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INFLUENCE OF MOISTURE ON THE GLASS TRANSITION OF A SPRAY-DRIED COMPOUND USING THE ISOSTEP^{TM} METHOD

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Abstract

The interaction among moisture content, solvent loss and glass transition temperature is relevant for processing of spray-dried pharmaceuticals, since the glass transition temperature determines the application range of a compound. Conventional Differential Scanning Calorimetry (DSC) does usually not allow to separate glass transitions from common kinetic effects like evaporation or crystallization. Based on classical DSC methods, the IsoStep^{TM} method allows the independent determination of heat capacities and kinetic effects, and thus, the separation of kinetic effects from effects arising from heat capacity changes. This technique is used to separate glass transition and evaporation processes, and to find the relation between moisture content and glass transition temperature for a pharmaceutical sample based on a modified Gordon–Taylor equation.

Keywords: DSC, evaporation, glass transition, moisture

Introduction

Pharmaceutical substances are frequently spray-dried in order to remove solvent residues that remain from the production process. The solvent content influences the phase behavior of the substances. In the case of amorphous or partially crystalline materials solvent residues may act as plasticizers and may have an influence on the glass transition. The glass transition temperature decreases with higher solvent content. This could be important for further processing since substances become often sticky above the glass transition. Therefore, it is necessary to know the dependence of the glass transition temperature on the solvent content.

Conventional Differential Scanning Calorimetry (DSC) is a well established technique for the investigation of glass transition. However, in the case of moist materials, glass transitions in DSC curves are often overlapped by predominant moisture loss peaks or annealing phenomena such as relaxation peaks. A technique which provides the capability of separation of such overlapping effects on the glass transition is Temperature

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Modulated DSC® (TMDSC). Royall and co-worker used this technique for the analysis of moisture uptake effects on the glass transition of pharmaceuticals [1].

On moist amorphous pharmaceutical compounds a separation of glass transitions from overlapping evaporation peaks by TMDSC was performed by Schubnell and Schawe [2] as well as a quantitative analysis of the glass transitions. Based on this work the newly developed and straight forward IsoStep™ method was applied for heat capacity determinations and simultaneous separations of an overlapping kinetic processes. In the experiments described in this paper, the kinetic process is the evaporation of water.

It is demonstrated that the dependence of the glass transition temperature on the moisture content can be determined efficiently and accurately by the IsoStep™ method.

A pharmaceutical compound was investigated. In order to avoid sticking of the powder during further processing the dependence of the glass transition temperature from the water content was investigated.

Experimental

The DSC experiments were performed using a Mettler-Toledo DSC 822^e connected to an intracooler and a Mettler-Toledo Thermogravimetrical Analyzer TGA/SDTA 851^e. Both systems are operated by the STAR^e Software where the DSC included the IsoStep™ DSC software option. For the mass-spectrometry (MS) measurements a Thermostar mass spectrometer (Balzers) was connected with the TG.

The IsoStep™ method combines a conventional heat capacity measurement with a quasi-isothermal kinetics evaluation method [3]. The characteristic temperature program is based on sequences of small temperature increases followed by isothermal segments for sample equilibration. The parameters of the temperature program (i.e. these are the time of the isothermal, the heating rate and step high of the heating steps) are not subject to any restrictions and can be varied during the measurement depending on the thermal event. As described by Mraw and Naas [4], the heat capacities are given by the heat flows of the temperature ramp segments. The isothermal segments contain the information about kinetic processes and can be used to evaluate heat flows caused by kinetic processes. A corresponding method, called Isothermal Stepping DTA, was developed by Doerr [5]. Because they are purely related to kinetic heat flows and do not contain any information about heat capacity changes, these curves are very suitable for water loss determination.

The measurements were performed with 1 K temperature increases and heating rates of 2 K min^{-1} followed initially by 30 s isothermal segments. The measuring cell was purged with nitrogen for all DSC and TG measurements.

The sample was a spray-dried mixture of two incompatible, amorphous, low molecular mass compounds with a remnant water content of about 6%. The dry mass contents of the components were 65% and 35%. The sample has two glass transitions. It becomes sticky above the first glass transition and liquid above the second one.

The samples with masses of about 8 mg were placed in aluminum crucibles sealed by standard pierced lids with 50 μm holes. Samples with different moisture contents were prepared by preheating at 80°C for different lengths of time.

Results

The uppermost curve in Fig. 1 is a DSC curve of a sample that was not preheated before starting the IsoStep™ experiment. The curve was measured with a heating rate of 1 K $\min^{-1}$. The heat capacity curve and the kinetic curve resulting from the IsoStep™ measurement are depicted below. There are several endothermic thermal events in the DSC curve but a clear interpretation of the DSC curve is obviously difficult. A better understanding can be obtained from the heat capacity curve: The step-like increases of the specific heat capacity c_p at approximately 68 and 120°C indicate two glass transitions which are caused by the two amorphous components contained in the sample. With this information given, the endothermic peaks of the DSC curve at about 60 and 125°C can be identified as enthalpy relaxation peaks overlaying a huge water loss peak. The enthalpy relaxation peak disappears after heating in the glass transition range and reappears after a few days storage at room temperature. The kinetic curve at the bottom is very similar to the DSC curve. The difference is explained by the heat flow contributions from the sample heat capacity which are not included in the kinetic curve. Because its baseline is free of any contributions from heat capacity changes, the kinetic curve was used for evaporation related evaluations.

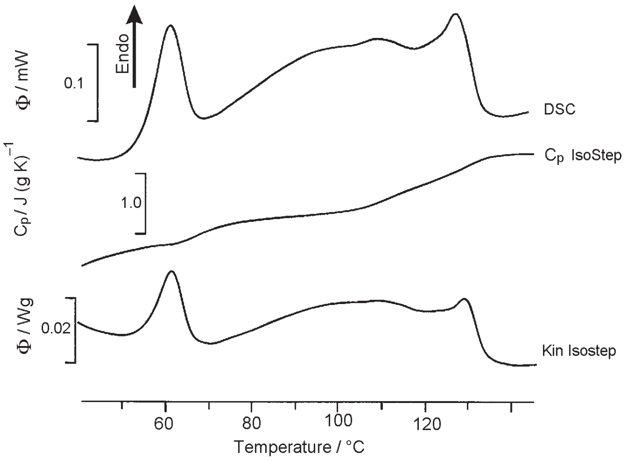

Fig. 1 DSC curve (heating rate: 1 K $\min^{-1}$) and the results of the IsoStep™ experiment of a not preheated sample. On top – DSC curve; middle – heat capacity curve; bottom – kinetic curve; Φ – heat flow

In order to vary the moisture content the sample was preheated at 80°C for different lengths of time. Prior DSC, IsoStep™ and TG experiments showed the reversibility of glass transition shifts and water absorption. As shown in Fig. 2 simultaneous mass loss measurements and evolved gas analyses proofed that the material

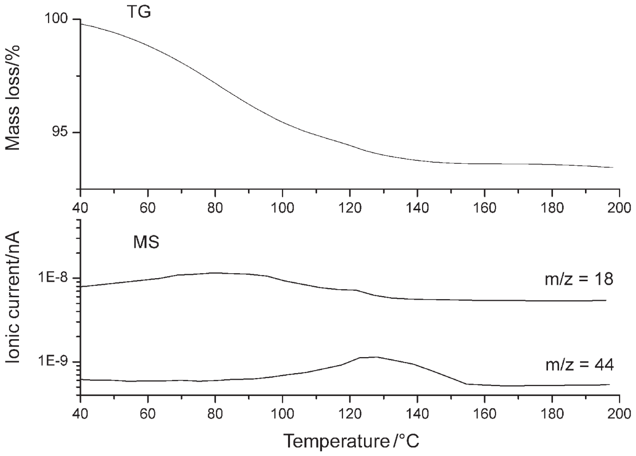

Fig. 2 TG curve of a heating experiment with 5 K min^{-1} (upper diagram). In the lower diagram the related mass spectrometer curves for the mass numbers 18 and 44 are shown

does not decompose at 80°C. The TG heating curve (heating rate 5 K min^{-1}, sample mass 30 mg) and the evolved gas analysis of water (m/z=18) indicate maximum water loss rates at about 80°C. At temperatures above 110°C a second specific mass signal with m/z=44 appears and indicates a decomposition process.

In order to perform a systematic investigation of the influence of water on the first glass transition at approximately 68°C (Fig. 1) the mass loss during preheating at 80°C is measured by TG. The measured curve is shown in Fig. 3 and the water losses after 20, 40, 60, 80 and 160 min are indicated. These preheating periods were chosen to prepare samples with different water contents for subsequent IsoStep$^{\text{TM}}$ experiments. The water content of each preheated sample and before starting an IsoStep$^{\text{TM}}$ experiment (Table 1) was determined from the mass losses measured in the TG experiment (Fig. 2).

As shown in the kinetic curve in Fig. 4, the enthalpy relaxation peak at approximately 60°C disappears after preheating at 80°C. The sample was preheated for 20 min before the measurement. Compared to the heat capacity curve of the sample without preheating treatment the glass transition has shifted from 68 to 72°C. From the TG measurement in Fig. 2 the water content before the IsoStep$^{\text{TM}}$ measurement was found to be 4.32%.

In order to take the additional water loss into account which occurs during the IsoStep$^{\text{TM}}$ experiment itself, the percentage of the remaining water evaporated before the glass transition was determined by evaluating the partial peak area of the evaporation peak up to the glass transition temperature on the kinetic curve (Fig. 4). The normalized partial peak area represents the specific evaporation enthalpy Δh_{e} related to the sample mass . The water loss during the IsoStep$^{\text{TM}}$ measurement Δw_{m} is given by

$$\Delta w_{\mathrm{m}} = \frac{\Delta h_{\mathrm{e}}}{\Delta h_{\mathrm{w}}} \quad (1)$$

where Δh_{w} is the specific evaporation enthalpy of water bound to the sample which was determined as Δh_{w}=2500 J g^{-1} [2].

The water content at the glass transition temperature w_{T_g} is

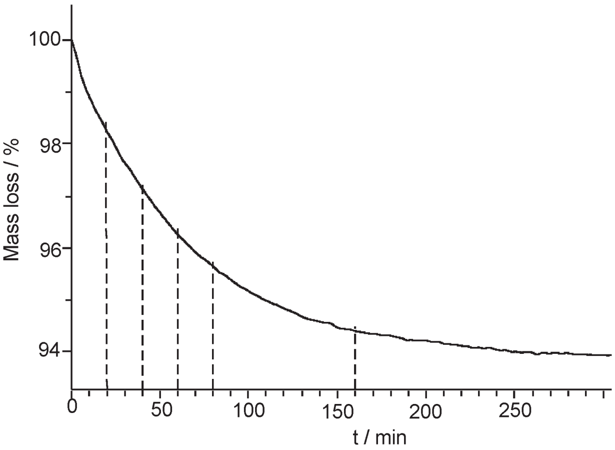

Fig. 3 Isothermal TG experiment of a 8.102 mg in a 50 µm pierced crucible at 80°C showing percentages of water loss after 20, 40, 60, 80 and 160 minutes of pre-heating

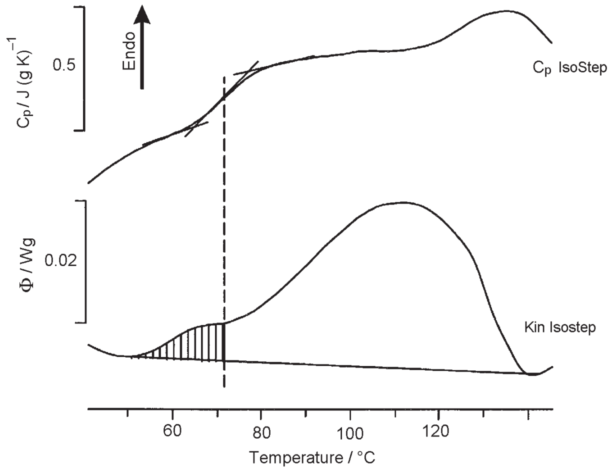

Fig. 4 Heat capacity and kinetic curve of the IsoStep$^{\mathrm{TM}}$ experiment after 20 min of pre-heating. In the heat capacity curve the glass transition temperature is evaluated. The determination of the evaporation enthalpy Δh_e from the partial area is shown on the kinetic curve

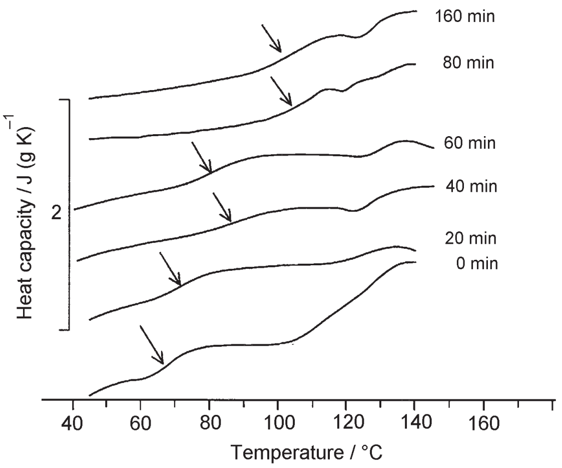

Fig. 5 Heat capacity curves obtained by the IsoStep^{TM} method for different preheating times. The preheating time is the parameter. The arrows indicate the glass transition temperature. Note: the moisture content at T_g is not only given by the preheating time period but also by the moisture loss during the IsoStep^{TM} experiment

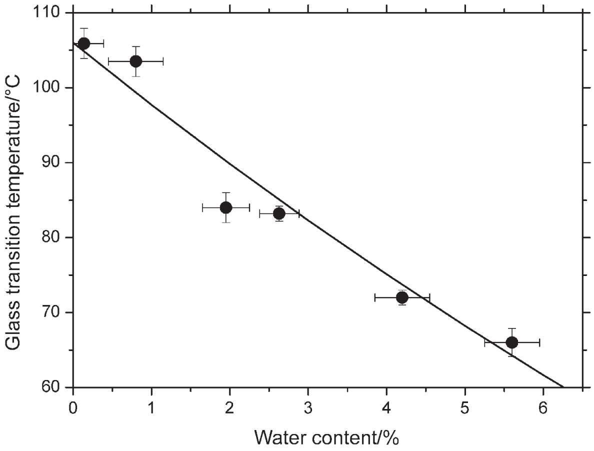

Fig. 6 Glass transition temperature of component *A* (T_g) *vs.* the overall water content (w_w) at T_g. The curve is a fit result of the Eq. (8)

$$w_{T_g} = w_{ini} - \Delta w_m \tag{2}$$

where w_{ini} is the initial water content after preheating and obtained from the TG measurement in Fig. 3. Using Eq. (2) the water content at the glass transition temperature was calculated.

The heat capacity curves are shown in Fig. 5 for various 80°C preheating periods. The glass transition temperature shifts to higher temperatures with increasing preheating periods and hence, decreasing moisture contents. The glass transition temperatures (indicated by the arrows) are determined from these curves. For a two-component system, containing one drug component and water, the relation between moisture content and glass transition temperature would be given by these results and could be displayed by a curve similarly to the one displayed in Fig. 6. Such a curve may be used to optimize industrial processing conditions. However, the sample investigated here is a three-component system, consisting of two drug components and water. For two incompatible drug components with a known molecular mass distribution, there will be only one additional unknown parameter describing the water distribution within the two components. By using the Gordon–Taylor equation and curve fitting, the water distribution can be determined and the relation between glass transition temperature and the water content described.

Discussion

The relationship between the glass transition temperature T_g and the fractional moisture uptake w_w of a two-component system can be described by the Gordon-Taylor equation [5]:

$$T_{\mathrm{g}}=\frac{w_{\mathrm{A}}T_{\mathrm{gA}}+Kw_{\mathrm{wA}}T_{\mathrm{gw}}}{w_{\mathrm{A}}+Kw_{\mathrm{wA}}} \tag{3}$$

where w_{A} and w_{wA} are the mass fractions of a compound *A* and water absorbed in *A*. T_{gA} and T_{gw} are the glass transition temperatures of the pure compound and water. *K* is an empirical parameter. This equation is often used for the quantitative estimation of the water dependence of the glass transition temperature of drugs [1].

Since the investigated system is a three-component system, consisting of water and the incompatible pharmaceutical compounds *A* and *B*, the Gordon–Taylor equation has to be modified accordingly. Particularly, the water distribution has to be taken into account as Δm_w, this is the water portion absorbed by component *B*. The mass fractions of Eq. (3) are then:

$$w_{\mathrm{A}}=\frac{m_{\mathrm{A}}}{m_{\mathrm{A}}+m_{\mathrm{wA}}-\Delta m_{\mathrm{w}}} \tag{4}$$

$$w_{\mathrm{wA}}=\frac{m_{\mathrm{wA}}-\Delta m_{\mathrm{w}}}{m_{\mathrm{A}}+m_{\mathrm{wA}}-\Delta m_{\mathrm{w}}} \tag{5}$$

where m_{A} is the dry mass of the component with the low temperature glass transition and m_{wA} the mass of water absorbed in *A*. The masses of Eqs (4) and (5) can be expressed by the measurable fractions w_{w}, the overall water content, and w_{Ad}, the mass fraction of the component *A* relative to components *A* and *B*:

$$w_{\mathrm{w}}=\frac{m_{\mathrm{w}}}{m_{\mathrm{A}}+m_{\mathrm{B}}+m_{\mathrm{w}}} \tag{6}$$

$$w_{\mathrm{Ad}} = \frac{m_{\mathrm{A}}}{m_{\mathrm{A}} + m_{\mathrm{B}}} \tag{7}$$

m_{B} and m_{w} are the masses of the component *B* and of water absorbed to *A* and *B*. Rearranging Eqs (6) and (7) and substituting in Eqs (4) and (5) a modified Gordon–Taylor equation is obtained

$$T_{\mathrm{g}} = \frac{T_{\mathrm{gA}} + \delta q_{\mathrm{w}} T_{\mathrm{gw}}}{1 + \delta q_{\mathrm{w}}} \tag{8}$$

where q_{w} is a measure of the water content:

$$q_{\mathrm{w}} = \frac{w_{\mathrm{w}}}{1 - w_{\mathrm{w}}} \tag{9}$$

The parameter δ depends on the relative amount of water in the component *A*:

$$\delta = \left(1 - \frac{\Delta m_{\mathrm{w}}}{m_{\mathrm{w}}}\right) \frac{K}{w_{\mathrm{Ad}}} \tag{10}$$

The parameter of Eq. (8) are determined by non-linear curve fitting of the data in Fig. 5. The glass transition temperature of water is assumed to be T_{gw}=136 K [6]. The fitting procedure results in a glass transition temperature of T_{gA}=379.5 K for compound *A* and δ=3.65. The fit-curve is shown in Fig. 6. If the parameter *K* is known, the affinities of both components for water absorption can be determined. An approximation of *K* is

$$K = \frac{\rho_{\mathrm{A}} T_{\mathrm{gA}}}{\rho_{\mathrm{w}} T_{\mathrm{gw}}} \tag{11}$$

where ρ_{A} and ρ_{w} are the densities of component *A* and water [1]. If a density of ρ_{A}=1.2 g cm^{-3} for a typical organic drug is assumed, *K* is estimated to be 3.35. The known ratio of the two compounds can be expressed as w_{Ad}=0.65. From Eq. (10) follows that $(1-\Delta m_{\mathrm{w}}/m_{\mathrm{wA}})$= 0.71. This means that 71% of the water is absorbed by component *A*. When the weight distribution of *A* and *B* is taken into account it follows that component *A* absorbs 10% more water than component *B*.

Conclusions

The IsoStep$^{\mathrm{TM}}$ method is a powerful tool for the separation of glass transitions and overlapping kinetic effects. Particularly, the separation of solvent evaporation and glass transition is an important application for process control in the production process of pharmaceuticals. The experiments allow to relate moisture contents to glass transition temperatures, and to thus find drying conditions that do not affect sample integrity, are appropriate for further sample processing and economic, in terms of required heat and time for drying.

The experiments have shown that the glass transition can shift from 68°C for a moist sample to 107.5°C for an almost completely dry sample. This means, for instance, that the moist sample is likely to be sticky at temperatures above 68°C. This will possibly affect the result of subsequent processing steps.

The intention of this paper was to introduce a method for finding a relation between moisture content and glass transition temperature and thus, to provide a practical tool for process optimization. Using a modification of the Gordon–Taylor equation the dependence of the the glass transition temperature from the moisture content can be described for a three-component system.

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