Effect of the Storage Conditions on the Tensile Strength of Tablets in Relation to the Enthalpy Relaxation of the Binder

F. Kiekens,[1] R. Zelko,[2] and J. P. Remon[1,3]

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INTRODUCTION

From a pharmaceutical technological standpoint, interactions mean those processes that take place during the preparation, storage and administration of a drug product and that may contribute to changes of the original state of active ingredients and/or additives and/or the dosage form as well. Amorphous polymer excipients are often highly reactive and unstable to mechanical and thermal stresses above their glass transition temperatures (T_g) and this may result in significant variation in some of their key physico-mechanical properties. Whilst many of those excipients, like various types of PVP polymers, have T_g values above the normal operating temperatures, the plasticising effect of residual solvents, absorbed water and other additives could affect their long term performance and stability in pharmaceutical dosage forms by a Tg reduction (1–3). The long term physical stability of amorphous pharmaceutical materials is controlled by the type and rate of their molecular motions (4,5). Physical aging in polymeric systems is the term used to describe the time dependence of changes in the behavior of an amorphous polymer held at temperatures below the glass transition. Volume relaxation and enthalpy relaxation are two manifestations of physical aging, and they can be used to follow this process (6). By use of differential scanning calorimetry (DSC) the structural relaxation in amorphous polymers can be investigated with a high reproducibility. During such a DSC experiment a polymer sample is subjected to a more or less complicated thermal history, which starts at a temperature T_0 (above the glass transition temperature) and involves periods of heating or cooling at constant rates as well as isothermal stages, finishing at a temperature T_1 in the glassy state. Then the specific heat at constant pressure is measured during a heating scan at constant rate between T_1 and T_0. The C_p versus T curve thus obtained depends on the thermal history of the sample and contains information about structural relaxation, which occured both in the process previous to the measurement and during the measuring scan itself (7).

Stubberud (8) reported on the weakening effect of moisture sorption on the tensile strength and the physical stability of compacts of crystalline and partly amorphous lactose, alone and in binary mixtures with PVP. Alderborn and Ahlneck (9) assessed the effect of air humidity on the post compaction changes in tensile strength of tablets formulated with different pharmaceutical excipients. They found that changes in tablet strength were probably due to a rearrangement of solid material within the tablet that was facilitated by sorbed water. Rees and Tsardaka (10) examined the effects of moisture on the viscoelastic deformation during compaction of modified starch using creep tests and Heckel plots. They reported that the moisture, by facilitating elastic and plastic deformation, not only altered the compression behaviour of the material, but also its recovery during decompression in the die.

The objective of this work was to study the enthalpy relaxation of PVP powder samples stored at different relative humidities and to find a correlation between the tensile strength of the compacts containing PVP and stored at the same relative humidities as the pure PVP powder samples, and the enthalpy relaxation during the applied isotherm recovery process of PVP powder samples stored under various conditions.

MATERIALS AND METHODS

Materials

Polyvinylpyrrolidone (PVP, Kollidon K25, BASF, Ludwigshafen, Germany) was selected as an amorphous binder and Microperl® AQ (Sovitec Glaverbel, Fleurus, Belgium) glass microspheres with a mean diameter of 38 μm, as an inert substrate for the preparation of tablets.

Tablet Preparation

12 batches of 6 tablets were produced using a wet granulation procedure, which consisted of 100 g Microperl® AQ and 10 ml of a 15% (w/v) PVP aqueous solution. Next the wet granulated mass was compressed into a specially designed punch and die-system using a force of 10 kg so forming 12 mm diameter tablets. The tablets were dried in a hot air drier at 60°C for 24 h (Memmert, ULE 600, Schwabach, Germany).

Storage Conditions

Two batches of the dried tablets were transferred into each of the 6 dessicators (at 25%, 35%, 45%, 55%, 65% and 75% R.H.) and stored at room temperature for two storage periods of 1 week and 1 month, respectively. PVP powder samples were also kept under the same storage conditions.

Water Content Determination

The determination of the water content of the PVP powder samples was performed by Karl-Fischer titration (Mettler Toledo DL 35, Lot, Belgium) using dry methanol and Hydranal® Composite 5 (Riedel-De-Haën, Seelze, Germany).

Morphology of PVP Samples

The morphological examination of stored PVP powder samples was performed by scanning electron microscopy (SEM, Jeol JSM, Japan).

[1] Laboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, B-9000, Gent, Belgium.
[2] Pharmaceutical Institute, Semmelweis University of Medicine, Hõgyes E. u. 7., H-1092 Budapest, Hungary.
[3] To whom correspondence should be addressed. (e-mail: jeanpaul.remon@rug.ac.be)

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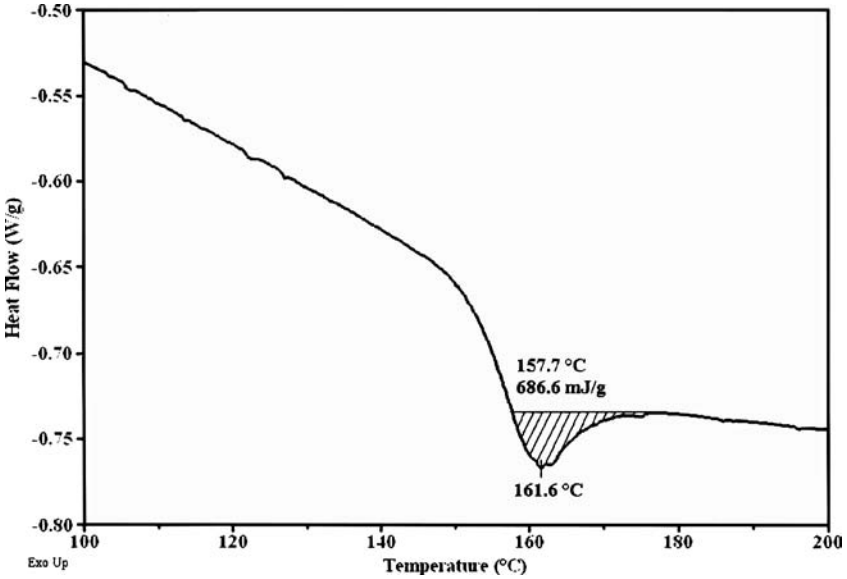

Fig. 1. The heat flow (W/g) versus temperature curves measured after an isothermal stage at the given ageing temperature of samples stored for 1 day at 75% R.H.

X-Ray Diffraction Measurements

XRD patterns of stored PVP powder samples were taken with a computer-controlled Diffractometer D5000, Cu, Kα (Siemens, Germany).

Thermal Analysis

After storage, the glass transition temperature and the maximal enthalpy recovery of the powder samples were evaluated using a differential scanning calorimeter (DSC 2920, TA Instruments, New Castle, DE, US) equipped with a liquid nitrogen cooling accessory. Approximately 2–5 mg samples were sealed in closed aluminum pans and transferred to the DSC-cell. After a primary cooling to −30°C, the sample was heated to 200°C and the glass transition temperature was determined using peak-analysis from the first derivative of the measured heat flow. The heating and cooling rates were always 20°C/min.

An 'expanded cooling/heating' procedure was applied to determine the maximum enthalpy recovery (1). The samples were subjected to a thermal history including an isothermal stage at temperature T_g-30 (aging temperature) with a duration of 30 minutes (aging time). The temperature changes of this procedure (heating to 195°C, cooling to −35°C, heating to 135°C and isotherm for 30 min, cooling to −35°C, and heating to 220°C), enabled the quantification of the molecular mobility of the polymer during the last heating run. The enthalpy relaxation endotherm was corrected for the change in heat capacity due to the glass transition phenomenon (Fig. 1) and the area under the corrected peak (ΔH) was divided by the measured glass transition temperature (T_g), yielding the change in heat capacity (ΔC_p). From this, the maximum enthalpy recovery (ΔH_∞) at any temperature is calculated (1) using following equations (Eq. 1 and Eq. 2).

$$\Delta C_p = \frac{\Delta H}{T_g} \tag{1}$$

$$\Delta H_\infty = (T_g - T)\Delta C_p \tag{2}$$

Tablet Hardness Tests

The hardness tests of tablets were performed on half of the compact-batches after a storage period of one week, while

Table I. The Glass Transition Temperature and the Water Content of the Stored Powder Samples at Different Relative Humidity

Relative humidity (%)	Glass transition temperature (°C; n = 2)	Water content (%w/w; n = 4)[a]		States glassy (G) rubbery (R)	Tablet tensile strength (Mpa)	
		1 week	4 weeks		1 week	4 weeks
Sample as received	164.8	4.1	4.1	G		
25	—[b]	9.5	9.5	G	1.24 ± 0.16	1.20 ± 0.18
35	—[b]	11.5	10.1	G	1.06 ± 0.17	0.90 ± 0.16
45	58.4	12.9	13.5	G	0.82 ± 0.11	0.66 ± 0.09
55	52.6	15.6	17.6	G	0.82 ± 0.10	0.58 ± 0.06
65	39.1	18.9	19.6	G + R	0.23 ± 0.03	0.36 ± 0.06
75	17.0	23.0	23.7	R	0.06 ± 0.01	0.06 ± 0.02

[a] In all cases the SD < 3%.
[b] Could not be measured (the water peak overlapped the transition).

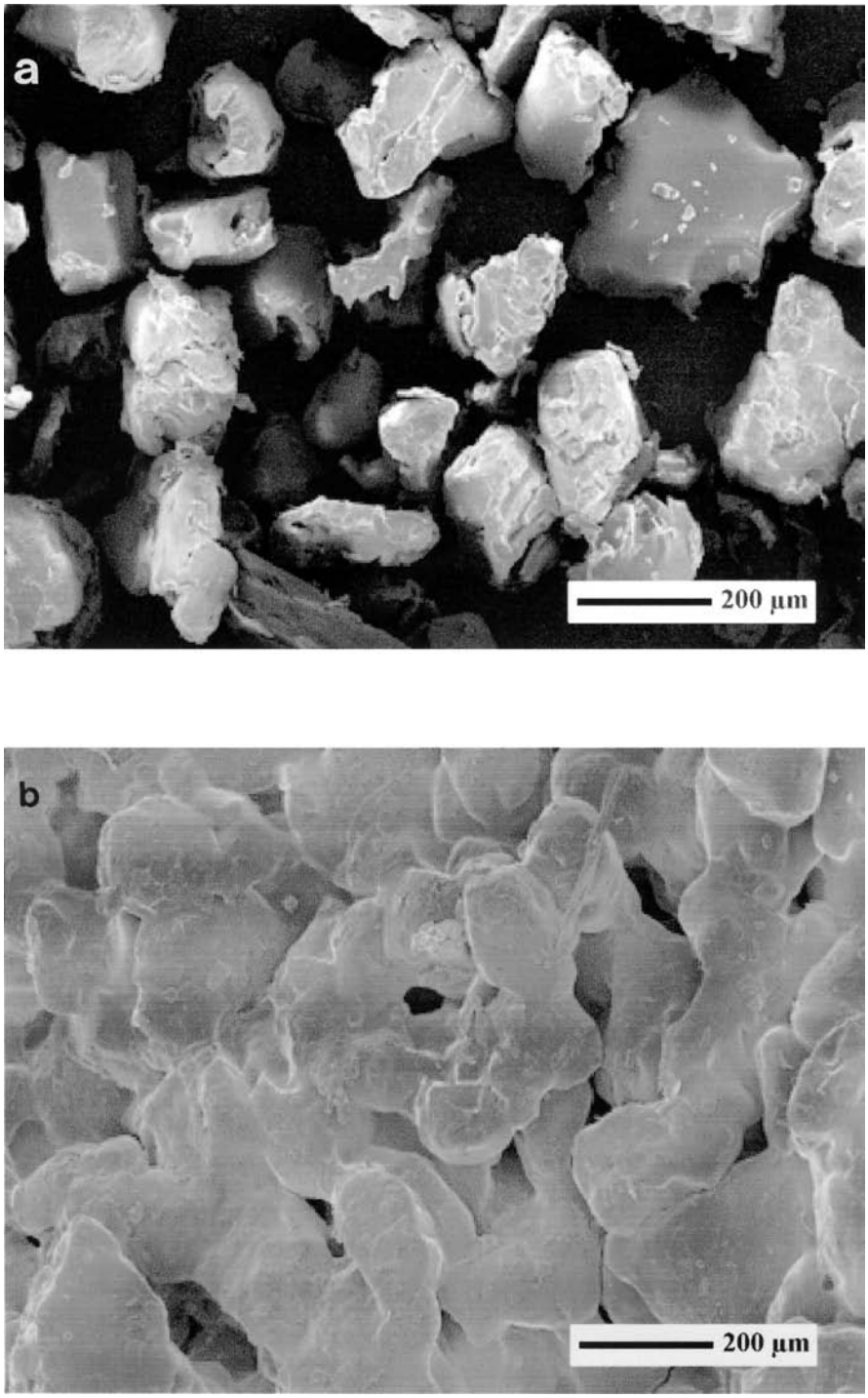

Fig. 2. (a) Scanning electron microscopy pictures of powder samples stored at 25% relative humidity (glassy state). (b) Scanning electron microscopy pictures of powder samples stored at 75% relative humidity (rubbery state).

the remaining part was stored further and tested for their hardness after 4 weeks (PharmaTest PTB 311, Hainburg, Germany). The tensile strength (σ) of tablets was determined (11) by the following equation (3).

$$\sigma = \frac{2P}{\pi Dt} \quad (3)$$

where P is the measured crushing force, D is the diameter and t is the thickness of the tablet.

RESULTS AND DISCUSSION

The measured glass transition temperatures (T_g) of the PVP powder samples (Table I) decreased as the relative humidity during storage and consequently the amount of absorbed

Table II. The Areas Under the Peak (ΔH), the Glass Transition Temperatures and the Calculated Heat Capacity Changes (ΔC_p) and Enthalpy Relaxation Values (ΔH_∞).

	1 day				4 weeks			
R.H. (%)	ΔH (mJ/g)	Tg (°C)	ΔC_p (mJ/g.°C)	ΔH_∞ (mJ/g)	ΔH (mJ/g)	Tg (°C)	ΔC_p (mJ/g.°C)	ΔH_∞ (mJ/g)
65	233	159.6	1.46	35.9	1681	164.3	10.23	299.7
75	687	157.7	4.36	99.0	843	165.6	5.09	154.5

water increased since the water present acted as a plasticizer. This is in agreement with the results reported by Oksanen and Zografi (12) describing similarly decreasing T_g values. The visual and scanning electron microscopy observations of the stored samples revealed that the polymer was in a glassy state (Fig. 2a) when stored up to 55% relative humidity and in a rubbery state at 75% (Fig. 2b). The samples stored at 65% changed progressively to the rubbery state as the storage time increased. The X-ray diffraction patterns showed that all samples remained amorphous, independently of the relative humidity during storage.

Fig. 1 shows the heat flow versus temperature curve, measured after an isothermal stage at the given aging temperature, presenting the peak that overlaps the glass transition. This curve was specific for samples stored at 65 and 75% R.H., independently of the storage time. Table II summarizes the measured and the calculated physicochemical properties—the quantified areas under the peak (ΔH), the calculated heat capacity changes (ΔC_p) and the enthalpy relaxation (ΔH_∞)—for PVP powder samples stored at 65% and 75% R.H., respectively. No enthalpy relaxation was observed in the case of PVP powder samples stored up to 55% R.H. These samples were in a rigid glassy state, and the applied aging time of 30 min of the experiments was not high enough to detect a characteristic endotherm at the glass transition temperature. At 65% and 75% R.H. the T_g of the PVP powder samples was reduced, and decreased below room temperature at 75% R.H., while the PVP underwent a transition from a rigid glassy state to a mobile rubbery state (2). Under the applied thermal history, enthalpy relaxation can be observed in the case of these samples. After a short storage period (1 day) at 75% R.H., the calculated enthalpy relaxation of the PVP powder sample was three times higher than that of the sample stored at 65% R.H. The latter can be explained by the fact that at 75% R.H. the whole sample was in a mobile rubbery state at room temperature. On the other hand, when the PVP was stored at 65% R.H. for a longer period, it underwent a transition from the glassy to the robbery state, increasing the mobility and consequently the enthalpy relaxation of the sample.

The tensile strength of the tablets after 1 week of storage decreased as the relative humidity increased up to 45% (Table I). An increase in tensile strength values was observed for the tablets stored at 55%, which again decreased further with increasing R.H. The tablets that were stored at 75% RH were too soft and deformed at touch. After 1 month of storage the same tendency but with lower stress values, was observed. At 65% R.H. the tensile strength value was higher than after 1 week of storage. At 75% R.H. the resulted rubbery state of the polymer binder plasticized the compacts so decreasing their tensile strength. Due to the glassy to rubbery transition at 65% R.H. during the 3 additional weeks of storage, along with the continuous swelling of the polymer, new binding places (new contact points) are created which increased the tensile strength of the compacts.

CONCLUSIONS

The expanded heating-cooling experiments enabled the evaluation of the PVP - water interaction during the storage at different relative humidities.

The time-dependent glassy to rubbery transition of the amorphous PVP, caused by the absorbed water during the storage, was followed by the enthalpy relaxation at the glass transition temperature of PVP. The glassy to rubbery transition of binder has a decisive impact on the physico-mechanical stability of tablets.

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