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Rapid communication

An approach to estimate the amorphous content of pharmaceutical powders using calorimetry with no calibration standards[1]

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Abstract

Numerous recent articles have focused on methods to determine the amorphous content of pharmaceutical drugs and excipients. While a variety of methods were used, they all share the fact that portions of amorphous and crystalline materials were blended together and used as calibration standards to enable the determination of the amorphous content of the 'unknown' sample. This communication proposes a pragmatic approach to estimate the amorphous content of pharmaceutical powders that does not require the preparation of blended crystalline/amorphous material and uses available calorimetric techniques. This approach has been adopted in the laboratory to quickly estimate amorphous contents of bulk drug substances and formulated powders for inhalation. © 1997 Elsevier Science B.V.

Keywords: Pharmaceutical powders; Amorphous content; Calorimetry

1. Introduction

Many articles published recently in this journal and elsewhere have focused on methods to determine the amorphous (noncrystalline) content of pharmaceutical drugs (Buckton et al., 1995; Clas et al., 1995; Ward and Schultz, 1995) and excipients (Saleki-Gerhardt et al., 1994; Buckton and Darcy, 1995a). While a variety of methods were used, ranging from differential scanning calorimetry (DSC) and microcalorimetry (Briggner et al., 1994) to moisture sorption gravimetry and powder X-ray diffraction (XRD) (Ahmed et al., 1996), they all share the fact that portions of amorphous and crystalline materials were blended together

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and used as calibration standards to enable the determination of the amorphous content of the 'unknown' sample. This communication proposes a pragmatic approach to estimate the amorphous content of pharmaceutical powders that does not require the preparation of blended crystalline/amorphous material and uses available calorimetric techniques. This approach has been adopted in the laboratory to quickly estimate amorphous contents of bulk drug substances and formulated powders for inhalation.

Buckton and Darcy (1995b) have shown that moisture sorption gravimetry (MSG) can detect the weight loss associated with the crystallization of 0.05% amorphous content in crystalline lactose, however, they were unable to quantitatively correlate the residual water content with the fraction of amorphous material present in the sample. Saleki-Gerhardt et al. (1994) also used MSG to estimate the amorphous content in sucrose. In this case, the water uptake of amorphous/crystalline sucrose blends (ranging from 2 to 100% amorphous content) was plotted versus percent disorder (i.e. % amorphous content) when the samples were exposed to relative humidities ranging from 7.6 to 32.4%. These investigators found that using MSG, amorphous contents as low as 1% were reproducibly detected.

A number of researchers have also shown microcalorimetry to be a useful tool for detecting the amorphous content of lactose. The microcalorimeter can measure the energy output from the sample when the amorphous fraction in the sample recrystallizes. By preparing 100% amorphous lactose and blending it to known concentrations with crystalline lactose monohydrate, Sebhatu et al. (1994) generated a plot of heat of crystallization at 25°C versus the known amorphous content. Using the slope of that plot, the energy output of an unknown sample was measured and the amorphous fraction calculated. With this technique, amorphous contents of less than 10% in samples were determined.

However, the disadvantage of all the above approaches is the use of 'calibration standards' consisting of amorphous/crystalline fractions. First, the preparation of 100% amorphous material can be rather time-consuming (in some cases, challenging) and the confirmation of no crystallinity is usually based on subjective or insensitive measurements (i.e. observation of no birefringence by optical microscopy or 'flat' powder X-ray diffraction patterns). The morphology and particle size of the crystalline and amorphous material can be quite dissimilar making blending difficult. Also, the homogeneity of the resultant amorphous/crystalline powder blend, especially at low amorphous fractions, is very difficult to confirm. Finally, it is questionable whether these physical blends are truly representative of amorphous content in processed samples. Given these deficiencies, an approach was developed to estimate amorphous contents in pharmaceutical powders using calorimetry with no calibration standards.

Many years ago, Hoffman (1958) proposed a simple equation to estimate the free energy change for crystallization at temperatures other than the melting temperature. If it is assumed that the change in entropy is zero at the crystallization temperature, T_c, then a similar equation may be written for the crystallization of an amorphous fraction in a sample. Eq. (1) shows that the enthalpy of crystallization, ΔH_c^{amor}, at T_c for the amorphous fraction is proportional to its enthalpy of fusion, ΔH_f^{amor}, at the melting temperature, T_m, and the factor, ΔT, which is the difference between T_m and T_c.

$$\Delta H_c^{amor} = \left(\Delta H_f^{amor}\frac{\Delta T}{T_m}\right)\left(\frac{T_c}{T_m}\right) \quad (1)$$

When a purely crystalline compound is heated to its melting point, the heat of fusion at that temperature is the loss of crystalline order. If it is assumed that ΔH_f^{amor} in Eq. (1) is the formation of crystalline order for the amorphous fraction at the melting temperature, then the amorphous content in a sample may be determined by taking the ratio of ΔH_f^{amor} to the heat of fusion at the melt for purely crystalline material, ΔH_f^{cry}:

$$\text{Amorphous Content} = \frac{\Delta H_f^{amor}}{\Delta H_f^{cry}} \quad (2)$$

If it is assumed that the energy output from a microcalorimetric measurement of the amorphous to crystalline conversion is the enthalpy of crystal-

Table 1
Calculation of the amorphous content of lactose using data from the literature

Amorphous lactose content[a]	Heat of crystallization[a] (ΔH_c^{amor}) at 25°C	$\Delta H_f^{amor} = \frac{\Delta H_c^{amor}}{(T_c/T_m)(\Delta T/T_m)}$	% Amorphous content $= \frac{\Delta H_f^{amor}}{\Delta H_f^{cry}}$
100	31.3	132.1	98
50	15.7	66.3	49
33	10.3	43.5	32
18	5.46	23.2	17
7.6	2.39	10.1	7.5
3.1	0.98	4.1	3.0

[a] Data from Sebhatu et al., 1994.

lization at T_c, (ΔH_c^{amor} in Eq. (1)), then ΔH_f^{amor} can be found by knowing T_m of the material. The heat of fusion at the melting point of purely crystalline material, ΔH_f^{cry}, may be determined from differential scanning calorimetry and the amorphous content determined by using Eq. (2).

To test the validity of this calculation, data from the literature on amorphous lactose were used. The first two columns in Table 1 show known amorphous contents of lactose and their enthalpies of recrystallization, ΔH_c^{amor}, at 25°C as determined by Sebhatu et al. (1994). Naini et al. (1996) has determined the melting temperature and the heat of fusion at the melt of lactose monohydrate crystals that were sieved to remove the fine particles. Using the melting temperature of 212°C, the crystallization temperature of 25°C and the ΔH_c^{amor} values determined by Sebhatu et al. (1994), ΔH_f^{amor} was calculated using Eq. (1) and is shown in the third column of Table 1. By dividing the enthalpy of crystallization of the amorphous fraction at the melting point by the heat of fusion of the crystalline material (ΔH_f^{cry} = 135 J/g), the amorphous content of the powder was estimated using only calorimetric data and is shown in the last column of Table 1. It can be seen by comparing the first and last columns that this estimation of amorphous content is in very good agreement with the values provided by Sebhatu et al. (1994).

This approach to estimating amorphous content was then used for a model powder for inhalation (Phillips and Byron, 1994), micronized methylprednisolone (MP). Comparison of the micronized powder to the bulk crystalline drug by XRD showed no obvious differences in peak intensities nor any telltale shifts in the diffraction baseline which is usually indicative of a large amorphous content (Chawla et al., 1994). However, it is well documented that XRD can detect no less than approximately a 10% amorphous content (Saleki-Gerhardt and Zografi, 1994). On the other hand, moisture sorption gravimetry data suggested that the micronized powder did possess an amorphous content as shown by the gravimetric weight loss at 90% RH (Fig. 1), indicative of the crystalline conversion of the amorphous material (Buckton and Darcy, 1995b). Both the micronized and unmicronized MP were heated in hermetically sealed pans at a rate of 10°C/min on a Perkin Elmer Model DSC-7. The DSC thermogram in Fig. 2 shows an exothermic event for the micronized MP at approximately 105°C, indicative of crystallization, whereas no thermal event was observed at that temperature for the bulk crystalline drug. It is important to note that in using the DSC technique, the exotherms corresponding to crystallization of the amorphous material may be heating rate dependent and the crystallization occurs over a range of temperatures. Thus, isothermal microcalorimetry is the preferred technique to measure the energy of recrystallization of the noncrystalline fraction.

When the micronized MP was sealed in an ampoule containing a 90% RH environment and placed in the microcalorimeter at 25°C, a thermal event indicative of the amorphous to crystalline transition did occur. The energy of crystallization

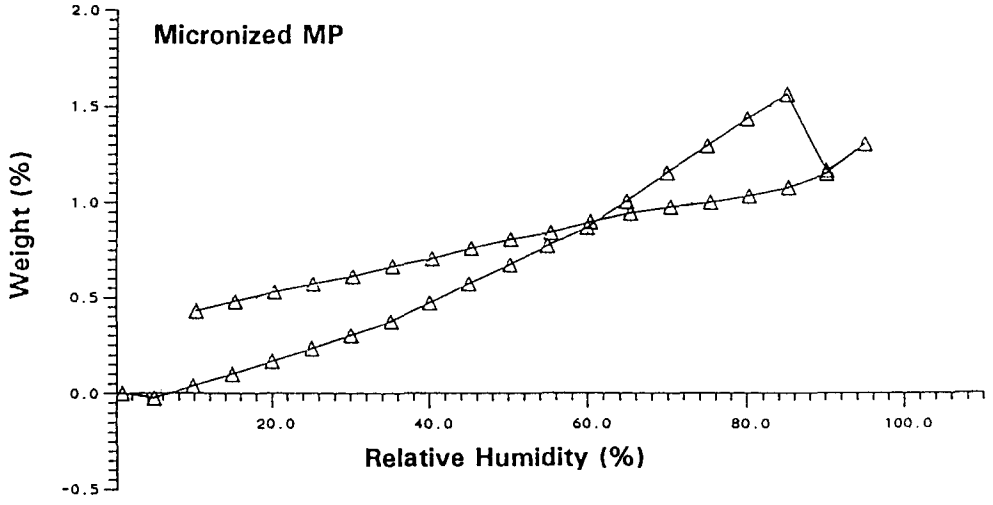

Fig. 1. The moisture sorption isotherm of micronized MP at 25°C.

at 25°C was 1.3 J/g ($= \Delta H_c^{amor}$ in Eq. (1)). DSC data for crystalline MP show a T_m of 235°C and a heat of fusion at the melt (ΔH_f^{cry}) of anywhere from 60 J/g determined by Guillory (1967) to values of 62 J/g (Phillips, 1991) and 79 J/g determined more recently (Phillips et al., 1996). This fairly large range in ΔH_f^{cry} is thought to be due to the fact that MP undergoes decomposition shortly after the melt. Using Eq. (1), ΔH_f^{amor} was calculated to be 5.4 J/g. The amorphous content in the micronized MP was then estimated to range from 6.8 to 9.0% depending on whether the upper or lower value for ΔH_f^{cry} of the bulk crystalline MP was used. While known standards of amorphous

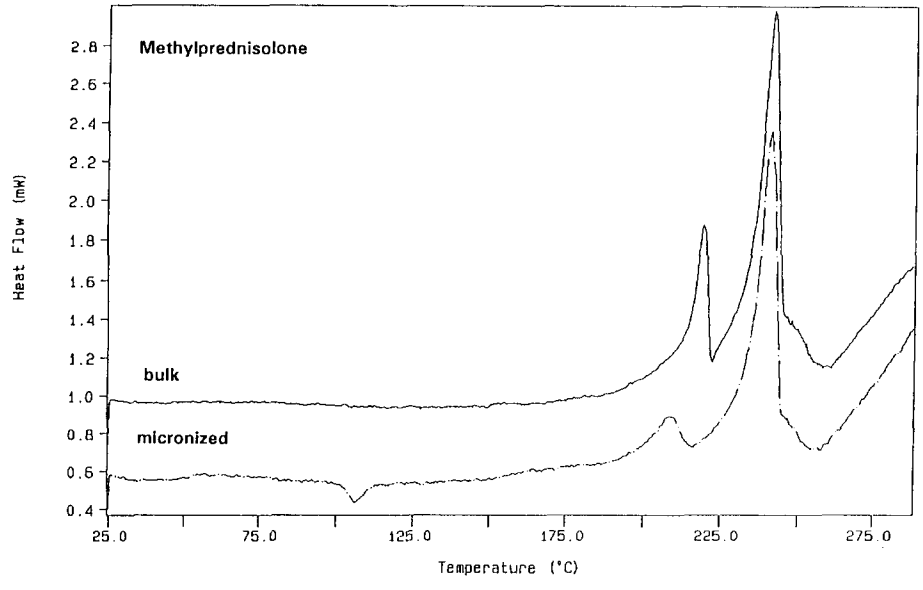

Fig. 2. A comparison of the thermal profile of micronized and unmicronized MP showing the exothermic event at approximately 105°C for the micronized material.

and crystalline MP were not prepared to confirm this estimate, it is consistent with the XRD, DSC and hygroscopicity data.

To summarize, a pragmatic approach was developed to estimate the amorphous content in pharmaceutical powders which does not require the preparation of calibration standards consisting of known amorphous and crystalline content. The enthalpy of crystallization of amorphous material at temperatures other than the melt may be scaled to the melting temperature using Eq. (1). The amorphous content of a sample may then be estimated by taking the ratio of the enthalpy of crystallization at T_m for the amorphous fraction to the heat of fusion of purely crystalline material. This approach will enable the quantitative estimation of amorphous content without having to perform the laborious task of producing 100% amorphous material, confirming its homogenous blending in known ratios with the bulk crystalline substance and generating a calibration curve using one of the existing techniques.

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