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Use of solution calorimetry to determine the extent of crystallinity of drugs and excipients

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Abstract

A solution calorimetry method was developed to quantitatively examine mixtures of amorphous and crystalline sucrose or warfarin sodium based on the energy differences between their solid forms. The heats of solution of crystalline sucrose, amorphous sucrose, clathrate warfarin sodium and amorphous warfarin sodium were 1474.08 ± 37.78 cal/mol, -3550.47 ± 51.04 cal/mol, -1.701 ± 0.041 cal/g and -7.386 ± 0.226 cal/g, respectively. The observed linear relationship between the heat of solution and the percent of the crystalline form present in the sample provided a rapid and convenient way to quantitatively determine the crystallinity of a common drug excipient (sucrose) and/or a complex system, such as the clathrate warfarin sodium (a complex of warfarin sodium, isopropyl alcohol and water). The solid state conversion process could also be monitored by measuring the energy changes associated with changes in crystallinity. © 1997 Elsevier Science B.V.

Keywords: Solution calorimetry; Sucrose; Warfarin sodium; Heat of solution; Solid state stability; Crystallinity

1. Introduction

Crystallinity plays an important role in drug dissolution rate, physical chemical stability, physics of tablet compaction, as well as drug bioavailability. Even a small amount of amorphous phase in a crystalline sample may significantly alter its physical chemical properties. Pikal et al. (1978) initially introduced solution calorimetry in the pharmaceutical industry for quantitative crystallinity determination by measuring the heats of solution of different forms of β-lactam antibiotics (Pikal et al., 1978). In the 1980s, Guillory and Erb studied solid-state properties of multisource pharmaceutical to determine the degree of crystallinity, to characterize polymorphic forms and solvates and to obtain quantitative information about the composition of binary mixtures of

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various polymorphic forms (Erb, 1984; Guillory and Erb, 1985). However, all of these studies were limited to simple drug substances. No one has reported the use of this method in the quantitation of the crystallinity of common drug excipients in solid dosage form development and/or in a complex drug system. The solution calorimetry method developed in this article is a rapid, accurate and convenient method to quantify crystallinity of various systems for pharmaceutical dosage form development and for quality control.

2. Theory

Solution calorimetry or isoperibol solution calorimetry is a thermal analysis technique in which the temperature change produced by a chemical or physical interaction during the mixing of two solutions or of a solid and a liquid in a constant temperature environment is monitored as a function of time. All of the work presented here was done using batch calorimetry, in which both reactants were placed in the calorimeter reaction vessel and mixed at the initiation of the reaction period.

The conceptual basis of isoperibol solution calorimetry could be expressed by the following one step reaction:

$$S + L \leftrightarrow SL_1 \tag{1}$$

where S and L are the amount of free substrate and ligand, respectively. In this equilibrium system, the standard enthalpy change is defined as $\Delta H°$, and the total heat effect Q is related to the moles of SL_1 produced and $\Delta H°$ (Tong et al., 1992), i.e.,

$$Q = SL_1 * \Delta H° \tag{2}$$

Since batch calorimetry measures the heat generated during the substrate dissolution process, therefore, SL_1 becomes the total sample amount used (equilibrium was reached very fast) and $\Delta H°$ was the heat of solution to infinite dilution in any fixed solvent L. Thus, the heat of solution could be obtained through the measurement of total heat generated in this process. As for a non-interacting binary system, the total specific heat of solution ($\Delta H_t°$) is the weight sum of the specific heats of the individual components (Erb, 1984; Craig and Newton, 1991a,b), such that

$$\Delta H_t° = X_a \Delta H_a° + X_b \Delta H_b° \tag{3}$$

where X and $\Delta H°$ are the weight fractions and heats of solution for two non-interacting substances.

In principle, any extensive property that varies smoothly with the fraction of the crystalline phase in crystalline/amorphous mixtures may be used to measure crystallinity. The heat of solution method is developed based on the energy difference between different crystalline forms and the amorphous one (Mathews et al., 1966; Motooka et al., 1969; Kishimoto et al., 1973; Hunt and Hsu, 1974; Filisko and Raghava, 1974; Temple and Zarzycki, 1975; Pikal et al., 1978; Erb, 1984; Guillory and Erb, 1985; Craig and Newton, 1991a,b). In practice, the crystallinity is determined by a linear relationship between the heat of solution and physical mixtures of the two standards in different ratios (Guillory and Erb, 1985).

3. Comparison of solution calorimetry method with other traditional or alternative techniques

Traditionally, X-ray powder diffraction is used most frequently for the initial identification of differences in morphology (Miller, 1966a,b; Lindenbaum and McGraw, 1985). Relative crystallinity could be determined by comparing the areas of the amorphous curves and the areas of the chosen crystalline peaks (Kaelble, 1967). In practice, it is obtained by X-ray scattering intensities using Ruland's method (Fukuoka et al., 1993). The method is simple and the result is relatively fast, yet there are several drawbacks. The biggest disadvantage is that it is not a precise measurement. The preferred orientation may cause a change in the scattering pattern which is not from the crystalline material itself. Although orientation effects could be eliminated by reducing the crystal size to fine powders by some sample treatment, such as grinding, such handling may reduce the crystallinity or induce phase transition. The method is not suited for a sample with

a complex scattering pattern, since isolation of the peaks may be difficult and the separation of amorphous scattering from the total diffraction pattern could be ambiguous (Pikal et al., 1978; Guillory and Erb, 1985). Sometimes, amorphous scattering is not necessarily the cause of a broad background, i.e. some low intensity peaks may exist in the background because of the effect of residual solvent in the sample.

Differential scanning calorimetry is another helpful technique for the quantitative determination of crystallinity. In this method, crystallinity is determined from the enthalpies of fusion or crystallization by measuring the area under the melting curves. The measurements should be performed with the same sample weight, scanning rate and inert gas flow rate, since all these factors may affect peak shape and intensity and cause errors in the results. This method is quite useful and accurate, especially for samples with complex X-ray powder diffraction pattern. However, the measurements are done at elevated temperatures, and therefore, it is valid only under the assumption or condition that there are no structure changes during the heating process. For those samples which are thermolabile, or with hydrates or solvates, the drug may undergo decomposition or release solvent before the melting point. Then, the use of this method is not appropriate. Overall, the application of this method is not universal (Pikal et al., 1978; Guillory and Erb, 1985; Lindenbaum and McGraw, 1985).

Isothermal microcalorimetry has been used in the study of crystallinity changes according to recent reports (Sebhatu et al., 1994; Briggner et al., 1994; Buckton et al., 1995a,b; Ahmed et al., 1996). The method has been developed on the basis that almost all physical and chemical processes are accompanied by a heat change and focused on the energy changes associated with the recrystallization process of amorphous powders at certain relative humidities or organic vapours and temperatures. The output is recorded in the form of rate of change of heat as a function of time. The differences in magnitudes for the area under the curve are directly proportional to the degree of crystallinity. Since isothermal microcalorimetry has a specific sensitivity of four orders of magnitude greater than conventional DSC, it is possible to quantify the percent amorphous content of powder samples with a resolution of at least 1%, which is considerably better than other techniques. The limitation of this technique is that it can only be used for those amorphous materials which crystallize spontaneously under certain relative humidities or organic vapours.

In solution calorimetry, the heat is directly measured without other invasive processes except dissolution or wetting of the materials. The measurement is performed at room or other desired temperature and the partially crystalline sample can be assumed to be a mixture of the two standard forms (amorphous and crystalline). If the amorphous material exists in its pure form, and the energy differences between the amorphous and crystalline material are large enough, this method is potentially more precise ($\pm 1\%$), with less artifacts and more definitive results than other methods. Qualitatively, the crystallinity obtained from this method and from X-ray diffraction patterns show a good correlation (Pikal et al., 1978). One disadvantage of the solution calorimetry method is that it includes the measure of the enthalpy of solution or immersion which usually includes several processes, such as the breakage of bonds, wetting, liquid penetration, solvation, possibly rearrangement and conformational changes etc. Quantifying these individual processes is fairly difficult. Craig and Newton (1991a) have established a model to try to quantify the solution process by correlating heat of solution data with DSC results. However, the method is limited to systems where the enthalpy of wetting is not changing with the change in crystal structure. Another disadvantage is that it requires 100% pure crystalline and amorphous standards. Pure materials received from different sources or generated by different methods may differ in heat of solution measurements. This method is also limited by the solvent. Thus, the solubility in the chosen solvent should be reasonably high to insure rapid dissolution. For a complex system, such as a formulation, other excipients in addition to the one investigated will at least wetted in the chosen solvent during this process. The heat produced during the dissolution process needs to

be calibrated by a known amount of heat. This correction can be calculated accurately over only a limited time period. This also limits the isoperibol method to experiments which are complete within 1–2 h (Beezer, 1980). The sensitivity of the method is also material dependent, for the energy difference between amorphous and crystalline forms may vary depending on the solid forms of the sample.

4. Selection of model compounds

4.1. Sucrose

Sucrose plays an important role in drug formulations. it may serve generally as a diluent in both chewable and nonchewable tablets (Lieberman and Lachman, 1980a). It has also been used as an additive to stabilize proteins to heat, to provide bulk for freeze-dried proteins and for tablet coatings (te Booy et al., 1992). Usually, these processes involve mixing, compression, lyophilization or spray-drying techniques, which may lead to the formation of a highly viscous, metastable, amorphous state, and cause sucrose to partially lose crystallinity. Only small amounts of sucrose should be added for these purposes, for it is somewhat hygroscopic. Also, large quantities of sucrose in the tablet formulation would cause the tablet to harden with time and interfere with the dissolution of the drug from the tablet (Lieberman and Lachman, 1980b). Therefore, it is desirable to develop a sensitive, accurate and convenient method in order to quantitatively determine the crystallinity of sucrose for sucrose containing products or formulations.

4.2. Warfarin sodium

Warfarin sodium is the sodium salt of 3-(α-acetonylbenzyl)-4-hydroxycoumarin. It is an anticoagulant which inhibits the synthesis of vitamin K-dependent coagulation factors and aims at preventing further extension of formed clots and secondary thromboembolic complications which may result in serious and possible fatal sequelae (Hiskey and Melnitchenko, 1965). There are two solid forms commercially available for this compound, one is a clathrate, the other is amorphous. Clathrate warfarin sodium is a complex of warfarin sodium and isopropyl alcohol and water. It is reported that clathrate warfarin sodium may gradually convert to its amorphous form above certain relative humidities with the simultaneous loss of IPA and moisture uptake (Hiskey and Melnitchenko, 1965). Accurate measurements of crystallinity loss during this conversion process is very difficult by traditional methods, such as DSC and X-ray powder diffraction, because of the complexity in the DSC thermograms and X-ray patterns. Therefore, it is of interest to find out whether solution calorimetry could be a precise method to quantify the crystallinity of a complex system like a clathrate.

5. Materials and methods

5.1. Materials

Crystalline sucrose, amorphous warfarin sodium, cupric chloride and magnesium chloride were purchased from Sigma (St. Louis, MO). Clathrate warfarin sodium was received from Beddle Sewyer (New York, NY). Both isopropyl alcohol and *n*-propanol were HPLC grade and purchased from Fisher Scientific (Fisher Scientific, NJ).

5.2. Methods

5.2.1. Preparation of amorphous sucrose

Amorphous sucrose was prepared based on the principle that rapid cooling may change the state of a crystalline solid, as developed in part by Carstensen and Van Scoik (1990). A 10% sucrose solution was prepared and placed in a burette and allowed to run into liquid nitrogen carefully by drops. The frozen spheres were transferred to petri dishes and put into a lyophilizer immediately. They were then lyophilized under 17.2 mTorr with the shelf temperature of -40°C for 48 h or until the frozen ice spheres the control Petri dish completely disappeared. Usually, the temperature at this time was 2°C. Then, the tem-

perature was increased to 8°C and 16°C for 0.5 h each. Finally, the temperature was raised to 25°C and kept overnight to eliminate residual moisture. After the sample was freeze-dried, the vacuum was broken with dry nitrogen. The petri dishes were transferred immediately into a vacuum desiccator and dried over P_2O_5 under vacuum for at least 24 h.

The quality of amorphous sucrose prepared was checked using DSC. All the DSC experiments were performed on a Perkin-Elmer model-4 thermal analysis system. The DSC-4 was calibrated by measuring the melting profile of high-purity Indium. One amorphous sucrose sphere (approximately 3 mg) was put in an open pan with an empty open pan as a reference. The temperature program was a linear ramp of 10°C/min from −20°C to 200°C. The cell was purged with nitrogen during the DSC scan. The measured T_g was 57°C which is consistent with literature reports (Roos and Karel, 1990a, 1991b). The amorphous sucrose obtained by this method was a fluffy fine powder.

5.2.2. Sample incubation at different relative humidities

All the warfarin sodium samples stored at 68% relative humidity were put in petri dishes as a thin layer of material in a desiccator with $CuCl_2$ saturated solution at 25°C. The volume of the salt and solution used was based on reports in the literature (Nyqvist, 1983). The chamber was equilibrated at room temperature for at least 24 h before use and a relative humidity gauge was put in the chamber during the sample incubation period for relative humidity monitoring.

5.2.3. Solution calorimetry method

Heat of solution measurements were carried out on a Hart Scientific model 4285 isoperibol calorimeter at 25°C. Distilled water was used as solvent and weighed to 25.00 g in each experiment since both sucrose and warfarin sodium are highly soluble in water. Heat calibration was conducted before each experiment and the energy equivalence obtained was used for the corresponding heat calculation. The measurement proceeded to completion under vigorous stirring with a rotation speed of 1000 rpm. The temperature change during the reaction was detected by the temperature sensor and converted by a electronic output circuit to a signal corresponding to the temperature change, and was recorded on a computerized data collection and analysis system. Preliminary studies using an empty batch device showed no discernible effect on the slope of the trace.

The total sucrose weight for the crystalline and amorphous mixtures was controlled between 0.040 g and 0.052 g, whereas the total weight for the clathrate and amorphous warfarin sodium was 0.069–0.070 g in order to avoid bias from sample weight differences. The total sample weight for isopropyl alcohol was 0.016 g. Because of the highly hygroscopic property of the amorphous sucrose, fresh amorphous sucrose was used in each measurement, and all the sampling processes were performed in a dry nitrogen glove bag.

The heat of solution of THAM and KCl were mesured periodically to confirm the reliability of the equipment and the experimental technique. The results showed good consistency with literature values (percent error less than 4%) (Craig and Newton, 1991a,b).

5.2.4. GC assay for IPA content determination in clathrate warfarin sodium

IPA content in clathrate warfarin sodium was analyzed on a Hewlett Packard 5890 series II gas chromatography system. A J&W Scientific DB-wax capillary column was used with 30 m in length, 0.5 mm in diameter and 1.0 μm in film thickness. The detector was a flame ionization detector (FID), and both the detector and injector temperature were 200°C. The flow rate of column He, auxiliary He + column He, detector H_2, detector air, split vent and purge vent were 3.5–4.0 l/min, 27 ml/min, 33 ml/min, 400 ml/min, 240 ml/min and 2.0 ml/min, respectively. The linear velocity was controlled at around 38 cm/s by measuring the retention time of butane. The injection volume was 1.0 μl for each run. *n*-Propanol was used as an internal standard. The retention times for IPA and *n*-propanol were min and 4.2 min, respectively. All the data analysis was done on a Hewlett Packard 3365 Chemstation.

5.2.5. Karl Fischer method

The water content of warfarin sodium was measured on a KF-coulometer 652, series 01 (Metrohm, CH-9100 Herisau, Switzerland). To obtain the highest accuracy of each measurement, different amounts of solid sample were added to the Karl Fischer reagent in order to reach the total water weight in the range of 100–500 μg. A blank value was subtracted from the measured water content in order to correct the bias caused by the atmosphere.

6. Results and discussion

6.1. Sucrose

The heat of solution of crystalline sucrose at 25°C in water was 1474.08 ± 37.78 cal/mol. The dissolution of crystalline sucrose in water is an endothermic process. This may be because the crystalline material is at the lowest energy state, and the interactions within the crystalline structure are stronger than the solvation process, resulting in an overall endothermic heat of solution. After controlling particle size to 90–110 mesh, the heat of solution of crystalline sucrose became 1418.33 ± 3.31 cal/mol. Little effect was found on the crystallinity of sucrose after grinding based on DSC results. Thus, particle size restriction may be an effective way to obtain better precision in heat of solution measurements. These heat of solution results showed very good consistency with the literature value of 1400 cal/mol in infinite dilute solution at 25°C (Franks, 1972).

The heat of solution of dry amorphous sucrose at 25°C in water was -3550.47 ± 51.04 cal/mol, which has never been reported in the literature before. Crystalline sucrose of 90–110 mesh was used for physical mixtures of crystalline and amorphous sucrose. A linear relationship of heat of solution and percent crystalline sucrose present in the sample was obtained with a R^2 value of 0.998 (Fig. 1), i.e.,

$$y = -3642.6 + 49.871x \quad (4)$$

where x is the percent crystalline sucrose present in the physical mixtures and y is the crystallinity.

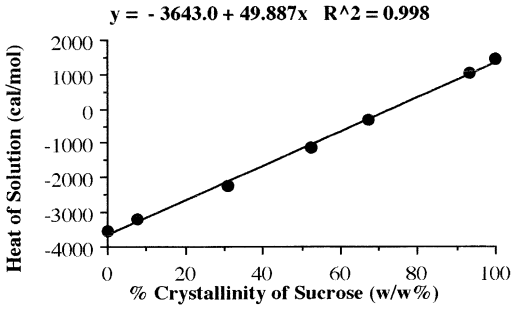

Fig. 1. The linear relationship between the heat of solution at 25°C in water and the weight percent crystalline sucrose present in the sample ($R^2 = 0.998$).

It showed very good reproducibility (%error < 5%). The linear relationship provides a simple and convenient way to accurately examine the crystallinity of sucrose, not only for simple mixtures, but also for sucrose containing formulations and coatings. If no chemical interactions and wetting problems exist between the components, the heat of solution of the formulation could be measured with and without sucrose present.

The conversion process of amorphous to crystalline sucrose was monitored (Fig. 2) at 32.5% relative humidity by heat of solution measurements every day. The crystallinity of sucrose could be estimated by correlating the heats of solution with the linear relationship obtained in Fig. 1. The crystallization process of amorphous sucrose was completed within 3 days which showed reasonable agreement with literature reports using a X-ray powder diffraction method (Palmer et al., 1956).

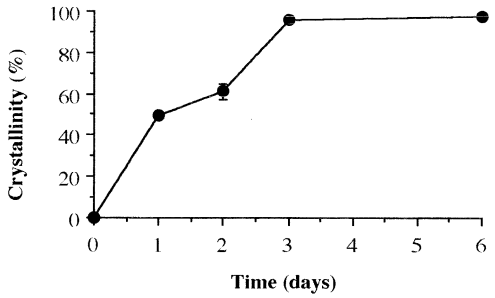

Fig. 2. The conversion profile from amorphous to crystalline sucrose 32.5% relative humidity and 25°C ($n = 3$).

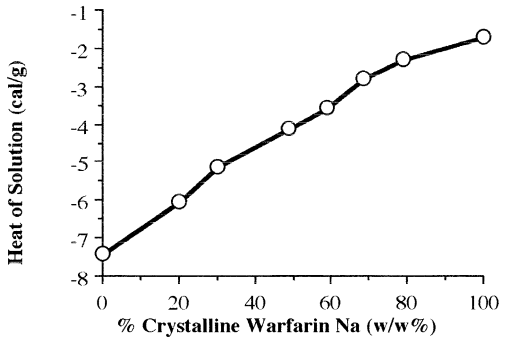

Fig. 3. The relationship between the heat of solution at 25°C in water and weight percent clathrate warfarin sodium present.

6.2. Warfarin sodium

Heats of solution of clathrate and amorphous warfarin sodium at 25°C in water were -1.701 ± 0.041 cal/g and -7.386 ± 0.226 cal/g, respectively. The dissolution processes of the clathrate and amorphous warfarin sodium were both exothermic, which is not very common for crystalline materials. This may be because of the complex structure of a clathrate system with more than one heat contributing component in it. Although warfarin sodium in the clathrate requires heat from the environment for bond breakage, IPA would evolve a larger amount of heat during the dissolution process in water because of the formation of hydrogen bonds. Therefore, the total result for this dissolution process became exothermic.

Heats of solution of physical mixtures of clathrate and amorphous warfarin sodium were measured at 25°C in water. Unlike the linear relationship obtained from simple systems, such as sucrose, the relationship of heat of solution and physical mixtures of warfarin sodium showed positive deviation from linearity (Fig. 3). The results showed good reproducibility with a percent error less than 5%. In this system, both warfarin sodium and isopropyl alcohol contributed to the heat changes observed during the dissolution process in water. The heat of solution of isopropyl alcohol at 25°C in water was found to be -47.83 ± 0.51 cal/g. Different percentages of IPA in the physical mixtures may be the cause of the positive deviation. A linear relationship ($R^2 = 0.987$) between heat of solution and percent crystalline warfarin sodium present was obtained after correcting the heat of solution for IPA content (Fig. 4), i.e.,

$$y_c = -7.0570 + 9.0240\mathrm{e} - 2x_c \quad (5)$$

where x_c is the per cent crystalline warfarin sodium present and y_c is corrected heat of solution. y_c could be calculated by following equation:

$$y_c = \Delta H_s - \mathrm{IPA}\% * \Delta H_{\mathrm{ipa}} \quad (6)$$

where ΔH_s and ΔH_{ipa} were the heat of solution of physical mixtures of warfarin sodium and IPA in water, respectively, and IPA% was the true IPA content in the sample. The IPA content in pure fresh clathrate warfarin sodium was determined by GC, and was 7.4%.

It is reported that clathrate warfarin sodium would convert to its amorphous state above certain relative humidities while losing IPA and taking up moisture (Hiskey and Melnitchenko, 1965). Yet, it was difficult to quantitatively determine the crystallinity of clathrate warfarin sodium during the clathrate diminishing process at various relative humidities using traditional techniques, such as X-ray powder diffraction and DSC. The difficulties with the X-ray powder diffraction method for this system can be attributed to the pattern complexity. The isolation of the peaks at certain angles was very difficult, especially after

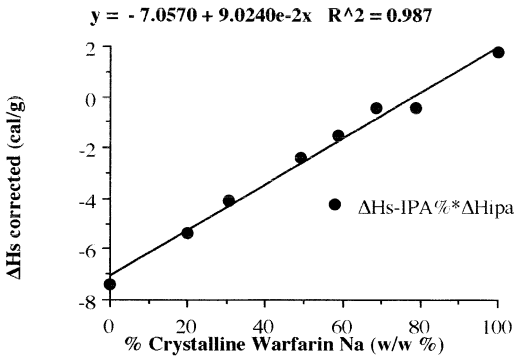

Fig. 4. The linear relationship between heat of solution corrected for IPA content ($\Delta H_s^{\mathrm{corrected}} = \Delta H_s - \mathrm{IPA}\% * \Delta H_{\mathrm{ipa}}$) at 25°C in water and weight percent crystalline warfarin present ($R^2 = 0.987$).

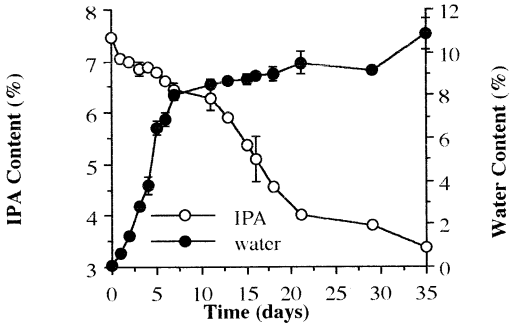

Fig. 5. IPA loss (solid line) and water uptake (dashed line) profiles of clathrate warfarin sodium at 68% relative humidity and 25°C ($n = 3$). All the sample points were corrected for either relative humidity or IPA content.

storing at 68% relative humidities for several days. Therefore, the comparison of peak intensities became very ambiguous and the results from peak to peak lost good consistency. Using the DSC method, the endothermic shoulder peak caused by the releasing of IPA right before melting made the heat of fusion calculation inappropriate for this system.

The crystallinity was successfully determined using solution calorimetry. Fig. 5 summarized the IPA loss as well as water uptake profiles at 68% relative humidity. All the IPA and/or water content presented in the profiles were corrected with either relative humidity or IPA content in the sample. The crystallinity of this converting process was monitored by heat of solution measurements. Fig. 6 showed the heat of solution profile of clathrate warfarin sodium before and after

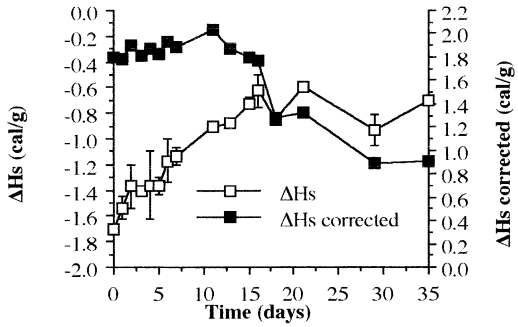

Fig. 6. Heat of solution profiles of clathrate warfarin at 68% relative humidity and 25°C before (solid line) and after (dashed line) correction for IPA content.

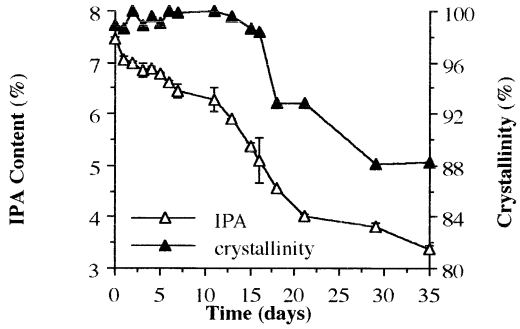

Fig. 7. Crystallinity loss profile (dashed line) of clathrate warfarin sodium at 68% relative humidity at 25°C. Comparison of IPA content (solid line) with crystallinity under the same experimental conditions.

correction for IPA content at 68% relative humidity. The heat of solution correction was done based on Eq. (6). Finally, the crystallinity of warfarin sodium at 68% relative humidity could be obtained by correlating the corrected heat of solution with Eq. (5) as shown in Fig. 7.

The conversion process could also be accurately monitored by heat of solution measurements. For example, the IPA loss and water uptake rate were very rapid during the first 8 days of storage at 68% relative humidity. It slowed down after that and effectively reached equilibrium (Fig. 5). These 8 days may be the induction period for the conversion process, since the crystallinity of the clathrate did not change during this period of time, but started to decrease after 10 days of storage (Fig. 7).

Heat of solution is a measure of energy change. It does not matter how complex the system is, the energy level is not going to change for the components if there is no phase change in the solid state. For example, Fig. 6 shows the heat of solution profile of clathrate warfarin sodium after correction for IPA at 68% relative humidity. There is no change in the heats of solution for the first 8 days storage, which clearly suggested that the energy level for the warfarin sodium component in the clathrate system remained the same. Therefore, solution calorimetry could also be a potential measure for the phase change in the solid-state, although isolation of the component may be a limitation in practice.

7. Conclusions

Solution calorimetry has been used to quantitatively determine the crystallinity as well as the solid state conversion processes of sucrose and warfarin sodium at differnt relative humidities. This type of study may also be potentially useful for examining crystallinity changes in the solid drug substances or the formulations during solid dosage form development. One of the challenges in using the method is to establish a linear relationship between the heat of solution and percentage of crystalline drug present in the sample. The requirement of pure crystalline and amorphous samples and choice of the solvent may limit the application of this method. In general, the method is useful for complex systems which have no chemical reaction between the drug and the other components. The chosen solvent must dissolve the drug relatively rapidly and at least wet the rest of the components in the system. It is also important to know or determine the effects of each component on the overall heat of solution.

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