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Letter to the Editor

Comments on "An approach to estimate the amorphous content of pharmaceutical powders using calorimetry with no calibration standards"

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Abstract

A recent article (Phillips, E.M., 1997. Int. J. Pharm. 149, 267–271) described the advantages of a simple calorimetric technique for determining the amorphous content of pharmaceutical powders. In this commentary the limitations of the suggested approach are reviewed and its apparent simplicity re-examined. © 1998 Elsevier Science B.V.

To the Editor,

A recent Rapid Communication published in the International Journal of Pharmaceutics (Phillips, 1997) described a method for "estimating the amorphous content of pharmaceutical powders using calorimetry with no calibration standards". The article stressed the advantages of the technique but only briefly noted its inherent assumptions and practical limitations. The commentary that follows offers some perspectives on the theoretical and experimental difficulties associated with this approach.

The technique that was described (Phillips, 1997) was based on the common practice of comparing the magnitude of enthalpic changes associated with the crystallisation and fusion processes. Since crystallisation and melting usually occur at different temperatures these enthalpies were 'corrected' to a common reference temperature (the crystallisation temperature) using a method developed by Hoffman (1958)[1]. In the article, considerable emphasis was placed on the simplicity of the described approach for determining the amorphous content of pharmaceutical powders, and the author advocated the use of two different

[1] A similar application of Hoffman's method has been described by Saleki-Gerhardt et al. (1994).

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experimental techniques—differential scanning calorimetry (DSC) to determine the enthalpy of fusion, and isothermal microcalorimetry to determine the enthalpy of crystallisation.

The use of differential scanning calorimetry (DSC) to quantify the heat of fusion of a crystallised material (ΔH_f^{cry}) can pose significant experimental difficulties and complications which were not mentioned in the communication. A sample of pure 100% crystalline material is required for accurate determination of ΔH_f^{cry} and obtaining such a sample may be just as 'time consuming' and 'challenging' (Phillips, 1997) as preparing a 100% amorphous reference standard. This is especially true for high molecular weight compounds which are becoming increasingly common pharmaceutical materials (e.g. antibiotics, proteins, peptides). It is also true that in many cases heating a crystallised material to high temperatures results in enthalpic changes which confound the determination of the heat of fusion. These changes may be associated with chemical or physical events (such as desolvation, polymorphic transitions, or decomposition) and can occur prior to or in conjunction with the melting process (Ford and Timmins, 1989). A good example of this phenomenon is to be found with the first material cited as an example in the communication—lactose monohydrate. Crystalline α-lactose monohydrate is readily dehydrated upon heating (at about 150°C) to form an anhydrous crystalline form (α or β), and this in turn melts with considerable decomposition (at about 220°C) (Sebhatu et al., 1994b). The additional physical and chemical processes that occur upon heating this material (dehydration, decomposition, isomeric conversion) can mean that it is difficult to isolate and accurately quantify the enthalpic changes associated with the melting process.

The use of microcalorimetry for determining the enthalpy of crystallisation adds considerable practical and theoretical complexity to the approach described. This technique is not facile and the interpretation of the experimental data can be challenging since in many cases crystallisation has to be triggered by use of an external stimulus. This is usually achieved by manipulating the relative humidity around the sample (as was the case for the lactose example given), but it can also be achieved by exposing the sample to organic vapours or other solids (Buckton and Darcy, 1995; Ahmed et al., 1996). Under such conditions the effects of interactions between the external stimulus and the sample (e.g. wetting, hydration, swelling) on the measured enthalpy changes need to be completely accounted for before any reasonable estimate of the amorphous content of a sample can be made (Ahmed et al., 1996). It should also be noted that if the crystalline solid which is formed in the microcalorimeter (e.g. hydrate) is of a different form to that which is melted in the DSC (e.g. anhydrate) then the enthalpic changes which are recorded cannot be directly compared.

At least one other specific and definitive experimental procedure would normally be required in addition to any calorimetric techniques to confirm that the enthalpy changes measured by these methods are in fact due to the crystallisation and melting processes, respectively, since the potential for erroneous enthalpic estimates due to concomitant chemical and physical processes (e.g. wetting, (de)hydration, decomposition) is considerable (Sebhatu et al., 1994a). It should be noted that even if the measured enthalpy changes can be shown to be indicative of recrystallisation and melting it is still necessary to confirm the total recrystallisation and melting of each sample using a definitive primary technique before reliable quantitative estimates can be made.

A major focus of the recent Communication was the elimination of the need to prepare mixtures of amorphous and crystalline materials for use as crystallinity reference standards. The title of the article actually claims the use of 'no calibration standards'. The proposed approach in fact uses a single 100% crystalline calibration standard for determining the heat of fusion of the fully crystallised material. It then relies upon the assumption that there is a linear relationship between the enthalpic changes measured during recrystallisation (expressed as a fraction of the heat of fusion of the fully crystallised material) and the amorphous content of the original sample. The use of such a 'two-point calibration' procedure (using the measured 100% crystalline and assumed

0% crystalline responses) will often lead to a inaccurate estimate of a sample's amorphous content. This is well illustrated by two recent reports which describe systematic studies of the crystallisation of two amorphous drug substances. In the first report the heat of crystallisation of partially amorphous indomethacin samples was measured by DSC and correlated with a determination of sample crystallinity by powder X-ray diffraction (Yoshioka et al., 1994). In the second article, solution calorimetry was used to determine the heat of solution of warfarin sodium samples, and their amorphous content was estimated from a knowledge of the properties of several amorphous, crystalline and partially amorphous reference samples (Gao and Rytting, 1997). In both of these studies there was significant non-linearity in the relationship between the measured enthalpic response (upon recrystallisation or dissolution) and the actual proportion of amorphous material present. In each instance the use of only a 100% crystalline calibration standard would have resulted in significant error in the estimates of the amorphous content of the powdered samples and any difficulties involved in the preparation of standard mixtures of amorphous and crystalline powders would have been offset by the increased robustness and accuracy of the crystallinity estimates obtained.

In conclusion, the recent Communication presents an idealised view of the proposed method for estimating the amorphous content of pharmaceutical powders from calorimetric measurements of the enthalpies of crystallisation and fusion. The described approach relies upon several important assumptions which need to be carefully examined and tested before reliable numerical estimates of a sample's amorphous content can be made. In addition, the advocated calorimetric methods are non-specific and need confirmation using definitive measures of crystallinity, and the use of at least one calibration standard (preferably more) is required.

References

Ahmed, H., Buckton, G., Rawlins, D.A., 1996. The use of isothermal microcalorimetry in the study of small degrees of amorphous content of a hydrophobic powder. Int. J. Pharm. 130, 195–201.

Buckton, G., Darcy, P., 1995. The influence of additives on the recrystallisation of amorphous spray dried lactose. Int. J. Pharm. 121, 81–87.

Ford, J.L., Timmins, P., 1989. Pharmaceutical Thermal Analysis: Techniques and Applications. John Wiley & Sons, New York.

Gao, D., Rytting, J.H., 1997. Use of solution calorimetry to determine the extent of crystallinity of drugs and excipients. Int. J. Pharm. 151, 183–192.

Hoffman, J.D., 1958. Thermodynamic driving force in nucleation and growth processes. J. Chem. Phys. 29, 1192–1193.

Phillips, E.M., 1997. An approach to estimate the amorphous content of pharmaceutical powders using calorimetry with no calibration standards. Int. J. Pharm. 149, 267–271.

Saleki-Gerhardt, A., Ahlneck, C., Zografi, G., 1994. Assessment of disorder in crystalline solids. Int. J. Pharm. 101, 237–247.

Sebhatu, T., Angberg, M., Ahlneck, C., 1994a. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int. J. Pharm. 104, 135–144.

Sebhatu, T., Elamin, A.A., Ahlneck, C., 1994b. Effect of moisture sorption on tabletting characteristics of spray dried (15% amorphous) lactose. Pharm. Res. 11, 1233–1238.

Yoshioka, M., Hancock, B.C., Zografi, G., 1994. Crystallisation of indomethacin from the amorphous state below and above its glass transition temperature. J. Pharm. Sci. 83, 1700–1705.

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