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Effect of moisture on polyvinylpyrrolidone in accelerated stability testing

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Abstract

Accelerated stability studies are a common approach for predicting the long-term stability of pharmaceutical formulations. However, in this study, a slowing of dissolution was observed for a formulation following storage at elevated temperature and humidity. The moisture sorption isotherm for the binder, polyvinylpyrrolidone (PVP), shows absorption of a significant quantity of water on exposure to elevated humidity. Modulated temperature differential scanning calorimetry (mDSC) has been used to demonstrate that moisture uptake will depress the glass transition temperature (Tg) of PVP to the conditions used in accelerated stability studies. Exposure to elevated temperature and humidity resulted in a change in the PVP from the glassy to the rubbery state. This conversion produces a change in the dissolution profile. Long-term stability studies conducted at temperatures and humidities below the Tg, would not have induced this change.

Keywords: Tablet; Dissolution; Differential scanning calorimetry; Glass; PVP

1. Introduction

The in vitro dissolution for oral solid dosage forms is commonly used to ensure consistent in vivo performance. The FDA guidelines for scale-up and post approval changes (SUPAC) provide a waiver for bioequivalence provided the same in vitro dissolution profile is obtained (FDA Guidance for Industry, 2000). For Class I compounds (high solubility and permeability) an in vitro dissolution of 85% drug release after 15 min is deemed sufficient to waive the requirement for in vivo bioequivalence testing (Amidon et al., 1995). Similar guidance has been issued by the European Medicines Evaluation Agency (EMEA Guidance, 2001).

Consistent dissolution profiles are not only important following changes to a process, but throughout the shelf life. The current ICH guidelines recommend long term stability testing at 25 °C/60% RH (relative humidity). Accelerated stability testing is performed at 40 °C/75% RH, or

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if significant change has taken place at this condition, then 30 °C/60% RH can be used as an accelerated condition (ICH Guideline Q1A(R), 2000).

The benefits of generating stability data rapidly at elevated temperature and humidity are clear. However, care must be taken in the interpretation of the data as the increase in temperature and humidity could lead to a change physicochemically, producing a modification in the mechanism of change, so that accelerated conditions are not truly predictive of the real time stability of the system. Any accelerated stability should be backed up with real time data to ensure assumptions are valid (Aulton, 1998).

The effects of changes in the physical form of polyvinylpyrrolidone (PVP) in tablet formulations has been reported. Kiekens et al. (2000) showed the impact of the glassy to rubbery transition of amorphous PVP on the physico–mechanical stability of tablets prepared with a PVP binder. They showed that the tensile strength of tablets of glass microspheres prepared with PVP increased when the storage conditions caused the PVP to undergo a transition from the rigid glassy state to a mobile rubbery state. The increase in tensile strength was related to the continuous swelling of the polymer, leading to the creation of new binding or contact sites.

Stubberud et al. (1996) demonstrated a weakening effect of moisture sorption on the tensile strength of compacts of lactose with and without PVP.

In this paper, the accelerated data from the dissolution testing of a formulation of a new chemical entity has been shown not to be predictive of the long term stability of the formulation. The binder utilised in the formulation was PVP and the data presented show that the change in dissolution rate is related to the amorphous binder going through a glass transition. The aim of the work was to use modulated temperature differential scanning calorimetry (mDSC) to correlate the Tg of PVP with the moisture content of the sample. This would be used in conjunction with the moisture sorption isotherms for PVP at a range of storage temperatures to determine the critical humidity at which the conversion would occur. This can predict the long term stability of the formulation in terms of the dissolution rate.

2. Materials and methods

The active in the formulation (compound A) is a pyrydazine derivative. It is a crystalline material, with a melting point above 100 °C, and is essentially non-hygroscopic up to 90% RH. The other components used in the study are microcrystalline cellulose (Avicel PH101, FMC Corporation, Newark, Delaware), lactose monohydrate (Foremost, Rothschild, Wisconsin), croscarmellose sodium (Ac-Di-Sol, FMC Corporation, Newark, Delaware), PVP K29/32 (ISP Technologies, Wayne, NJ), hydroxypropyl cellulose (HPC) (Klucel EXF, Hercules Inc., Wilmington, Delaware), sodium lauryl sulphate (Albright and Wilson, Barcelona, Spain) and magnesium stearate (Mallinckrodt, St. Louis, MO).

Two batches of tablets were prepared using either PVP or HPC as the binder. In each case, compound A was mixed with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and PVP or HPC in a high shear mixer granulator (Fukae Powtec). A solution of sodium lauryl sulphate in water was then added and wet massed until a suitable granule was obtained. The wet mass was dried in a fluid bed dryer (Aeromatic Strea-1). The dried granule was milled and subsequently lubricated with magnesium stearate in a tumble blender (Turbula) for 1 min. The lubricated granule was compressed (Manesty F-Press) with 1/4 round, normal concave tooling to an average hardness of 7 kP.

The stability storage of the tablet samples was in chambers with controlled temperature and humidity. The chambers were set at 5 °C/50% RH, 25 °C/60% RH, 30 °C/60% RH, 40 °C/20% RH and 40 °C/75% RH.

Dissolution testing (USP II apparatus) using 0.01 M hydrochloric acid, with paddles rotating at 50 rpm. The quantity of drug dissolved was determined by a HPLC assay. Three tablets were tested at each sample point.

mDSC analysis was performed using a TA Instruments DSC 2920 with mDSC capability

and refrigerated cooling system, purged with nitrogen, analysed in hermetically sealed aluminium pans. The samples were cooled to −20 °C, followed by a heating rate of 2 °C/min, a modulation amplitude of 2 °C and a period of 60 s was used for each sample. Curve fitting of the Tg data was performed using Kaleidagraph software package (version 3.09, Synergy Software).

The moisture content of the PVP was obtained by thermogravimetric analysis (TA Instruments TGA 2950), heated at 5 °C/min from 25 to 200 °C under a nitrogen purge.

The moisture sorption isotherms for PVP were obtained using an automated moisture balance fitted with a video capture device (Surface Measurement Systems, London, UK). The true density was determined using a helium pycnometer (Quantachrome Corporation, Camberley UK). The porosity and pore size distributions of the samples were obtained using a mercury porosimeter (Quantachrome Corporation, Camberley, UK).

3. Results and discussion

Compound A meets the criteria for solubility and permeability (Biopharmaceutical Classification System for class I compound). The dissolution data obtained for the two formulations, prepared with either HPC or PVP as the binder, and following stability storage are shown in Tables 1 and 2. The dissolution profiles for the two formulations are slightly different. However, this is as expected by the physicochemical properties of the binder systems. In both cases, the dissolution rate is sufficient to comply with the requirements for a fast dissolving dosage form, as defined in the current FDA and EMEA guidelines for class I compounds (> 85% dissolved in 30 min).

For the formulation prepared with HPC as binder, after 24 weeks there is essentially no change in the dissolution profile for any samples stored at the conditions tested. In contrast, for the formulation prepared using PVP as the binder, there is a slowing of the dissolution, with the percent dissolved at 15 min being reduced from approximately 80 to 48%. There was no change observed in any of the other stability conditions, and indeed after 1 year of storage at 30 °C/60% RH, there was no change observed. Clearly storage at 40 °C/75% RH is not predictive of the longer term stability of this system at 30 °C/60% RH.

As this dissolution change is only seen with the PVP based formulation, and not the HPC formulation, it is reasonable to conclude that the mechanism underlying the change is related to the PVP. This analysis has not considered the role of the other components of the formulation, and specifically any influence the drug or excipients may have on the Tg of PVP. It has been shown by Nair et al. (2001) that the presence of various drugs in PVP films can have a significant plasticising effect and further reduce the Tg. These interactions would only act to further reduce the Tg of the PVP, but would not impact on the overall conclusions from the study. As there is no change in dissolution observed on storage at

Table 1
Dissolution data following stability testing for tablets prepared with PVP as the binder

Time on test (weeks)	Condition (°C/% RH)	Dissolved (range) %				
		10 min	15 min	20 min	30 min	45 min
24	5/50	62 (58–66)	79 (78–80)	87 (86–88)	94 (94–95)	97 (97–98)
24	25/60	59 (50–65)	78 (71–82)	86 (82–89)	94 (91–96)	98 (97–99)
24	30/60	60 (56–66)	79 (76–81)	88 (86–90)	95 (93–96)	98 (97–100)
24	40/20	63 (56–69)	80 (77–83)	88 (86–90)	95 (93–96)	98 (96–99)
24	40/75	33 (27–35)	48 (45–49)	57 (56–58)	68 (67–69)	79 (78–81)
61	30/60	67 (62–83)	83 (78–86)	88 (85–90)	94 (92–96)	97 (95–98)

Table 2
Dissolution data following stability testing for tablets prepared with HPC as the binder

Time on test (weeks)	Condition (°C/% RH)	Dissolved (range) %				
		10 min	15 min	20 min	30 min	45 min
24	5/50	91 (90–93)	97 (95–99)	98 (97–100)	100 (99–101)	100 (99–102)
24	30/60	95 (92–97)	95 (97–100)	100 (98–101)	100 (98–101)	100 (98–101)
24	40/75	93 (91–94)	98 (97–99)	100 (99–101)	100 (99–101)	100 (99–101)

30 °C/60% RH, it can be concluded that the additional plasticising effects of the drug and excipients are insufficient to reduce the Tg to below 30 °C, when stored at 60% RH.

It is known that PVP is a relatively hygroscopic material, and the moisture sorption isotherm, Fig. 1, shows that at 25 °C PVP will absorb approximately 5–10% moisture at 10% RH, but that this increases significantly as the relative humidity above the samples is increased. On exposure to 80% RH, the sample will absorb approximately 40% moisture, based on the dry mass of sample.

On heating amorphous polymeric materials, such as PVP, there is a change in the heat capacity of the material as it moves from the glassy to the rubbery state. This conversion is reversible and so can be seen on both the heating and cooling curves. The reversibility of the conversion also allows for the step change to be isolated from non-reversible events during heating by the modulated signal of the mDSC (McPhillips et al., 1999). A sample mDSC trace for PVP is shown in Fig. 2, and the Tg is indicated.

Addition of a plasticiser causes a reduction in the Tg of the polymeric material. Water vapour is a well known plasticiser, particularly for polymeric materials such as PVP. The impact of water on the Tg of PVP has been studied by storing PVP samples at a range of humidities. The water content of the samples was determined by TGA. A sample TGA trace is shown in Fig. 3. Attempts to identify the Tg of the PVP within the formulation in situ were unsuccessful. The sensitivity of the mDSC was insufficient to observe the change

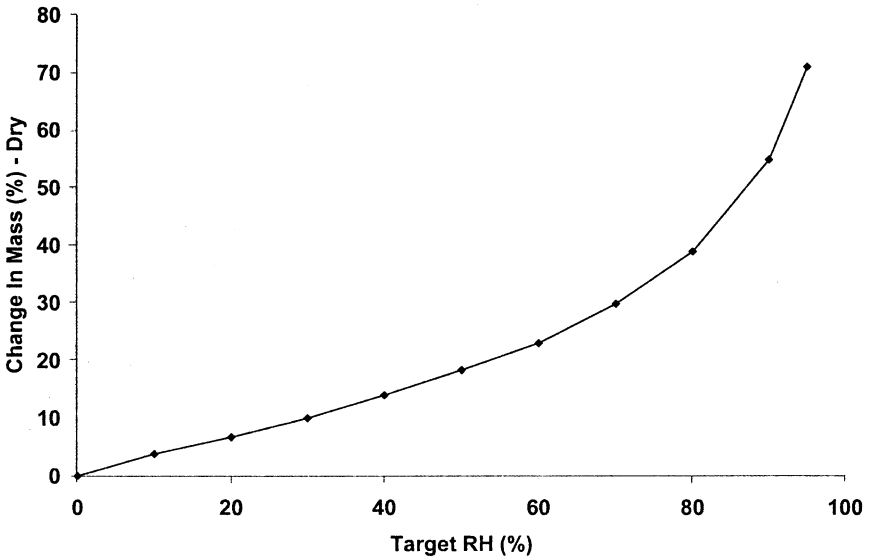

Fig. 1. Moisture sorption isotherm for PVP at 25 °C.

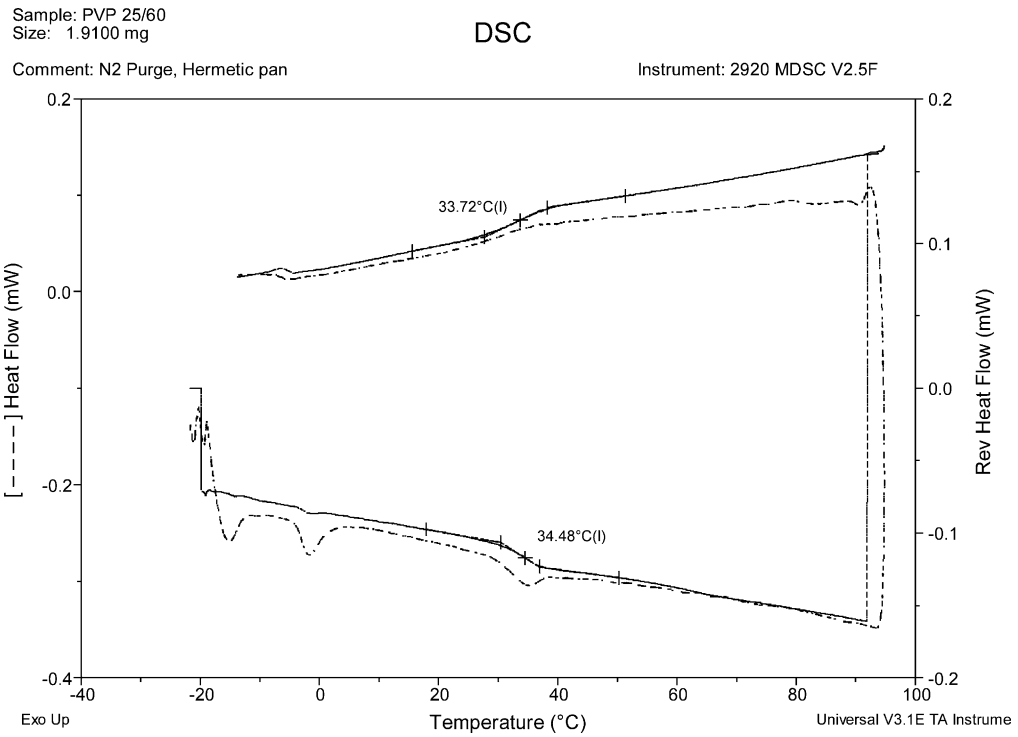

Fig. 2. mDSC trace for PVP following equilibration at 25 °C/60% RH, showing Tg of 33.72 °C on heating, and 34.48 °C on cooling.

in heat capacity of the polymer when in the formulation at a level of less than 5%.

The effect of water content of the glass transition temperature of PVP is shown in Fig. 4, and the results are in agreement with those reported by Oksanen and Zografi (1990). As the water content is increased, the Tg is depressed from around 458 K for dry PVP to around 320 K for samples containing in excess of 15% water. These data have been fitted to the Gordon–Taylor Eq. (1) to model the effect of water on the Tg of PVP (Gordon and Taylor, 1952):

$$\mathrm{Tg} = \frac{w_1 \mathrm{Tg}_1 + k w_2 \mathrm{Tg}_2}{w_1 + k w_2} \tag{1}$$

where Tg is glass transition temperature a PVP/water sample. Tg_1 is the glass transition temperature of anhydrous PVP, Tg_2 is the glass transition temperature of water (−135 °C), w_1 and w_2 are the weight fractions of PVP and water, respectively, and k is a constant.

The equation is based on the additivity of free volumes of the individual components in an ideal mix. The constant k, which is a measure of the interaction between the components can be approximated using Eq. (2) (Simha and Boyer, 1962).

$$k \approx \frac{\rho_1}{\rho_2} \frac{\mathrm{Tg}_1}{\mathrm{Tg}_2} \tag{2}$$

where ρ_1 and ρ_2 refer to the true densities of the components. The values used for the true densities of PVP and water were 1.18 and 1.00 g/cm^3, and for the Tgs 458 and 138 K were used, respectively, (Stubberud et al., 1996).

Fig. 4 shows that on storage at elevated humidity, the Tg for PVP is depressed to below the storage temperatures used in these studies. This would result in the PVP within the formulation converting from the initial glassy state to the

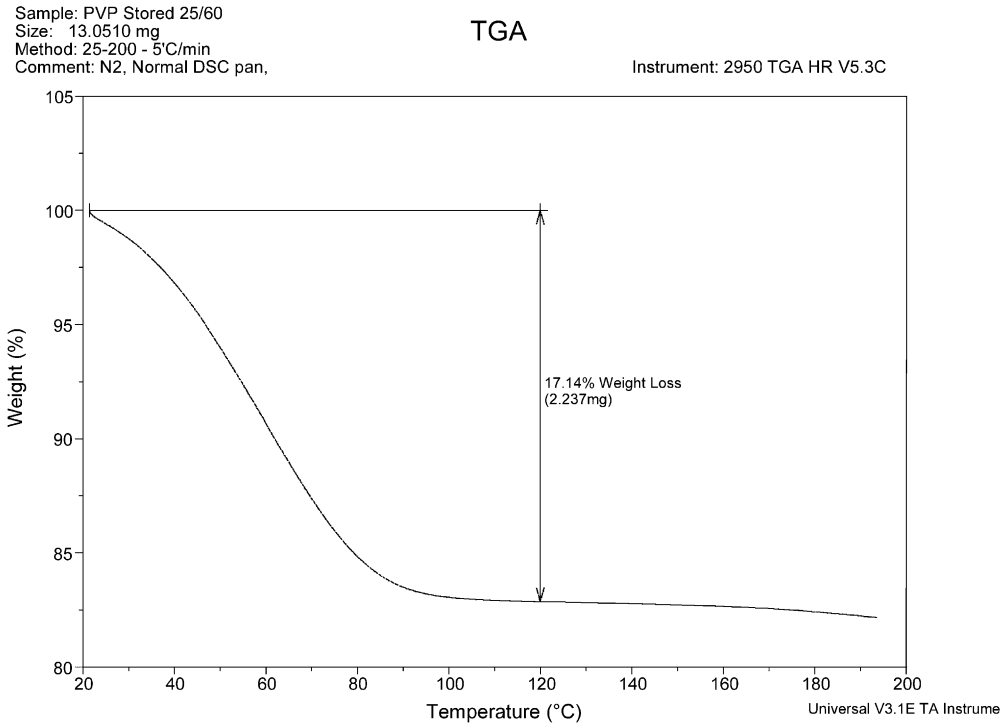

Fig. 3. TGA trace for PVP, following equilibration at 25 °C/60% RH, showing water content of 17.14%.

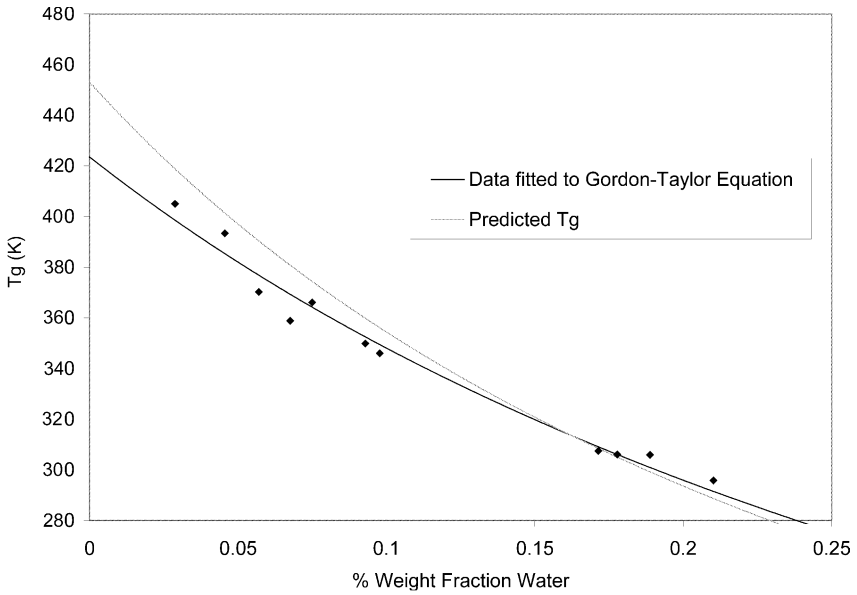

Fig. 4. Effect of water content on the Tg of PVP. Actual data fitted to Gordon–Taylor equation and compared with predicted Gordon–Taylor fit.

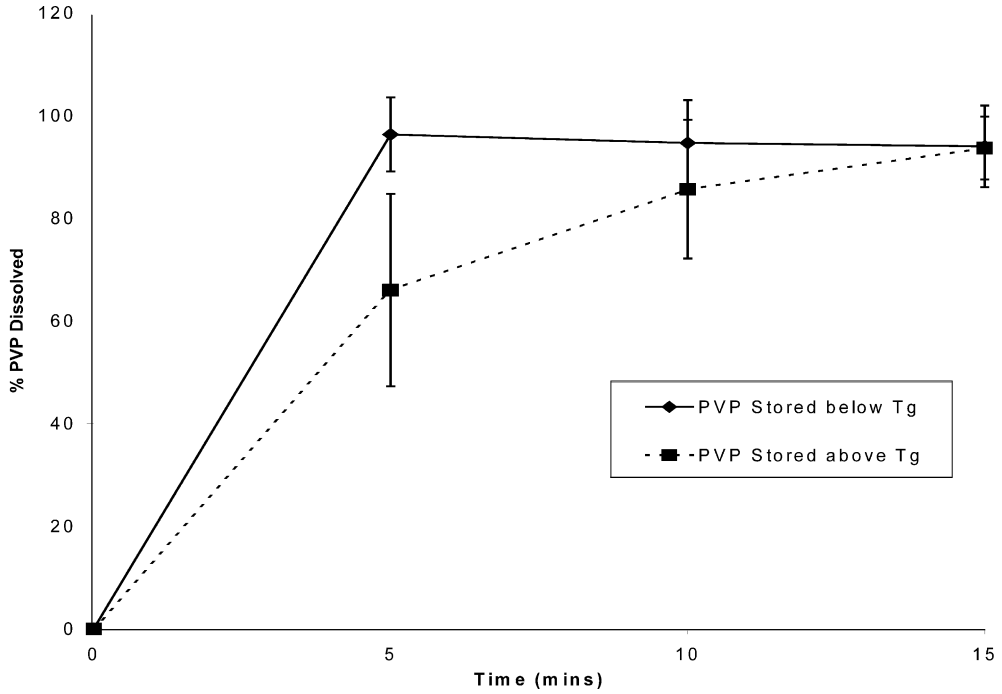

Fig. 5. Dissolution of PVP following storage either above or below the Tg.

rubbery state. It is proposed that this transition is responsible for the slowing of dissolution observed during tablet storage.

The dissolution behaviour of pure PVP stored above and below the Tg has been studied and the results are included in Fig. 5. In each case the sample was equilibrated at room temperature prior to dissolution testing. This would result in any materials stored above the Tg reverting back to the glassy state, so any observed difference would be due to changes in the physical structure of the material when stored in the rubbery state. The results show that the dissolution rate for PVP that has gone through the Tg and been stored in the rubbery state, i.e. stored above the Tg, is slower than that for material which has remained in the glassy state throughout the study, i.e. stored below the Tg.

This change in the dissolution of the PVP correlates with a change in the pore structure of the material. Fig. 6 shows the pore distributions for PVP stored either above or below Tg. The plot of $dV/d(\log d)$ against pore diameter shows the relationship between the volume of mercury intruded as a function of the pore diameter. It can be seen that the sample stored above the Tg has a lower overall porosity and smaller mean pore size. It is postulated that this change in porosity may have arisen for the material stored above the Tg as the viscosity of the PVP will have reduced, leading to a greater mobility of the material and the loss of pore structure.

The behaviour of HPC under the same conditions is significantly different. A classical glass transition as shown for PVP was not seen by mDSC under similar conditions. This is in line with previous studies (Kararli et al., 1990) that reported that dynamic mechanical analysis (DMA) did not demonstrate a primary Tg for HPC. The polymer was shown by hot stage microscopy to melt at 190–195 °C. It is proposed that this absence of a primary Tg for HPC means that, in contrast to the observations for PVP, the physical state of the HPC polymer remains unchanged on

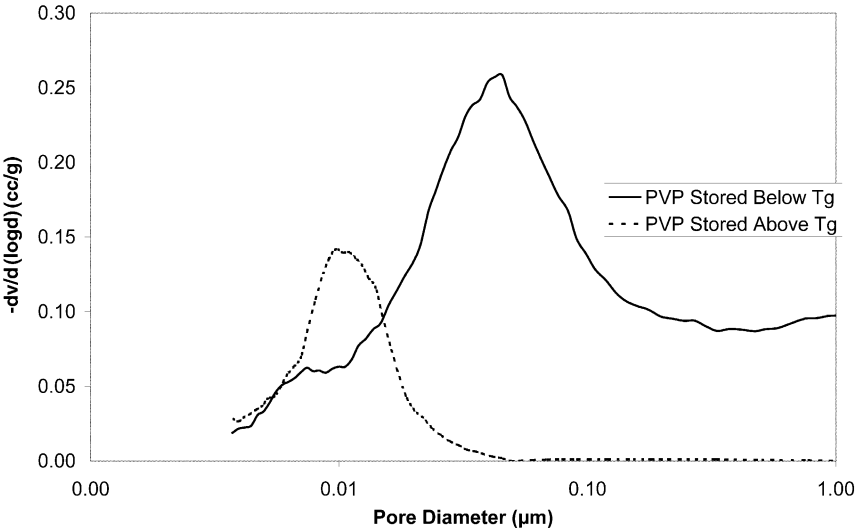

Fig. 6. Comparison of pore size distribution by mercury porosimetry for PVP stored either above or below the Tg.

stability and consequently the slowing of dissolution attributed to PVP is not seen for the HPC samples.

4. Conclusions

Modulated temperature DSC has been used to determine the Tg of PVP. This material absorbs significant quantities of water at elevated humidity. The water can act as a plasticiser and depress the Tg from approximately 170 to below 40 °C. In contrast, HPC does not exhibit a primary glass transition. This depression of Tg for PVP but not HPC has been correlated with a slowing in tablet dissolution observed for a PVP based formulation.

It is proposed that exposure of the PVP based formulation to elevated humidity, depressed the Tg of the binder to below the storage temperature. The PVP then went through a conversion from the glassy to rubbery state. This conversion produced a densification and reduction in porosity of the binder, and this change in the physical state of the amorphous polymer led to the change observed in tablet dissolution rate. The HPC system does not go through the same physical change and no change in dissolution rate was observed.

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