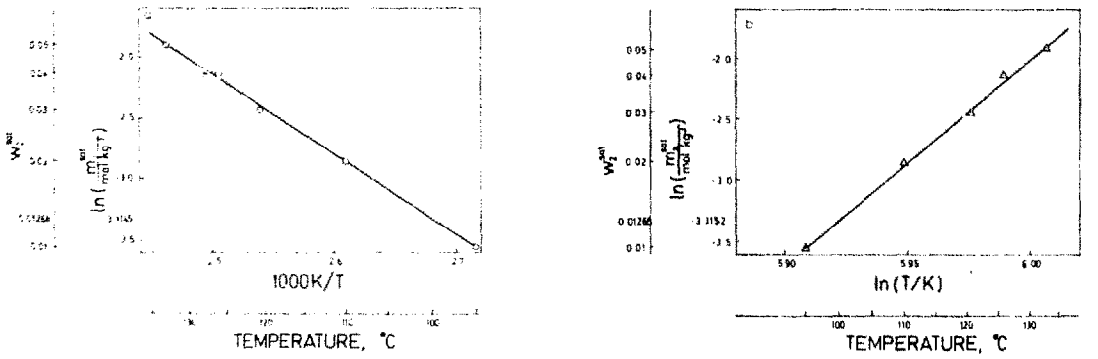

Fig. 3. Plots of the temperature dependence of the logarithm of the molal solubility, m_2^{sat}, (and the mass fraction solubility, w_2^{sat},) of griseofulvin in polyoxyethylene 10 stearyl ether (Brij 76): (a) according to van 't Hoff (1886): Eqn. 2, $\Delta H_2 = 54.4$ kJ·mol^{-1}, $r = -0.9992$); and (b) according to Hildebrand et al. (1970): Eqn. 4, $\Delta S_2 = 141$ J·K^{-1}·mol^{-1}, $r = 0.9991$). The dotted lines refer to interpolation at 373.15K (100°C) from which (a) gives $\Delta G_2^{\theta} = -10.3$ kJ·mol^{-1} and $\Delta S_2^{\theta} = 118$ J·K^{-1}·mol^{-1} while (b) affords $\Delta G_2^{\theta} = -10.3$ kJ·mol^{-1} and $\Delta H_2^{\theta} = 42.3$ kJ·mol^{-1}, the standard state being a hypothetical solution of unit molality ($m_2 = 1$ mol·kg^{-1}) which has the properties of an infinitely dilute solution.

dilute solutions, m_2 is proportional to x_2 and since it may be no less accurate to assume that $m_2 \propto a_2$ than to assume $x_2 \propto a_2$. It is generally inappropriate to express solubility in molar concentration units ($mol \cdot dm^{-3}$), since the density of the solution decreases appreciably with increasing temperature, thereby causing ΔH_2 and ΔS_2 to be in error unless corrected for the appropriate temperature coefficient of the density.

For the purposes of comparison, the standard state may be taken to be a hypothetical solution of unit molality ($m_2 = 1\ mol \cdot kg^{-1}$) which possesses the properties of an infinitely dilute solution at a defined temperature, T'. This temperature may be the biological temperature, 310.15K (37°C) for drugs in suppository excipients (Liversidge and Grant, 1982), or 373.15K (100°C) for griseofulvin in fatty acids (Grant and Abougela, 1982) and for griseofulvin in certain other pharmaceutical excipients, as in Fig. 3. The standard free energy of solution is then given by

$$\Delta G_2^\theta = -RT \cdot \ln m_2^{sat}(\text{at } T') \tag{5}$$

From ΔG_2^θ and ΔH_2 (by the van 't Hoff (1886) plot, e.g. Fig. 3a) ΔS_2^θ may be calculated. Alternatively, from ΔG_2^θ and ΔS_2 (by the Hildebrand (1952) plot, e.g. Fig. 3b) ΔH_2^θ may be calculated. The two different types of plot may yield slightly different values of ΔH_2 and ΔS_2 on account of the slightly different assumptions inherent in the approximate relations represented by Eqns. 2 and 4. Thus, although data obtained from temperature coefficients of solubility may not be particularly accurate, the proposed synthetic method readily enables approximate thermodynamic quantities of the solution process to be calculated for the purposes of comparison of the various excipients in pre-formulation studies of a given drug. The data so obtained may be complementary to those determined chromatographically (Horn and Ditter, 1982) but may be more easily determined experimentally.

The possibility of thermal decomposition of the drug substance should, of course, be checked after any thermal method of analysis, such as DTA, TM and the proposed synthetic method. Significant decomposition of the drug in the molten excipient matrix could cause some lowering of the measured temperatures, a lack of validity of Eqns. 2 and 4 and the introduction of errors into the phase diagram (e.g. Fig. 1) and into the solubility plots (e.g. Fig. 3). In some cases the molten excipient may react chemically with the drug or may catalyze its decomposition. For example, polyoxyethylenes rapidly inactivate penicillin and bacitracin, are incompatible with phenols (Martindale. 1982), and catalyze the decarboxylation of sodium sulindac at elevated temperatures (Selby, 1978). The drug used in the present work, griseofulvin, is relatively stable up to its melting point and thin-layer chromatography (TLC; Townley, 1979) of the drug-excipient mixtures after thermal analysis showed no new spots that could be attributed to decomposition products of the drug. Furthermore, the linearity of the derived solubility plots in Fig. 3 and the high correlation coefficients shown in Table 1 militate against the decomposition of griseofulvin. In general, however, whenever the proposed SM or other thermal method is used for phase solubility analysis, the possibility of thermal decomposition of the drug in the molten excipient matrix should be borne in mind or some independent analytical

method should be applied to determine the chemical integrity of the drug in question. For this purpose, chromatographic methods, such as TLC or HPLC, may be particularly valuable.

The criteria for equilibrium in the proposed synthetic method are stated in the Materials and Methods section. An additional criterion for equilibrium might be the reversibility of the dissolution process, corresponding to growth of crystals of the solute at a temperature just below the equilibrium solubility temperature (about 0.5–1.0°C less). This criterion may be quite valid and reliable for pure solvents of low viscosity. In general, however, it must be borne in mind that crystal growth is a process of mass transfer and its rate decreases with increasing viscosity of the solution, corresponding to decreasing diffusivity of the solute and is, moreover, frequently inhibited by the presence of crystal 'poisons', such as surfactants and traces of impurities in the solvent (Buckley, 1951; Mullin, 1972). Since pharmaceutical excipients frequently exhibit relatively high viscosities and often consist of mixtures of molecules, the criterion of reversibility of crystal dissolution and crystal growth may not be fair or reliable and has been omitted from the present method. The criteria stated for equilibrium are in practice quite sufficient to ensure that the solubility temperatures actually measured are uniformly close to the true equilibrium values and the results obtained support this.

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