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A New Gravimetric Method to Calculate Low Levels of Amorphous Content

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A new method to quantify low amorphous contents using DVS was developed using organic vapours. The difference in sorption capacity between crystalline and amorphous phases was used to determine amorphous contents below 1%. This new method is compared with four established methods for measuring amorphous contents using gravimetric vapour sorption techniques.

Introduction

Amorphous materials in pharmaceutical formulations yield complex and challenging problems concerning the performance, processing, and storage of these products. The presence of amorphous materials can be wanted or unwanted, depending on the desired or undesired unique properties of the amorphous state. Also, during the processing of pharmaceutical solids (e.g. milling, spray drying, tablet compaction, wet granulation, and lyophilization), various degrees of disorder in the form of crystal defects and/or amorphous regions may be generated. Even relatively low levels of amorphous material (<10%), may have a detrimental impact on the stability, manufacturability and dissolution characteristics of the formulated drug product. For these reasons, determining the amount of amorphous material is critical in the formulation of pharmaceutical powders.

There are several techniques available to quantify moderate to high levels of amorphous material in powders. Some of these techniques, with their approximate percentage amorphous content detection limits in parenthesis, include: differential scanning calorimetry (10%), density (10%), powder x-ray diffraction (5%), thermal stimulated current spectroscopy (2%), solution calorimetry (1%), FT-Raman (1%), Near IR (1%), and modulated differential scanning calorimetry (1%). However, there are few techniques available to quantify amorphous contents below 1%. These techniques, with their detection limits, include: solid state NMR (0.5%), microflow calorimetry (0.5%), and parallel beam powder x-ray diffraction (0.4%). One of the most sensitive techniques is gravimetric vapour sorption (~0.2%). There are several methods in the literature using gravimetric vapour sorption techniques to quantify amorphous contents [1,2,3,4]. All of these methods are based on different vapour affinities for the amorphous and crystalline phases.

All of the gravimetric methods require measuring materials with known amorphous contents to establish a calibration curve. This is typically done by producing physical mixtures of 100% amorphous and 100% crystalline materials in known proportions. Once the amorphous content calibration curve is determined, the sorption properties of samples with unknown amorphous contents can be measured and compared to the known standards. The approach developed by Zografi, et al [1] measures water vapour

isotherms of the various crystalline and amorphous mixtures. At a particular relative humidity (RH), the equilibrium water vapour uptakes are plotted versus the known amorphous content. The result is a straight line to which unknown amorphous contents can be compared. With this technique, the samples must not be exposed to relative humidity levels that will cause a recrystallisation event. Therefore, the technique is typically limited to low relative humidity levels (i.e. below 40% RH).

The method of Buckton and Darcy [2] utilizes a water vapour induced recrystallisation event to determine the amorphous content. Further, the material must form a hydrate with known stoichiometry upon recrystallisation. To illustrate this technique the authors used an amorphous lactose sample that recystallises to form α-lactose monohydrate. As in the previous technique, water vapour sorption isotherms are collected. However, in this technique, the sample is exposed to a relative humidity, which will force a water-induced recyrstallisation event. Then, a water vapour desorption isotherm is collected on the 100% recrystallised sample. At the end of the desorption isotherm, the sample will retain a characteristic amount of water due to formation of a hydrate. The increase in weight from the starting point of the first sorption cycle to the end of the desorption cycle will be directly related to the amount of amorphous material. This technique assumes that all of the amorphous material has been fully recrystallised. This can be a incorrect assumption, especially if the sample agglomerates, thus 'shielding' water molecules from the amorphous phase. Additionally, the recrystallisation event might be a slow process. This technique is further limited by the necessity of forming a known hydrate.

The method of Mackin et al [3] again uses a recrystallisation event to determine amorphous contents. The partially amorphous sample is initially dried, then exposed to a partial pressure (water or organic solvent) below where sample recrystallisation occurs. Then, the sample is exposed to a high enough partial pressure to force a recrystallisation event. Finally, the now

recrystallised sample is exposed to the same partial pressure as previously (below where recrystallisation occurs). Assuming no hydrate or solvate formation, the difference in uptake between the partially amorphous and recrystallised material is directly related to the amount of amorphous material in the sample. Similar to the method of Buckton, this technique assumes that 100% of the amorphous phase has been recrystallised. However, this technique is not suitable for materials that will form a hydrate or solvate upon recrystallisation.

Another gravimetric technique by Van Oort [4] is also based on solvent-induced recrystallisation. In this technique, the sample is exposed to a step-change in partial pressure or relative humidity above the recrystallisation limit. Then, a plot of the first derivative of the mass change (dm/dt) versus time is produced. If the sample is 100% crystalline, there will only be one peak above zero in the dm/dt versus time plot. If there is any amorphous to crystalline transition, the dm/dt versus plot will have two peaks: one greater than zero and one less than zero. The relative areas of these peaks are related to the amount of amorphous material in the sample. As with some of the other methods, this technique is limited to systems for which a recrystallisation event can be solvent-induced.

Theory

This study is an extension of the well-known approach developed by Zografi, et al [1]. Instead of using water vapour where the RH range is limited to prevent recrystallisation, this study measures octane isotherms. As with water vapour isotherms, the amorphous material will have a greater octane vapour sorption capacity than the crystalline material. Therefore, the differences in octane uptake between crystalline and amorphous contents can be used to calculate the amount of amorphous material in a sample.

Using a vapour like octane has several distinct advantages. First, octane is a molecule with dispersive properties that will typically wet the sample surface and not interact strongly with the

material. This will limit the chances of octane forcing any sample recrystallisation. Therefore, the entire partial pressure range can be used. If no recrystallisation occurs, then the octane sorption is completely reversible and multiple cycles can be run on the same sample to obtain repeat measurements. Finally, the sorption of organic vapours like octane is typically much faster than water.

Method

Dynamic vapour sorption (DVS) is a well-established method for the determination of vapour sorption isotherms. The DVS instrument used for these studies measures the uptake and loss of vapour gravimetrically using a SMS ultra-balance with a mass resolution of ±0.1 μg. The high mass resolution and excellent baseline stability allow the instrument to measure the adsorption and desorption of very small amounts of probe molecule. The vapour partial pressure around the sample was controlled by mixing saturated and dry carrier gas streams using electronic mass flow controllers. The temperature was maintained constant at 25 ±0.1 °C, by enclosing the entire system in a temperature-controlled incubator.

Alpha-lactose monohydrate was used as a model pharmaceutical material. The 100% amorphous lactose was obtained by spray drying. The amorphous lactose was stored over desiccant at 3 °C, to limit any recrystallisation. The crystalline α-lactose monohydrate was pre-conditioned at 90% relative humidity (RH) for 24 hours followed by storage in a desiccator over anhydrous calcium sulphate. This procedure was performed to ensure a 100% crystalline starting material. Partially amorphous lactose mixtures were prepared by combining known amounts of spray-dried, amorphous lactose with 100% crystalline lactose.

The lactose samples were placed into the DVS-1 instrument where they were dried in a 100-sccm stream of dry air (< 0.1% relative humidity) for 12 hours. The sample was exposed to the following octane vapour partial pressure profile: 0.01, 0.02, 0.03, . . . , 0.10, 0.20, . . . , 0.90, and 0.95 p/po. The partial pressure was then decreased in an identical manner back down to 0.00 p/po. A second sorption/desorption profile was measured to check for any irreversible sorption effects and obtain repeat measurements. At each stage the sample mass reached equilibrium. The sorption isotherms were calculated from the equilibrium mass values at each partial pressure.

Results

Octane isotherms were measured for 100% amorphous lactose, 100% crystalline lactose and a range of amorphous and crystalline lactose mixtures. The amorphous material will typically have a higher surface area and surface energy, thus a higher octane adsorption capacity. Figure 1 displays octane sorption isotherms for 100% crystalline (red) and 100 % amorphous (blue) samples.
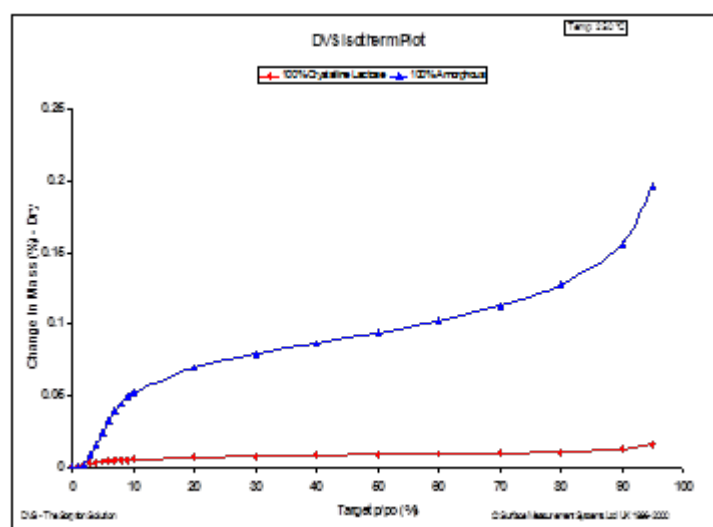

Figure 1. Octane sorption isotherms for 100% crystalline and 100% amorphous lactose.

At 0.95 partial pressure of octane, the percentage change in mass was 0.197% (based on dry mass) for the amorphous sample, compared to only 0.0158% for the crystalline material. The uptake at 0.95 partial pressure of octane scales with percent amorphous content (see Figure 2).
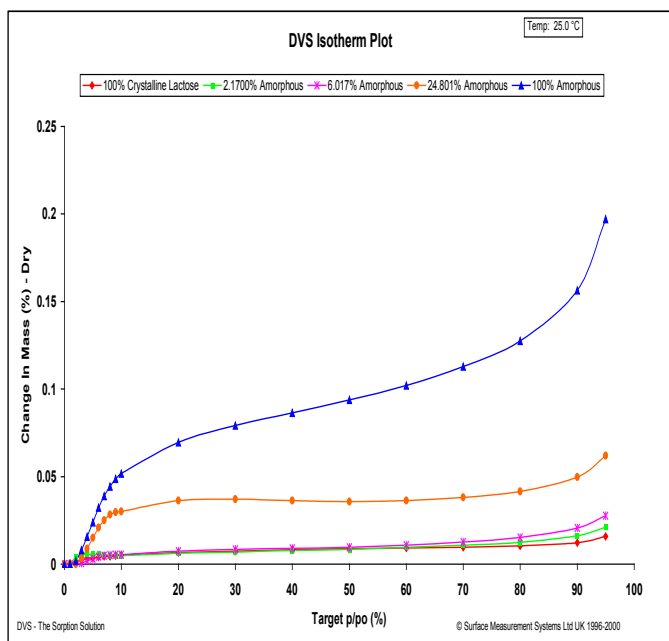

Figure 2. Lactose octane sorption isotherms for a range of known amorphous contents.

The equilibrium percent change in mass at 0.95 p/po of octane was used as the lone measured parameter to obtain an amorphous content calibration curve with known mixtures of amorphous and crystalline lactose. Figure 3 reveals an excellent linear relationship between the octane vapour uptake at 0.95 p/po and the percentage amorphous content. From this calibration curve, it is possible to determine the amorphous content of an 'unknown' sample. The error bars on the measurements (0.0005% change in mass) combined with the linearity of the fit indicate an accuracy of ±0.3% in the amorphous content determination. A lactose sample was purchased from ACROS and the octane isotherm was measured on the DVS. The uptake at 0.95 p/po was 0.0194%, resulting in a 0.9 ±0.3% amorphous content.
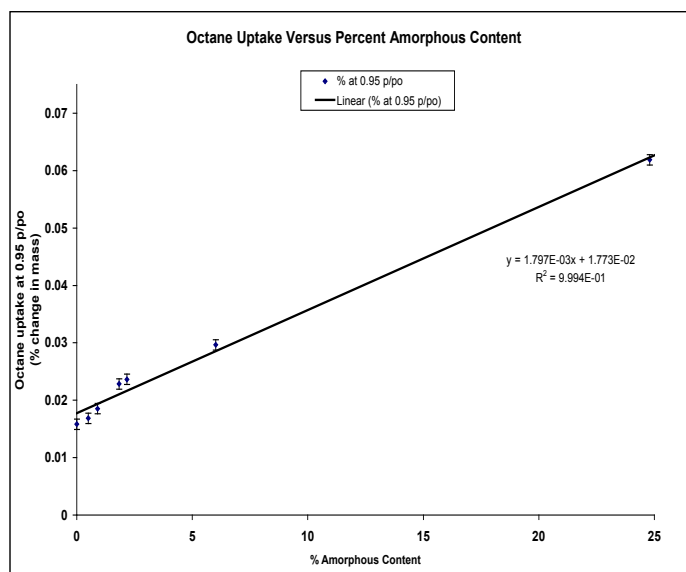

Figure 3. Octane vapour uptake versus amorphous content (calibration curve).

The method used to determine amorphous content for these studies has some distinct advantages over previous gravimetric techniques. First, the technique does not require a solvent-induced recrystallisation. Recrystallisation is required for the methods used in references 2, 3, and 4. Additionally, this method does not require the formation of a hydrate/solvate with a known stoichiometry, as in reference 2. Octane vapour does not typically induce any morphological transformations in the sample, so the entire partial pressure range may be studied, unlike water vapour based methods [1]. Finally, the kinetics for octane adsorption is relatively fast (compared to water), so experimental throughput can be faster.

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Conclusion

A new method was developed for determining low levels of amorphous contents. Using known amorphous and crystalline lactose standards, octane vapour isotherms were used to create an amorphous content calibration curve. From this curve, samples with unknown amorphous contents could be determined with an accuracy of ±0.3 percent. This technique is applicable to a wide range of pharmaceutical powders without the limitations of previous gravimetric methods.

Acknowledgement:

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