What is the True Solubility Advantage for Amorphous Pharmaceuticals?

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Purpose. To evaluate the magnitude of the solubility advantage for amorphous pharmaceutical materials when compared to their crystalline counterparts.

Methods. The thermal properties of several drugs in their amorphous and crystalline states were determined using differential scanning calorimetry. From these properties the solubility advantage for the amorphous form was predicted as a function of temperature using a simple thermodynamic analysis. These predictions were compared to the results of experimental measurements of the aqueous solubilities of the amorphous and crystalline forms of the drugs at several temperatures.

Results. By treating each amorphous drug as either an equilibrium supercooled liquid or a pseudo-equilibrium glass, the solubility advantage compared to the most stable crystalline form was predicted to be between 10 and 1600 fold. The measured solubility advantage was usually considerably less than this, and for one compound studied in detail its temperature dependence was also less than predicted. It was calculated that even for partially amorphous materials the apparent solubility enhancement (theoretical or measured) is likely to influence *in-vitro* and *in-vivo* dissolution behavior.

Conclusions. Amorphous pharmaceuticals are markedly more soluble than their crystalline counterparts, however, their experimental solubility advantage is typically less than that predicted from simple thermodynamic considerations. This appears to be the result of difficulties in determining the solubility of amorphous materials under true equilibrium conditions. Simple thermodynamic predictions can provide a useful indication of the theoretical maximum solubility advantage for amorphous pharmaceuticals, which directly reflects the driving force for their initial dissolution.

KEY WORDS: amorphous; crystal; solubility; dissolution.

INTRODUCTION

The existence of drugs and excipients in multiple physical forms (*e.g.*, polymorphs, isomers) provides pharmaceutical scientists with an opportunity to select the preferred form(s) of the materials used in a formulation. This is very useful since critical properties, such as particle morphology and solubility, frequently vary between the different physical forms of a material. The amorphous form of pharmacologically active materials has received considerable attention because in theory this form represents the most energetic solid state of a material (Figure 1), and thus it should provide the biggest advantage in terms of solubility and bioavailability (1). Additionally, it may provide significant changes from the usual crystalline form in terms of its mechanical properties, such as elastic modulus.

For different crystalline forms (*e.g.*, polymorphs) the improved solubility of higher energy structures can be reliably estimated from a knowledge of the thermodynamic properties of the different forms (2). This is most simply achieved when data for the melting point, heat of fusion, and heat capacity of each form are available (*e.g.*, (3)). In many cases it is also possible to directly measure the improvements in solubility and biopharmaceutical performance for such metastable crystal systems (4,5). A consideration of the data in the literature indicates that improvements in solubility resulting from the use of alternate crystal forms can be expected to be as high as two fold (see later for details), and increases in maximum human plasma concentrations of up to six fold may be achieved (4).

The measurement and estimation of the solubility and bioavailability improvements that can be attained by using an amorphous form of a drug presents a more significant challenge because of the far from equilibrium nature of the amorphous state. Thermodynamic predictions of solubility enhancements have not been widely reported because of the difficulties involved in accurately characterizing amorphous drugs in terms of equilibrium thermodynamic properties. Similarly, the determination of meaningful experimental solubilities for amorphous pharmaceutical materials has been found to be extremely difficult because of the tendency for such materials to rapidly revert to the crystalline state upon exposure to small quantities of solvents (*e.g.*, water vapor). Several reports in the literature indicate that the solubility advantage for amorphous drug forms may be quite significant, for example, 1.4 fold for indomethacin (6), 2 fold for cefalexin (7), 2.5 fold for tetracycline (8), and approximately 10 fold for a macrolide antibiotic (9) and novobiocin acid (10). Notably almost all workers cite significant experimental difficulties during solubility measurements due to crystallization of the amorphous drug, and thus their reported experimental solubility ratios are probably underestimates of the true values for these materials. Only a few pharmacokinetic investigations have been reported (in animals) (*e.g.*, (11)), however these indicate that one should expect quite large improvements in the biopharmaceutical performance of amorphous drugs.

In summary, in contrast to polymorphic crystalline drug forms, a simple method to estimate the theoretical maximum solubility of amorphous pharmaceuticals has not yet been proposed, nor has a consistent accurate method for assessing their apparent equilibrium solubilities been reported. Thus, the objective of the work reported herein was to use a simple thermodynamic approach to estimate the theoretical maximum solubility improvement that can be achieved using amorphous compounds and to compare the resulting values with conventionally measured solubility data. It was hoped that this approach would provide an estimate of the increased driving force for the dissolution of amorphous drug forms and indicate its relation to experimentally determined solubility values. To achieve this objective the thermal properties of several drugs were measured using differential scanning calorimetry for use in the solubility calculations. Experimental solubility values were measured directly and/or collated from the literature and then compared to the predicted values.

MATERIALS AND METHODS

Materials

Indomethacin, a hydrophobic poorly water soluble drug, was chosen for detailed characterization and study. Several

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other drugs (*i.e.*, glibenclamide, griseofulvin, hydrochlorthiazide, polythiazide) were studied in less detail. All compounds were obtained in their thermodynamically most stable crystalline form from Sigma Chemical Co., St. Louis, MO. The metastable α-polymorph of indomethacin was prepared by precipitation from a saturated methanol solution with water. The amorphous form of each compound was produced by quench cooling molten material in liquid nitrogen. The identity of the different drug forms was established using differential scanning calorimetry and powder X-ray diffraction experiments (see below). All solid samples were stored in a dry environment (over silica gel) and were presented for analysis as powders of less than 120 US mesh size (~ 125 μm).

Thermal Analysis

Powder samples of 5–10 mg were analyzed by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) using a Seiko-220 thermal analysis system (Haake, Paramus, NJ). Both TGA and DSC experiments were performed in a dry nitrogen atmosphere (60–100 ml/minute), heating the samples at a rate of 10°C/minute from ambient temperature to above their melting point(s). Calibration of the instruments with respect to temperature and/or enthalpy was achieved using high purity standards of indium, tin and gallium. Sample pans were made of alodined aluminum and were used with a vented cover. The mean results of triplicate determinations are reported.

Powder X-ray Diffraction

Powder x-ray diffraction measurements were used to confirm the crystalline or amorphous nature of the starting materials and to identify the solids remaining in suspension at the end of the solubility experiments. A Scintag XDS-2000 instrument (Scintag, Cupertino, CA) with a nickel filtered copper radiation source was used and scans were taken between 2° and 70° 2θ. Samples were presented as lightly compacted powder disks.

Solubility Predictions

Predictions of the relative solubilities of the various crystalline and amorphous forms of each drug were performed according to the method of Parks and co-workers (12,13). In this method the solubility ratio (σ^a/σ^c) of the two forms (amorphous = a; crystalline = c) being examined at any given temperature (T) is considered to be directly related to the free energy difference (ΔG) between those two forms (Fig. 1):

$$\Delta G_T^{a,c} = - R\ T\ \ln\ (\sigma_T^a/\sigma_T^c) \quad (1)$$

where R is the gas constant. The difference in free energy is estimated from the entropy (S) and enthalpy (H) differences between the two forms:

$$\Delta G_T^{a,c} = \Delta H_T^{a,c} - (T\ \Delta S_T^{a,c}) \quad (2)$$

and these enthalpy and entropy differences are calculated from the melting points (T_f^c), enthalpy and entropy of fusion (ΔH_f^c & ΔS_f^c), and isobaric heat capacities (C_p^c, C_p^a) as follows:

$$\Delta H_T^{a,c} = \Delta H_f^c - (C_p^a - C_p^c)(T_f^c - T) \quad (3)$$

$$\Delta S_T^{a,c} = \Delta S_f^c - (C_p^a - C_p^c)(\ln\ (T_f^c/T)) \quad (4)$$

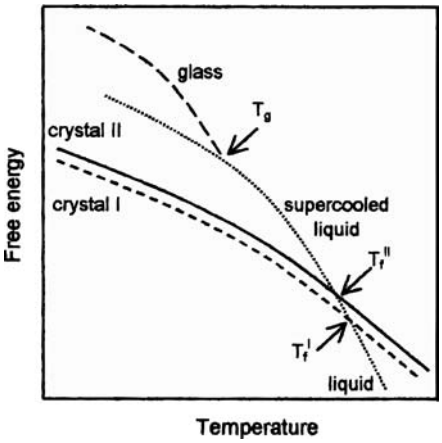

Fig. 1. Schematic free-energy diagram for amorphous and crystalline materials (see text for explanation of abbreviations).

$$\Delta S_f^c = \Delta H_f^c/T_f^c \quad (5)$$

This simple approach treats the amorphous form as a pseudo-equilibrium solid state at all temperatures below the melting point, and it is analogous to that which has been successfully used to estimate the relative solubilities of different crystalline polymorphs (2,14). In such instances the heat capacity difference between the two forms (ΔC_p) is usually assumed to be constant, and has often been approximated by $\Delta C_p \approx 0$ or $\Delta C_p \approx \Delta S_f$ when experimental heat capacity data at the temperatures of interest are not available (15–17). In this study actual data for the heat capacity of the amorphous and crystalline forms of indomethacin (18) were used for the calculations, and comparisons were then made with results attained using the commonly applied approximations. Heat capacity differences between the glassy and equilibrium supercooled liquid forms measured at the glass transition (ΔC_{pTg}) were also available for each of the materials studied and were used for some of the solubility predictions.

Solubility Measurements

Solubility measurements for indomethacin in deionized water were made using a closed, flat-bottomed, water-jacketed, glass vessel (70 mm height × 70 mm diameter) with an overhead 3-blade propeller stirrer operating at ~300 rpm. After equilibration at the desired temperature an excess of powdered drug was placed in the empty vessel, the stirrer started, and then two hundred milliliters of water were added to the vessel. At regular intervals a sample (~15 ml) of the liquid phase was withdrawn through a 0.22 μm filter and replaced with deionized water of the same temperature. Following dilution with a standard solution of indomethacin in 50:50 methanol/water, the concentration of indomethacin in each sample was determined by UV-visible spectrometry at wavelengths of 266 and 318 nm. Solubility versus time profiles (over a 120 minute period) were determined at least four times for each form of the drug and at three different temperatures (5°C, 25°C, 45°C). The coefficient of variation for replicate determinations was approximately five percent and mean values are reported.

Table 1. Thermal Properties of Different Forms of Indomethacin Measured by Differential Scanning Calorimetry

Form	T_g (°C)	ΔC_{pTg} (J/gK)	T_f^c (°C)	ΔH_f^c (J/g)
γ-Crystal	—	—	162	102
α-Crystal	—	—	156	101
Amorphous	42	0.41	—	—

RESULTS

Characterization of Raw Materials

The experimentally determined thermal properties of the different forms of indomethacin are summarized in Table 1, and these results are in close agreement with those previously reported (19,20). The two polymorphic crystal forms differed in their melting point by approximately 6°C and were energetically very similar. The amorphous form was a glass at room temperature and required moderate heating (to above 42°C) to attain the equilibrium supercooled liquid state. The identity of the various indomethacin forms was confirmed using X-ray powder diffraction experiments and comparison to reference data (19). The thermal properties of the other drugs studied were taken from the literature (3–5,12,13, 21) or measured by DSC. These results are presented in the footnote to Table 2.

Solubility Predictions

The predicted solubility ratios for the amorphous and α-crystal forms of indomethacin relative to the γ-crystal form are summarized in Table 2. A detailed analysis of these predictions will be included in the discussion section. The solubility ratios calculated for the other drugs considered are also summarized in Table 2. The magnitude of the predicted solubility advantage for different crystalline polymorphs ranged from 1.1 to 3.6 fold, whereas the predicted solubility ratio for the amorphous drug forms varied between 12 and 1652 fold.

Solubility Measurements

The experimentally determined solubility versus time profiles for the various indomethacin forms are shown in Figs. 2a, 2b and 2c. At 5°C the enhanced solubility of the amorphous form relative to the γ-crystal is clearly seen. A maximum solubility for the amorphous form occurred at approximately 10 minutes and the solubility of the γ-crystal form reached a constant value at approximately the same time in the experiment. At 25°C the maximum in the solubility versus time profile for the amorphous form was more pronounced. The peak solubility occurred within the first 10 minutes of the experiment and the solubility of the amorphous form was consistently greater than that of the γ-crystal form. At 45°C the peak solubility for the amorphous form occurred very rapidly and declined equally quickly. The α-crystal polymorphic form also had a modestly improved solubility relative to the γ-crystal form at 45°C. The maximum solubility ratios attained at each temperature for the indomethacin forms are summarized in Table 3, along with selected data for other drugs which have been reported in the literature. These literature data were chosen based on their apparent reliability and the possibility of being able to compare them with predicted values (*i.e.*, both thermodynamic and solubility data were available). The experimental

Table 2. Predicted Solubility Ratios for Indomethacin and Other Drug Compounds

Compound	Forms	Solubility ratio[a]	Comment
This work:			
Indomethacin	α-crystal/γ-crystal	1.1 - 1.2	45°C
Indomethacin	amorphous/γ-crystal	38 - 301	5°C
		25 - 104	25°C
		16 - 41	45°C
Literature:			
Carbamezapine (3)	III-crystal/I-crystal	1.7 - 2.1	2°C
		1.7 - 2.0	12°C
		1.6 - 2.0	17°C
		1.6 - 1.9	26°C
		1.6 - 1.8	40°C
		1.5 - 1.7	58°C
Chloramphenicol palmitate (4)	A-crystal/B-crystal	3.6	30°C
Iopanoic acid (21)	II-crystal/I-crystal	2.3 - 2.8	37°C
Mefenamic acid (5)	I-crystal/II-crystal	1.5	30°C
Glibenclamide[b]	amorphous/crystal	112 - 1652	23°C
Glucose (12,13)	amorphous/crystal	16 - 53	20°C
Griseofulvin[c]	amorphous/crystal	38 - 441	21°C
Hydrochlorthiazide[d]	amorphous/crystal	21 - 113	37°C
Iopanoic acid (21)	amorphous/I-crystal	12 - 19	37°C
Polythiazide[e]	amorphous/crystal	48 - 455	37°C

[a] The range of values reflects the use of different ΔC_p values for the calculations (see text for details).
[b] Glibenclamide: T_g = 58°C, ΔC_{pTg} = 0.45 J/g/K, T_f = 177°C, ΔH_f = 108 J/g.
[c] Griseofulvin: T_g = 91°C, ΔC_{pTg} = 0.36 J/g/K, T_f = 221°C, ΔH_f = 107 J/g.
[d] Hydrochlorthiazide: T_g = 112°C, ΔC_{pTg} = 0.31 J/g/K, T_f = 274°C, ΔH_f = 104 J/g.
[e] Polythiazide: T_g = 73°C, ΔC_{pTg} = 0.34J/g/K, T_f = 220°C, ΔH_f = 97 J/g.

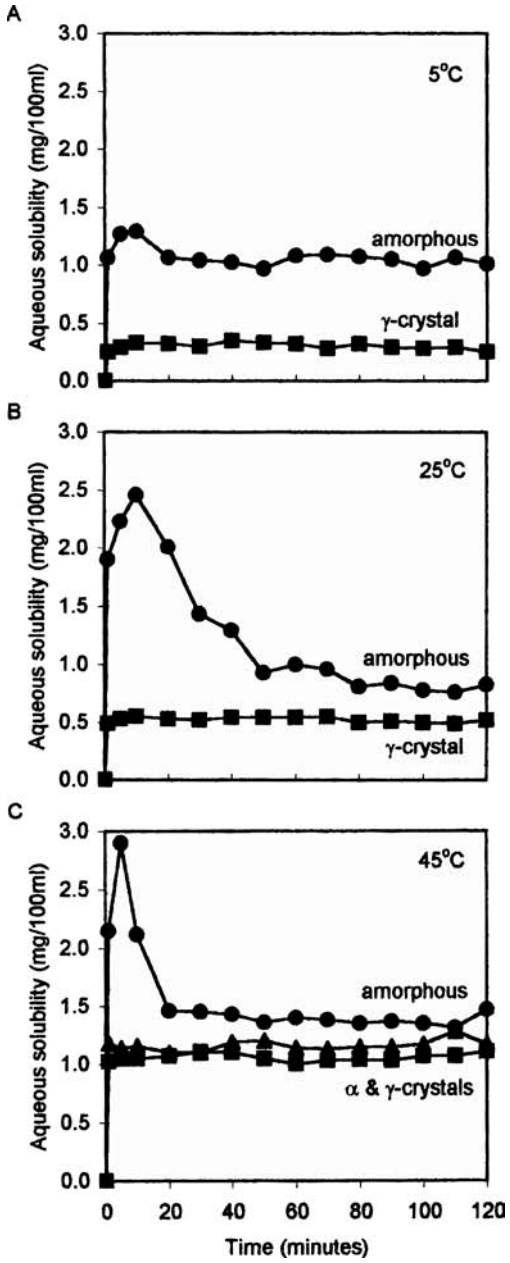

Fig. 2. Experimental aqueous solubility profiles for amorphous and crystalline indomethacin (● amorphous; ■ γ-crystal; ▲ α-crystal) (A) at 5°C (B) at 25°C (C) at 45°C.

solubility ratios varied between 1.1 and 4.0 for the crystalline polymorphs and 1.1 and 24 for the amorphous forms.

Characterization of Undissolved Material

Immediately after each experimental solubility determination with the different forms of indomethacin the solid material suspended in the dissolution medium was recovered. This was achieved by filtration and vacuum drying, and the recovered material was then analyzed by DSC, TGA and powder X-ray diffraction. The identities of the solid materials were ascertained by comparison to reference data (19) and are summarized in Table 4.

DISCUSSION

Predicted Solubilities

The solubility ratios predicted for the amorphous indomethacin from 0°C to the crystalline melting point using the different heat capacity approximations are shown in Fig. 3a. Because of the relatively large difference in free energy between the crystalline and amorphous forms of the drug the magnitude of the predicted solubility ratio is considerably higher than that recorded for the α-crystal polymorph. The temperature dependence of the solubility ratio for the amorphous form is approximately logarithmic in all instances and the solubility ratio increases with decreasing temperature. Whereas for typical crystalline polymorphs the effects of changes in ΔC_p are quite small (15–17) the effects on the predictions for the amorphous form are quite large. Comparison of the predictions for the amorphous indomethacin made using the approximations $\Delta C_p^{a,c} \approx 0$, $\Delta C_p^{a,c} \approx \Delta C_{ptg}$ or $\Delta C_p^{a,c} \approx \Delta S_f^c$ with that made using experimentally measured heat capacity data reveals some interesting features. For the experimental heat capacity data the prediction follows the case where $\Delta C_p^{a,c} \approx \Delta C_{pTg}$ above T_g. At T_g, where the heat capacity changes, there is a stepwise change in the predicted solubility ratio and the predicted values below T_g follow the case where $\Delta C_p^{a,c} \approx 0$. The case where $\Delta C_p^{a,c} \approx \Delta S_f^c$ provides an intermediate estimate of the solubility ratio at all temperatures. It can be clearly seen from this analysis that there should be a significant stepwise increase in the solubility advantage at the glass transition temperature and the most appropriate ΔC_p approximation is different above and below T_g. These features were not noted by Parks and co-workers in their studies of the solubility of amorphous glucose because all of their work was performed at temperatures above the glass transition temperature (12). The significance of these findings to the behavior of pharmaceutical dosage forms containing amorphous drug forms with glass transition temperatures which are close to physiological and/or ambient temperatures (*e.g.*, indomethacin) is obvious.

Experimental Solubilities

The experimentally measured solubilities of amorphous indomethacin were consistently greater than those of the γ-crystalline form over a 40°C range in temperature and for a period of at least two hours following the start of the solubility determinations (Figs. 2a, 2b & 2c). The peak solubility for the amorphous indomethacin always occurred within the first 10–15 minutes of the experiment and was as much as two fold greater than the 'steady-state' solubility achieved at the end of the experiments. It appeared that the higher the temperature the more pronounced was the peak in the solubility versus time profile. Over the duration of the solubility experiments the amorphous starting material partially converted to the two most common crystalline polymorphs (Table 4). This change in phase may have been mediated by dissolution in and supersaturation of the aqueous dissolution media. Alternatively, it may only have been necessary to expose the solid amorphous indomethacin to the solvent molecules in order to trigger crystallization in the solid state (22). Whatever the means of interconversion, it is clear that initially the amorphous drug was very highly soluble in the aqueous dissolution medium but that the maximum level of supersaturation relative to the solubility of the

Table 3. Experimental Solubility Ratios for Indomethacin and Other Drug Compounds

Compound	Forms	Solubility ratio	Comments
This work:			
Indomethacin	α-crystal/γ-crystal	1.1	45°C, water
Indomethacin	amorphous/γ-crystal	4.4	5°C, water
		4.5	25°C, water
		2.8	45°C, water
Literature:			
Carbamezapine (3)	III-crystal/I-crystal	1.3	2°C, 2-propanol
		1.4	12°C, 2-propanol
		1.2	17°C, 2-propanol
		1.2	26°C, 2-propanol
		1.1	40°C, 2-propanol
		1.1	58°C, 2-propanol
Chloramphenicol palmitate (4)	A-crystal/B-crystal	4.0	30°C, 35% *t*-butanol (aq.)
Iopanoic acid (21)	II-crystal/I-crystal	1.6	37°C, phosphate buffer (aq.)
Mefenamic acid (5)	I-crystal/II-crystal	1.3	30°C, dodecyl alcohol
Glibenclamide (30)	amorphous/crystal	14	23°C, buffer (aq.)
Glucose (12,13)	amorphous/crystal	24	20°C, methanol
		21	20°C, ethanol
		16	20°C, isopropyl alcohol
Griseofulvin (29)	amorphous/crystal	1.4	21°C, water
Hydrochlorthiazide (23)	amorphous/crystal	1.1	37°C, HCl & PVP (aq.)
Iopanoic acid (21)	amorphous/I-crystal	3.7	37°C, phosphate buffer (aq.)
Polythiazide (23)	amorphous/crystal	9.8	37°C, HCl & PVP (aq.)

γ-crystal form could not be sustained. Thus the measured solubility of the amorphous drug declined to a nearly constant level within a period of about 20–60 minutes. Similar dissolution kinetics have been previously reported for many metastable drug and excipient forms and they were not unexpected in this study. The correlation of the transformation kinetics *in-vitro* to the *in-vivo* situation is unknown, however it can be appreciated that it is likely that some level of *in-vivo* solubility enhancement would be achieved with the amorphous form of indomethacin (11).

The range of temperatures that was selected for the experimental solubility determinations is typical of that encountered by pharmaceutical products during their normal manufacture, packaging, storage, and use. Over this temperature range the expected increases in solubility with temperature were clearly seen for both the amorphous and γ-crystal forms of indomethacin (Figs. 2a, 2b, 2c; Table 3). Interestingly the steady-state solubility of the amorphous form at 5°C was approximately equal to that of the stable γ-crystal at 45°C. The alterations in solubility with temperature were of a similar magnitude for both forms and might have been amenable to a detailed thermodynamic analysis if data were available at a greater number and wider range of temperatures. Previous workers have used van't Hoff plots to quantitatively compare the energetics of solubility for different polymorphic drug forms (*e.g.*, (14)), however it is not clear that this approach is valid for amorphous materials. In these experiments the maximum temperature studied was slightly above the glass transition temperature of the amorphous indomethacin where the drug is in an equilibrium supercooled liquid state, whereas the other two temperatures studied were significantly below T_g where the drug is in the non-equilibrium glassy state. A definitive resolution of the temperature effects in such complex circumstances is beyond the scope of this study, and is suggested as a potential area for future work.

Comparison of Predicted and Experimental Solubilities

The experimentally determined solubility ratios for the amorphous indomethacin appear to follow qualitatively the predicted trend with temperature, however the absolute measured solubility ratios were markedly less than those expected (Fig. 3b; Tables 2 & 3). The latter behavior can also be seen when comparing predicted solubility ratios for several other amorphous drugs with experimental values reported in the literature (Tables 2 & 3), and there appears to be no overall correlation between the predicted and measured solubility ratios for the range of amorphous drugs considered. Despite this discrepancy

Table 4. Identity of Indomethacin Forms Recovered After Solubility Determinations

Starting form	5°C	25°C	45°C
γ-crystal	γ-crystals	γ-crystals	γ-crystals
α-crystal	—	—	α-crystals
Amorphous	Mixture: amorphous & α-crystals	Mixture: amorphous, γ-crystals & α-crystals	Mixture: amorphous & α-crystals

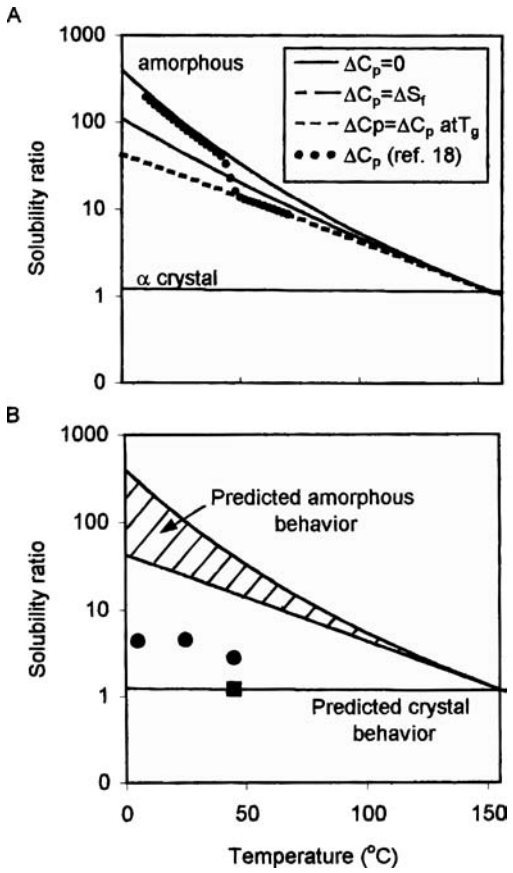

Fig. 3. Solubility ratio for indomethacin forms (versus γ-polymorph) as a function of temperature. (A) predicted behavior, (B) experimental data for amorphous, (●) and α-crystal, (■) forms compared to predictions.

the solubility ratios for the amorphous forms are all noted to be much greater than those predicted or measured for the corresponding polymorphic crystal forms.

The most likely explanation for the widespread non-concordance between the predicted and experimental solubility ratios for the amorphous drugs is that the amorphous substances cannot achieve their maximum theoretical solubility under practical experimental conditions because of the strong driving force for crystallization in the presence of the dissolution media. Several previous workers have tried to avoid this problem by adding crystallization inhibitors to their dissolution media (*e.g.*, (9,23)), however the use of such crystallization poisons is likely to alter the equilibrium solubility of the crystalline and/or amorphous forms so this approach could not be utilized in this work. The importance of the difference between the theoretically and experimentally determined solubility ratios should not be overlooked. The experimental problems which result from working with metastable systems are unavoidable, so experimental solubility values, whilst very useful for determining practical *in-vitro* solubility behavior of amorphous materials (*e.g.*, during dissolution testing), will never be able to indicate the maximum possible solubility advantage. The results of the thermodynamic predictions will probably never be actualized *in-vitro* or *in-vivo* due to the physical instability of the amorphous materials, however they can provide an indication of the theoretical driving force for the initial dissolution of the amorphous compound under any given conditions. They may also permit the comparison of different systems (*e.g.*, glass versus supercooled liquid) based on an equal set of theoretical constraints without concern for differing experimental limitations (*e.g.*, variable crystal nucleation rates). Clearly both theoretical and practical approaches have their merits and each is necessary in order to fully understand the solubility behavior of amorphous pharmaceutical systems.

It should be noted that in contrast to the amorphous-crystalline system described above, the experimental solubility ratio for the indomethacin polymorphs was in close agreement with that predicted from the thermal properties of the crystalline forms (Fig. 3b; Tables 2 & 3). From a consideration of the published data for solubilities of other several crystal polymorphs and the predicted values of their solubility ratios (Tables 2 & 3; (24–26)) this agreement appears to be quite common for crystalline pharmaceutical materials. It may be concluded as an aside that for many polymorphic forms of drug substances and excipients experimental solubility increases of as much as two fold will be common, improvements of as much as four fold possible, and thermodynamic predictions of the solubility improvements reasonably accurate.

Pharmaceutical Significance

The results of this study when combined with those of earlier workers provide a clearer picture of the theoretical and experimental solubility advantages that may be expected when working with amorphous pharmaceutical materials. These solubility enhancements are significant, and might reasonably be expected to have a marked impact upon the *in-vitro* and *in-vivo* performance of pharmaceutical dosage forms containing amorphous materials. It has been suggested that the relatively modest solubility differences between crystal polymorphs should be a significant cause for concern when formulating pharmaceutical products because of possible differences in their *in-vivo* performance, particularly for poorly water soluble drugs such as indomethacin (27). The level of concern is sufficient that there are published guidelines for developing drugs with multiple crystal forms, as well as FDA sponsored symposia to discuss their practical implications (28). Published pharmacokinetic data for the polymorphs of chloramphenicol palmitate (measured solubility ratio ~4.0 and predicted ratio ~3.6 at 30 °C) demonstrate measurable differences in human biopharmaceutical performance (~6 fold difference in C_{max}) (4), whereas data for polymorphs of mefenamic acid (measured solubility ratio ~1.3 and predicted ratio of ~1.5 at 30 °C) show no significant difference in their human *in-vivo* pharmacokinetics following a single oral dose (5). Based on these results it has been proposed that the practical biopharmaceutical consequences of solubility differences between crystal polymorphs are directly related to the magnitude of their solubility differences (5), and it appears that such effects might reasonably be expected to become clinically meaningful at solubility ratios of approximately two fold and higher, assuming that ±50 % intersubject variability is typical.

The experimental and theoretical solubility ratios for the amorphous drugs considered in this work are generally much greater than those for the corresponding crystal polymorphs (Tables 2 & 3), but to date the level of scientific, regulatory,

and clinical concern regarding the relative biopharmaceutical performance of fully or partially amorphous drugs has typically been much less than that for crystal polymorphs. Using a simple graphical representation (*e.g.*, Fig. 4) it is possible to show that even quite low levels of amorphous character in a drug substance (<10%, such as that induced by normal pharmaceutical manufacturing processes) could cause theoretical solubility increases of far greater than two fold. Elamin and co-workers (29) have reported that low levels of amorphous character induced in griseofulvin by milling, which were undetectable by differential scanning calorimetry, can readily result in solubility differences of two fold or more. Thus, it may reasonably be concluded that the occurrence of sufficient amorphous character in pharmaceutical systems to cause significant *in-vitro* and *in-vivo* solubility differences is likely to be widespread, may often be undetected, and should commonly be expected to result in significant differences in biopharmaceutical performance. This study illustrates that *in-vitro* solubility measurements may provide a viable method of demonstrating the solubility enhancement of the amorphous material, but such experiments need to be supported by theoretical estimates of the maximum driving force for dissolution based on the thermodynamic properties of the amorphous and crystalline materials.

CONCLUSIONS

Amorphous pharmaceuticals are markedly more soluble than their crystalline counterparts, however, their experimental solubility advantage is typically less than that predicted from simple thermodynamic considerations. This appears to be the result of difficulties in measuring the true equilibrium solubility of amorphous materials. Thermodynamic predictions can provide a useful indication of the theoretical maximum solubility advantage for amorphous pharmaceuticals and an estimate of the driving force for their initial dissolution. Based on a comparison with polymorphic crystal forms of drug compounds the clinical relevance of solubility increases for amorphous drug forms is likely to be significant, even in systems which are only partially amorphous.

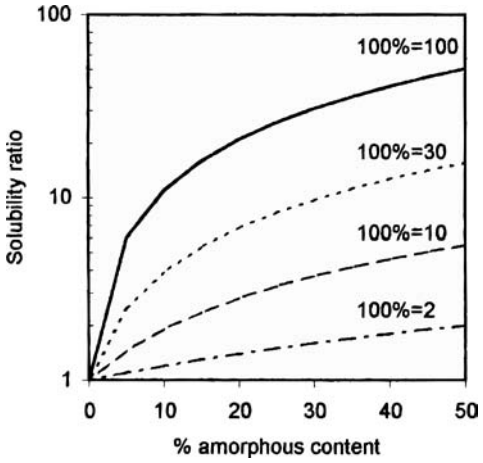

Fig. 4. Calculated solubility ratio for partially amorphous material as a function of amorphous content (Solubility ratio for 100% amorphous sample: 2 (-·-·-·), 10 (-----), 30 (·····), 100 (——)).

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