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Determination of the glass transition temperature of difficult samples by Flash DSC

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Crystalline pharmaceutical substances often decompose immediately before or during melting. To determine the glass transition temperature, the substance must be melted and then cooled as rapidly as possible so that decomposition and crystallization do not occur. In many cases, the heating and cooling rates of conventional DSCs are not high enough for this purpose. The METTLER TOLEDO Flash DSC however offers new possibilities. This is illustrated in this article using prednisolone as an example.

Introduction

Amorphous forms of active pharmaceutical ingredients (APIs) are often preferred in order to obtain the highest level of bioavailability. Amorphous APIs are only stable in the glassy state below the glass transition temperature (T_g). Above the T_g , they can crystallize. This can have a large effect on bioavailability.

APIs are often crystallized from solution in order to obtain the purest form. Conversion to the amorphous state can be achieved by grinding the crystals, whereby the temperature of the material being ground must not rise above the T_g during grinding [1, 2]. Knowledge of the glass transition temperature of amorphous APIs is therefore important both from the point of view of storage and from process engineering.

To determine the glass transition temperature of a (crystalline) starting material, the material must be melted and then cooled as rapidly as possible so that no decomposition or crystallization occurs. In many cases, the heating and cooling rates of conventional DSCs are inadequate for this purpose.

The Flash DSC offers new possibilities with heating and cooling rates of up to 40,000 K/s (heating) and 4,000 K/s (cooling). This allows a substance to be heated up to several hundred degrees and then cooled within a few milliseconds [3, 4]. In this short time interval, practically no decomposition can occur. This makes it possible to determine the glass transition temperatures of crystalline substances that would have decomposed in a conventional DSC during the comparatively slow melting process [5].

In this article, we illustrate the procedure using prednisolone as an example.

Prednisolone is a synthetic corticoid used to treat inflammation. Prednisolone is available as the anhydride in two stable polymorphic forms and as a sesquihydrate [6]. The expected solid-solid transition between the two anhydrides should occur between 120 and 130 °C. This has however previously not been observed [6].

The form stable at room temperature (Form I) melts between 236.5 and 239 °C [6]. The high-temperature form (Form II) melts between 224 and 228 °C [6].

The melt is thermally unstable and decomposes [7]. Form I is however stable at room temperature and is commercially available.

Experimental details

The experiments were carried out using prednisolone (Form I) from Sigma Aldrich (P6004, purity >99%) with METTLER TOLEDO DSC 1 and Flash DSC 1 instruments. Sample preparation for the Flash DSC involved first spreading a small amount of prednisolone over a glass disk. Small crystals were then selected under the microscope of the Flash DSC and placed on the Flash DSC sensor (see Figure 3). The Flash DSC was operated at heating and cooling rates of 1000 K/s and 100 K/s. The conventional DSC measurements were performed at heating rates of 0.5, 2 and 10 K/min.

Results

Figure 1 displays the first DSC heating runs of prednisolone samples (Form I) at heating rates of 0.5 K/min, 2 K/min and 10 K/min. The measurement curves were normalized with respect to sample mass and heating rate for better comparison. It can be seen that the temperature of the melting peak is strongly dependent on the heating rate used for the measurement. Besides this, an exothermic decomposition peak is observed immediately after the endothermic melting peak. Finally, the peak areas differ quite considerably at the different heating rates. This can be explained by the decomposition of prednisolone during the heating ramp. The decomposition products act as contaminants and lead to a decrease in the melting point. The longer the sample has for decomposition (i.e. the lower the heating rate), the greater the degree of decomposition and the lower the melting point. The apparent dependence of the melting point on the heating rate is therefore a result of decomposition during the heating ramp.

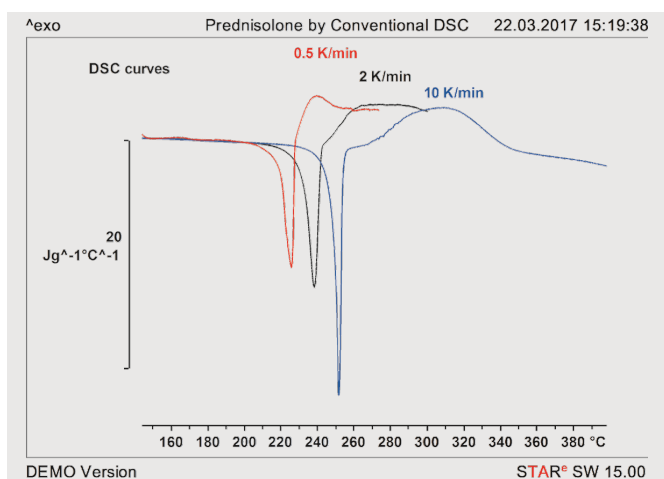


Figure 1. Melting and decomposition of prednisolone measured by conventional DSC. The DSC curves have been normalized with respect to sample mass and heating rate.

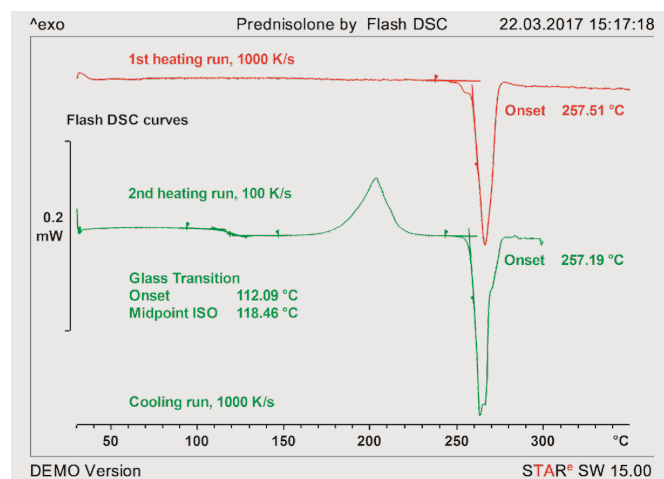


Figure 2. First and second heating runs of prednisolone.

Figure 2 shows the curve (red) obtained when prednisolone (Form I) is heated in the Flash DSC at 1000 K/s. A sharp melting peak is observed at 257.5 °C. There is however no indication of decomposition. If the sample is cooled from the melt at 1000 K/s and then heated at 100 K/s (green curve) a glass transition is observed at 118 °C. The material then crystallizes. This is followed by melting at the same temperature as in the first heating run (257.2 °C, within the limits of measurement uncertainty).

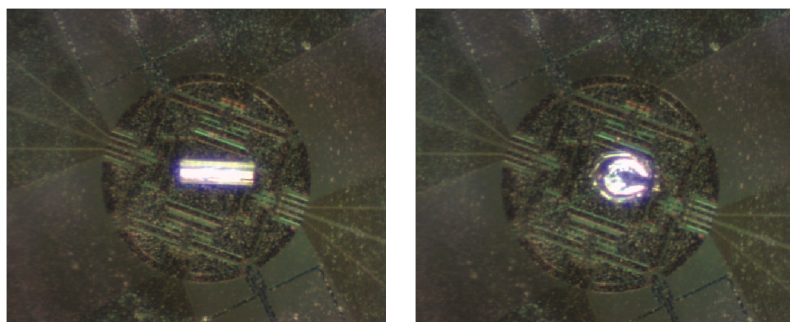


Figure 3. Prednisolone on the Flash DSC sensor before (left) and after melting (right).

Figure 3 shows the prednisolone sample on the Flash DSC sensor before and after the two heating runs. The images show that no decomposition occurred (no change in color of the sample; the change in the shape of the sample is due to the melting and recrystallization of the sample). The melting point measured with the Flash DSC corresponds to the melting point of prednisolone (Form I) that has not been contaminated with decomposition products.

Conclusions

Thanks to the high heating rates that can be achieved with the Flash DSC 1, it is possible to separate the melting and decomposition of substances whose decomposition begins together with or immediately before melting. The glass transition temperature of such substances can be determined after rapid cooling of the non-contaminated melt.

In the case of prednisolone, a glass transition temperature of 118 °C was measured at a heating rate of 100 K/s. Prednisolone can therefore easily be made amorphous by grinding at room temperature. The temperature of the prednisolone during grinding must not however exceed about 112 °C (onset of T_g). The melting point of the form of prednisolone stable at room temperature (Form I) was also determined (257.2 °C). This is appreciably higher than the temperature of 236.5 to 239 °C published in the literature [6]).

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Publishing Note:

This application has been published in the METTLER TOLEDO Thermal Analysis UserCom No. 45.