Volume 17, Number 4
PHREEB 17(4) 373–496 (2000)
ISSN 0724-8741

PHARMACEUTICAL RESEARCH

An Official Journal of the American Association of Pharmaceutical Scientists

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Volume 17, 2000 (12 issues) $840.00 (outside the U.S., $985.00). Prices for individuals subscribers certifying that the journal is for their personal use, $160.00 (outside the U.S., $187.00).

Periodicals postage paid at New York, N.Y., and at additional mailing offices. Postmaster: Send address changes to *Pharmaceutical Research,* Kluwer Academic/Plenum Publishers, 233 Spring Street, New York, N.Y. 10013-1578.

Printed in the USA.

What is the True Solubility Advantage for Amorphous Pharmaceuticals?

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Received September 20, 1999; accepted December 19, 1999

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:

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

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

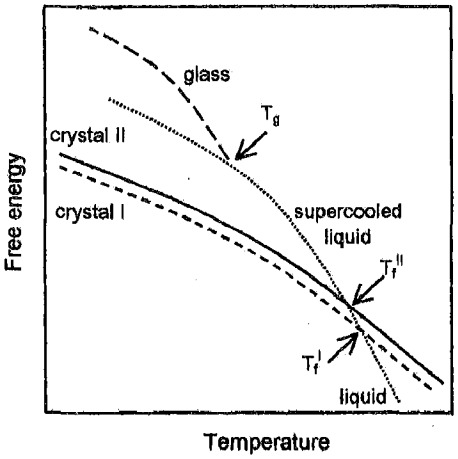

Fig. 1. Schematic free-energy diagram for amorphous and crystalline materials (see text for explanation of abbreviations).

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

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^o (°C)	ΔH_f^o (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.

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