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HyperDSC studies of amorphous polyvinylpyrrolidone in a model wet granulation system

Graham Buckton [a,b,*], Akintayo A. Adeniyi [a], Mark Saunders [b], Ameet Ambarkhane [b]

[a] *Department of Pharmaceutics, School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom*
[b] *Pharmaterials Ltd., Science and Technology Centre, Earley Gate, Whiteknights Road, Reading RG6 6BZ, United Kingdom*

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Abstract

Measurements of the properties of amorphous materials are very important to help in the understanding of how materials behave during manufacture, storage and use of medicines. However, there are few methods that are suited to the study of amorphous materials, especially if in multi-component systems or model formulations. The goal here was to explore the potential for the use of HyperDSC to study a model granulation system. It was found that the sensitivity of HyperDSC was such that the glass transition (T_g) of polyvinylpyrrolidone (PVP) could be detected in granules made with realistic levels of this binder. The measured T_g in the granules, even after drying, was very different to that of PVP alone and to PVP in physical mixtures with lactose. It is argued that the granulation process has resulted in the dissolution of some lactose and that the amorphous binder holding the granules together is in fact a solid dispersion of PVP and lactose. Based on the standard Gordon–Taylor equation it was estimated that the solid dispersion contained 50% of PVP and lactose. Given that solid dispersions have a tendency to crystallise on storage, it could be expected that changes in the binder properties will occur with time after granulation. We believe that this is the first measurement of in situ properties of a binder in this way and opens the possibility of studies on formulated systems.

Keywords: Amorphous; Granulation; Binder; PVP; Lactose; HyperDSC (or fast scan DSC)

1. Introduction

There is now a major research effort in studies relating to physical form of pharmaceuticals. This is true within multinational pharmaceutical companies where there are very large groups involved in understanding how physical form will impact on the processing, stability and biopharmaceutical properties of active pharmaceutical ingredients, as well as in smaller companies (although often through outsourcing to contract research organisations) and in academic departments. Studies of actives and excipients will give rise to a better control and understanding of how medicines are manufactured and how to optimise their properties. Furthermore, there are many intellectual property issues around physical form, leading to extension of patents for innovators and to disputes and challenges from potential generic manufacturers. One major, and mostly unresolved issue, is to be able to study properties of individual materials within formulated products. For example studies of the amorphous form can be complex with a single component (whether active or excipient) not least because many methods struggle to detect the presence of the amorphous state (e.g. X-ray diffraction) and/or are subject to interference from other components of the formulation (e.g. spectroscopy). There is therefore a real need to be able to study the properties of amorphous materials in the presence of formulation components, ideally in realistic proportions. The challenge that is explored in this study is to attempt to measure properties of an amorphous binder with a traditional tabletting excipient, to test detection sensitivity. The technique that has been used is high speed differential scanning calorimetry.

High speed differential scanning calorimetry (HyperDSC) allows samples to be scanned at very fast rates and, as the heat flow per unit of time is larger for any thermal event at fast scan rates, provides greater detection sensitivity. Recently we have shown that HyperDSC provides a valuable method by which to detect small quantities of amorphous lactose in mixtures of

* Corresponding author. Tel.: +44 207 753 5858; fax: +44 207 753 5858.
E-mail address: Graham.Buckton@ulsop.ac.uk (G. Buckton).

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amorphous and crystalline lactose (Saunders et al., 2004) and also that the glass transition of polyvinylpyrrolidone (PVP) can be detected when it is mixed in small quantities with lactose (Saklatvala et al., 2005). In the previous publication (Saklatvala et al., 2005) it was shown that modulated temperature DSC (TA Instruments 2920, heating rate 2 °C/min; modulation of 2 °C period of 60 s) was able to detect the glass transition (T_g) of PVP in a mixture of PVP and lactose which contained 40% PVP, but not possible to detect the PVP transition when the mixture was 30% PVP. With HyperDSC it was possible to detect the T_g of PVP in mixtures containing as little as 5% PVP, and furthermore, the heat capacity (C_p) steps measured for T_g of PVP with HyperDSC were broadly proportional to the PVP content in the lactose/PVP mixtures, demonstrating that it was potentially possible to quantity the PVP content from step change in C_p.

It was previously demonstrated that the shift in T_g due to water content was essentially the same for PVP when using either modulated DSC or HyperDSC (Saklatvala et al., 2005).

Thus, the previous work has shown that it is conceptually possible to measure the behaviour of a binder in a granulation, even when it is present in realistic (rather than elevated) proportions in the formulation. The hypothesis is that HyperDSC is a potential technique for studies of small changes in minor components of real formulated systems which would offer a real advance in our understanding of changes in formulated systems either between batches or on storage. The purpose of this paper is to consider real granulations of lactose and PVP and to assess the extent to which HyperDSC can be used to study the properties of such systems.

2. Materials and methods

PVP was K30, molecular weight 40,000 from Fluka Chemicals. Lactose monohydrate (hereafter referred to as lactose) was Zeprox, Borculo Whey Products, Cheshire UK. Both were passed through a 425 μm sieve to disaggregate, but otherwise used as received.

The DSC experiments were undertaken using a Perkin-Elmer Diamond DSC with non-hermetic aluminium pans and helium flush, unless otherwise stated below. Calibration was with indium. Sample mass was in the region of 3 mg for powders and up to 10 mg for granules, and scan rates were varied between 20 and 500 °C/min. In order to detect the T_g of PVP clearly it was necessary to first heat the sample to 165 °C for 30 s, then cool to 30 °C before the measurement was undertaken. Each experiment was repeated three times and T_g was measured as the value at the mid-point of the transition (the "half height method"). Thermogravimetric analysis was undertaken using a Perkin-Elmer TGA 7.

Powder mixtures were prepared by placing a known mass of PVP and lactose in a Turbula mixer and mixing at 60 rpm for 20 min. The volume of the powder in the glass mixing jar was never greater than ca. 25% of the total volume of the jar. The mixed samples were stored in a desiccator over P_2O_5 until tested.

Granules were prepared by making a 12% (w/v) solution of PVP in distilled water. The PVP solution was then gradually added (slow, near dropwise, pouring) to 200 g of lactose in a planetary mixer (Kenwood Chef), with sufficient mixing to ensure uniform appearance. Sub lots of the wet mass were then screened through either a 45, 120, 250, 355 or 710 μm sieve, yielding granules of different sizes. The granules were then collected on glass Petri dishes and dried in an oven at 60 °C until constant weight was achieved. The dried granules were then sieved through a stack of sieves and the sieve sections collected, and then stored in glass bottles in a desiccator over P_2O_5.

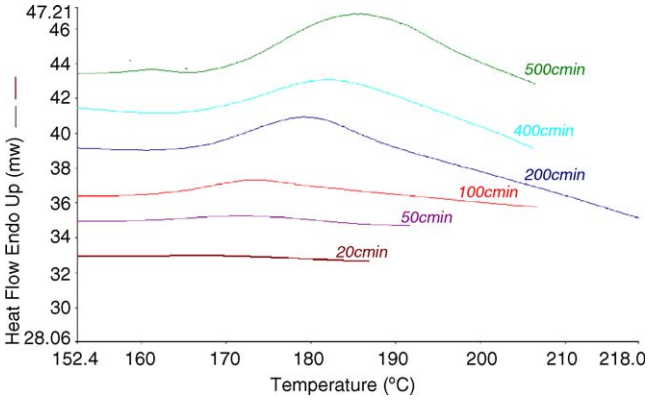

Fig. 1. The T_g of PVPK-30 measured at various scan rates from 20 to 500 °C/min.

3. Results and discussion

3.1. The effect of scan rate on the T_g of PVP

It is known that DSC scan rate can impact on the measured T_g (for example: Fukuoka et al., 1986, 1991; Kerc and Srcic, 1995), and that values of T_g for PVP range between 168 and 171 °C (e.g. Hancock et al., 1998) depending upon the molecular weight, polydispersity and water content. The results obtained for the T_g at different scan rates, all for 3 mg samples that had been dried over P_2O_5, are shown in Fig. 1 from which it can be seen that the faster the scan rate the easier it is to see T_g, and the higher the measured value becomes. These data are tabulated in Table 1 showing that the T_g shifts from 162 to 169 °C and the width of the transition increases from ca. 4 to 12 °C as scan rate is increased. These data allow the activation energy of the glass transition to be determined by plotted the log of heating rate (K/min) as a function of the reciprocal of absolute temperature of T_g. Amorphous materials are often described as strong and fragile glass formers, where strong glasses are more resistant to temperature changes and show Arrhenius behaviour for their relaxation processes (Ediger et al., 1996). The fragility (m) of the glass is often linked to the activation energy (A_e) using the following equation, where R is the gas constant:

$$m = \frac{A_e}{2.303RT_g} \quad (1)$$

Thus, calculation of the activation energy will allow the fragility to be measured. High values of fragility (tending to 100) are typical of fragile materials (see for example Bell et al., 1995). Such an approach has been used by Hancock et al. (1998) who

Table 1
The effect of heating rate on the measured T_g of PVP K-30

Heating rate (°C/min)	Onset T (°C)	T_g mid-point (°C)	End of transition (°C)	[delta]C_p (J/g K)	Width of T_g (°C)
20	161.7 (1.8)	163.7 (0.5)	165.5 (0.1)	0.022	3.7
50	162.6 (1.8)	165.8 (0.1)	169.5 (0.2)	0.029	6.9
100	163.1 (1.3)	166.7 (0.3)	170.3 (0.1)	0.033	7.2
200	166.8 (2.5)	172.2 (1.4)	177.6 (0.2)	0.172	10.7
400	168.2 (0.45)	174.1 (0.9)	179.9 (1.6)	0.181	11.65
500	169.2 (1.0)	174.7 (1.0)	180.1 (3.5)	0.169	12.02

have shown the activation energy for PVP K30 to be 398 kJ/mol for a heating rate range of 5–30 K/min. In the current study the Arrhenius plot (Fig. 2) showed excellent linearity over a heating rate range of 20–500 K/min ($r^2 = 0.99$), yielding an activation energy of 389.4 kJ/mol for the T_g. This activation energy allows the fragility of the glass to be calculated (see Hancock et al., 1998) and the value was found to be 46.0, being similar to the value determined by Hancock et al using a narrower heating rate range. These data demonstrate that the T_g process is the same over the wide heating rate range studied here and give confidence that work carried out at 500 K/min can be related to the transitions measured using more conventional scan rates. Whilst it was anticipated that the T_g process would remain the same, this has not been demonstrated previously at such scan rates, it was possible that the rapid scan rates would alter the nature of the transition (perhaps due to artefacts which could have resulted if, for example, the sample was not in equilibrium with the fast heating rates).

3.2. Limit of detection of PVP in physical mixtures with crystalline lactose monohydrate

Previously we (Saklatvala et al., 2005) have shown that it was possible to detect the T_g of PVP in the presence of crystalline lactose at a level of 5% (w/w), this was not a minimum value as no lower mixtures were studied. In the current work we have explored the mixtures down to 2% (w/w) and have been able to construct a plot of amorphous content as a function of step height (heat capacity change) which is presented in Fig. 3.

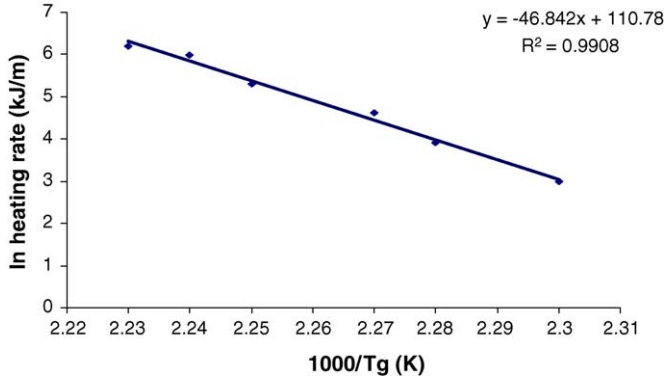

Fig. 2. Log of heating rate (kJ/mol) vs. 1000/T_g (K).

It can be seen (Fig. 3) that it is possible to detect and indeed quantify (at least to a reasonable extent) the PVP content well below 5%, and certainly to 2–3% PVP content. In view of this relationship, granule systems were studied in which PVP was present as 3% (w/w) in lactose. This is not an unrealistic PVP loading for granulated systems, although it would obviously be possible to have granules with lower PVP loadings.

3.3. Studies on granules of PVP and lactose

By definition granules are larger than powders and as the HyperDSC method involves very short run times, there is a real question about whether it will be possible to achieve temperature equilibrium rapidly in a sample if contact between the sample and the DSC pan is limited (for example due to a large particle size). Data for scans on different sieved size fractions of PVP 3% lactose granules are presented in Table 2. It can be seen that there was no difference in T_g response across the size range, indicating that heat transfer through the granules was rapid and that the PVP content was readily detectable in all granule sizes.

Despite the similarity of T_g values for each granule size, there was a large difference between the value obtained for granules (T_g of ca. 140 °C) and that measured for physical mixtures of

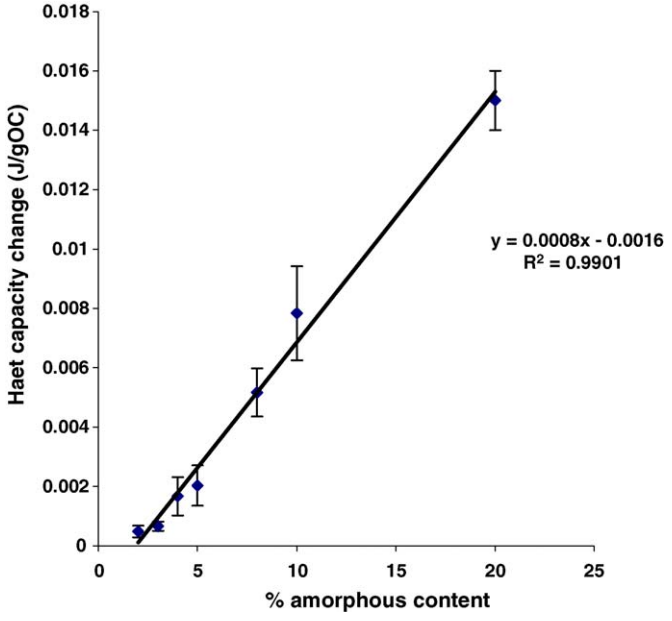

Fig. 3. Heat capacity change as a function of amorphous content (content of PVP) in physical mixtures with lactose.

Table 2
The effect of granule size on the measured T_g for granules containing 3% PVP in lactose

Granule size (μm)	Onset temperature (°C)	T_g mid-point (°C)	End temperature (°C)	Width (°C)
40–120	140.9 (4.9)	145.2 (1.5)	149.8 (1.0)	8.9
120–255	139.5 (0.8)	144.9 (0.2)	148.9 (0.4)	9.4
255–300	139.3 (3.8)	145.8 (1.5)	150.5 (0.4)	10.8
300–425	140.9 (0.1)	146.2 (0.7)	151.2 (0.5)	10.2
425–500	140.3 (1.2)	145.2 (2.1)	149.6 (1.9)	9.3
500–710	142.4 (0.6)	146.4 (0.6)	150.6 (0.6)	8.2

PVP and lactose (see Table 1 with T_g values of ca. 169 °C). There are various factors that can alter T_g, one major one being water content. Obviously there is a loss of hydrate water from lactose at ca 150 °C and this water could possible affect the measured T_g, however there should really be no difference in this water loss of granules or mixtures, especially as the data show that granule size is not a significant factor for T_g. However, the water loss from granules and mixtures was measured using thermogravimetric analysis. These data (Fig. 4) show the loss of lactose hydrate water at ca. 150 °C and show substantial free water loss for the physical mixture and for PVP alone, but negligible free water loss for the lactose granule. Despite the high free water content for the physical mixture the T_g that was measured was high (presumably due to water desorption in advance of T_g), whereas as the T_g was low for the granule despite no significant water content. It follows that the T_g of the granule has been depressed due to a factor other than water content.

The granule was formed by adding an aqueous solution of PVP to lactose and it is possible that some lactose dissolved forming a saturated solution with PVP in water. When the granule formed it seems that the solid amorphous region is a mixture of amorphous lactose and PVP as a stabilised solid dispersion. The lower T_g reflects the mixture or two components (lactose and PVP) and using a simple approach (the well known Gordon–Taylor equation with T_g for lactose 113 °C and density 1.43 g/ml and PVP T_g 169 °C (Table 1) and density 1.25 g/ml) it can be shown that the amorphous state would contain about equal proportions of PVP and lactose. Clearly, the calculation of the PVP/lactose concentration is relying on the assumptions that are central to the Gordon–Taylor equation, which are an assumption of volume additivity and ideality, however, this is usually a reasonable approximation for many systems.

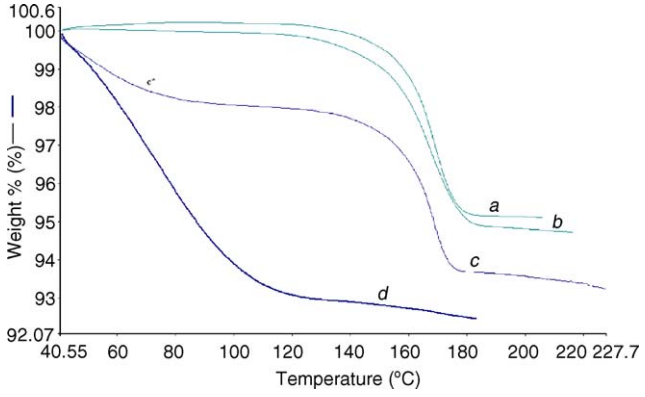

Fig. 4. Thermogravimetric analysis data for (a) crystalline lactose monohydrate, (b) PVP–lactose granules containing 3% PVP, (c) PVP–lactose mixture and (d) PVP.

We believe that this is the first time that it has been shown that binders in granulations are made up of the binder and a dissolved material as a solid amorphous dispersion. The ability to measure and understand the properties of granules could open up new opportunities, for example the study of why tablets change physico-chemical properties on storage. Using the example of a PVP and lactose formulation it would be conceivable that the solid dispersion of amorphous lactose and PVP could change over time to yield crystalline lactose bridges which may well lead to changes in tablet tensile strength. Whilst this application has not been explored as yet, it is a reasonable possibility and certainly the chances of being able to study it are now much enhanced.

4. Conclusion

Although this work has been carried out on a relatively simple system (two component), it shows several things, firstly that HyperDSC provides a technique with which it is possible to study small amounts of amorphous material in a model granulation. Beyond this it shows that the granule is in fact bound together with an amorphous phase that is composed of lactose and PVP in approximately equal proportions. We are not aware of such measurements or observations in the literature on granulated systems.

Whilst development to more complex formulations will inevitably bring further challenges there are encouraging signs that a greater understanding can be obtained on formulated systems and the physical form of materials included there in.

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