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Vitreous State Characterization of Pharmaceutical Compounds Degrading upon Melting by Using Fast Scanning Calorimetry

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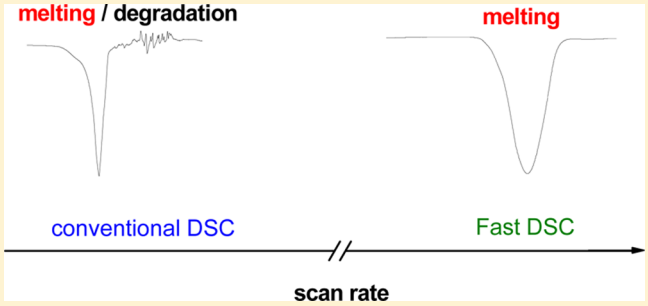
ABSTRACT: Fast scanning calorimetry, a technique mainly devoted to polymer characterization, is applied here for the first time to low molecular mass organic compounds that degrade upon melting, such as ascorbic acid and prednisolone. Due to the fast scan rates upon heating and cooling, the substances can be obtained in the molten state without degradation and then quenched into the glassy state. The hydrated form and the polymorphic Form 1 of prednisolone were investigated. It is shown that once the sesquihydrate dehydrates, a molten product is obtained. Depending on the heating rate, this molten phase may recrystallize or not into Form 1.



INTRODUCTION

When a substance degrades before or upon melting, it is made impossible, using conventional techniques, to obtain the nondegraded molten state and then to get the vitreous material. Indeed, degradation kinetics is often much faster than the time required to freeze a molten material. As a consequence, for such compounds, the glass transition temperature (T_g) or other phase transitions cannot be experimentally determined. Fast scanning chip calorimetry provides an interesting alternative in such cases.[1−5] The relative recent flash differential scanning calorimeter (FDSC) (Mettler-Toledo, Schwerzenbach, Switzerland) allows one to reach very fast scan rates up to 40 000 and 4000 K·s^{-1} upon heating and cooling, respectively.[6,7] With such scan rates, one can imagine melting a material without degrading and, almost instantly, freezing it in its glassy state at room temperature. When few minutes are needed to scan a temperature range of 300 K by conventional differential scanning calorimetry (DSC), less than 1 s is required by FDSC. At this very fast response time, the degradation process does not have time to manifest itself.

In order to check this assumption, two substances known to degrade upon melting were studied using the FDSC technique.

L-Ascorbic acid, also called vitamin C (VC), a natural compound with antioxidant properties, is known to be very unstable upon melting, where the thermal degradation is enhanced.[8] When relatively high scan heating rates are applied using conventional DSC (few tens of degrees per minute), the thermal degradation is bypassed during melting.[8] However, it is not possible to trap the nondegraded liquid to bring it to the glassy state due to the too low cooling rate applicable by conventional DSC. The second studied molecule is prednisolone, a synthetic corticoid, which is also known to degrade upon melting.[9] Prednisolone crystallizes in two anhydrous polymorphic forms, Forms 1 and 2, and one sesquihydrate.[10,11] As regards the DSC signals presented in ref 11 for melting of prednisolone, one can actually say that prednisolone degrades upon melting. Form 1 is reported to be the most stable polymorph at ambient conditions of temperature and pressure,[10,11] which is the solid form commercially available. This form can also be obtained by dehydration of the sesquihydrate.[10,11] After dehydration, a recrystallization into Form 1 occurs upon heating.[11] The sesquihydrate is studied here to understand the recrystallization process observed after dehydration and determine the possible glass transition after quenching and heating the dehydrated form.

The knowledge of the glass transition point is important from a pharmaceutical point of view for two reasons. The first one is that the amorphization of a material can often be the result of grinding during pharmaceutical operations. It was shown that materials milled at temperatures below their T_g were observed to become completely amorphous when materials milled at temperatures above their T_g were subject to transform in metastable polymorphs.[12,13] The second reason is that the amorphous form presents better bioavailability.[12]

MATERIALS AND METHOD

L-Ascorbic acid, with purity higher than 98.5%, was purchased from Acros Organics. Prednisolone with purity higher than 99% was purchased from Sigma-Aldrich. The commercial powder is in the polymorphic modification Form 1. The sesquihydrate

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was obtained by slow evaporation of different solvent batches (methanol, ethanol, and acetone containing water traces) from saturated prednisolone solutions.

FDSC experiments were carried out with a Mettler-Toledo Flash DSC1 at scan rates up to 100 K·s^{-1} upon cooling and up to 1000 K·s^{-1} upon heating. The measuring cell was continuously flushed with nitrogen gas, and cooling was achieved using a Huber TC 100 intracooler. Temperature calibration was carried out by using high-purity indium. A small crystal of few tens of nanograms was placed under a microscope directly on the active area of the sample side of the sensor. The active area of the sensor was circular with a 500 μm diameter. Unfortunately, due to the technique limits, the sample weight could not be determined for such experiments. Therefore, the obtained results are qualitative regarding the enthalpy.

RESULTS AND DISCUSSION

L-Ascorbic acid was analyzed by FDSC upon heating and cooling. By using a scan rate of 1000 K·s^{-1} upon heating, the substance was melted without any visible degradation in the liquid state, as shown by the FDSC sensor taken just after melting (Figure 1).

The melting point is obtained at 198 °C (Figure 2), close to the melting temperature previously reported, that is, at 193 °C.[1]

Just after melting, a 0.1 s isotherm was performed, followed by a cooling rate of 100 K·s^{-1} on the molten material. Next, a second heating ramp was carried out, and the glass transition was observed at a temperature close to 55 °C. Interestingly, this approximately equals 2/3 of the melting temperature (temperature in Kelvin), as expected from the Beanan–Kauzmann rule.[14]

The above results may be explained by the fact that, in this range of scan rates, the material is molten in 0.2 s and, in two seconds, the molten liquid is brought to room temperature in a vitreous state. In total, the sample is for approximately 0.1 s above the melting temperature where, at slow scan rates, degradation is observed. These very short times make it so that degradation does not have time to take place to an observable extent. Because the size of the crystal dropped on the sensor active area is very small, heat-transfer-related effects like thermal lag are negligible.

Upon heating prednisolone Form 1 with a 1000 K·s^{-1} scan rate, a single endothermic peak is visible on the FDSC curve (Figure 3) at a temperature approximately the same as the one previously found in ref 11, that is, 258 °C.

The absence of visible degradation of prednisolone in the molten state was evidenced by the FDSC photograph taken just after melting (Figure 4).

After quenching the molten prednisolone, a second heating ramp was then applied. As seen in Figure 3, the glassy state is characterized by a T_g equal to 123 °C, which is, as for VC, approximately equal to 2/3 of the melting temperature.

Interestingly, when a 1000 K·s^{-1} scan rate was applied to the vitreous material, no further crystallization was observed after the glass transition (Figure 3), whereas for lower scan rates, such as 100 K·s^{-1}, the molten prednisolone recrystallized into Form 1 before melting (Figure 5).

The prednisolone sesquihydrate has been studied at different heating rates from 10 to 1000K·s^{-1}. Initially, the sample is heated up to the dehydration at 180 °C and then quenched. The FDSC photograph allowed us to observe that after dehydration, a molten state is also obtained (Figure 6).

When the molten prednisolone obtained from the dehydration–melting process was quenched at room temper-

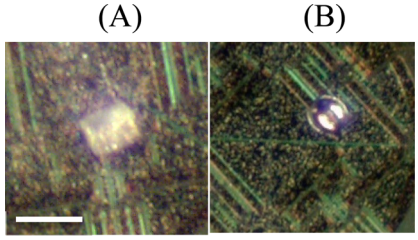

Figure 1. Photograph of L-ascorbic acid on the FDSC sensor taken before (A) and after (B) melting (scale bar = 100 μm).

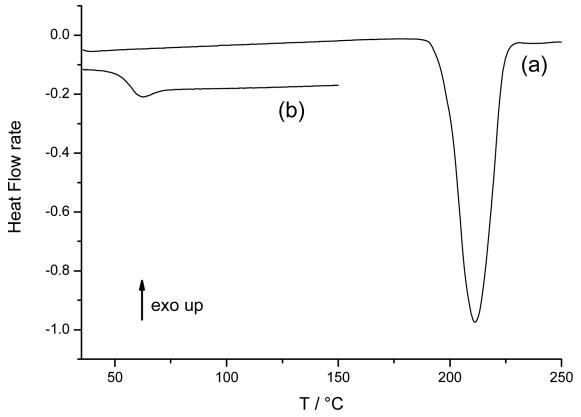

Figure 2. FDSC curves of L-ascorbic acid obtained at a 1000 K·s^{-1} scan rate. (a) First heating, (b) second heating.

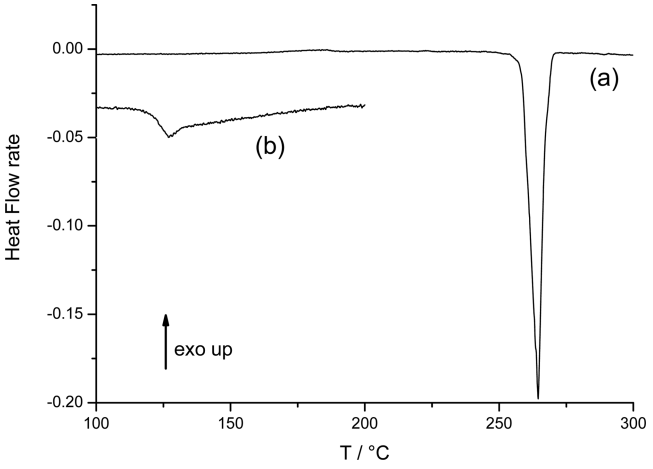

Figure 3. FDSC curves of prednisolone Form 1 heated at a 1 000 K·s^{-1} scan rate. (a) First heating, (b) second heating.

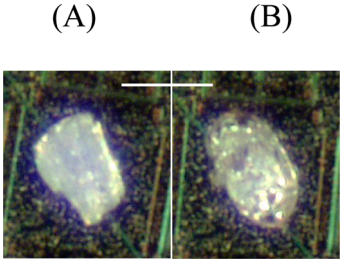

Figure 4. Photograph of prednisolone on the FDSC sensor taken before (A) and after (B) melting (scale bar = 100 μm).

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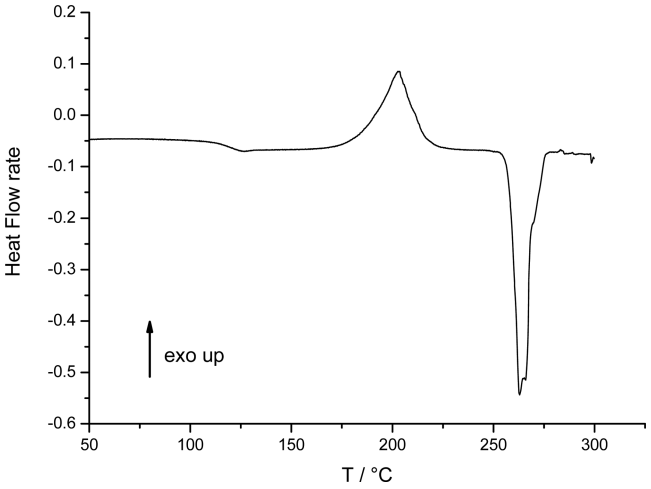

Figure 5. FDSC curve of glassy prednisolone heated at a 100 K·s^{-1} scan rate.

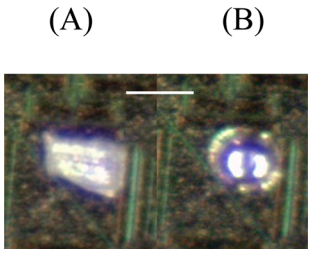

Figure 6. Photograph of prednisolone on the FDSC sensor taken before (A) and after (B) dehydration (scale bar = 100 μm).

ature and heated again, the same glass transition was observed at approximately 120 °C.

As observed in Figure 7 and as previously reported,[11] upon heating the sesquihydrate, an endothermic peak manifested at 150 °C. Taking into account what we observed above, this peak can be now attributed to a dehydration−melting process. As for the amorphous material, when a scan rate of 1000 K·s^{-1} was applied, no crystallization into Form 1 took place after dehydration (Figure 7A).

However, when the FDSC experiments were carried out with a lower heating rate of 100 K·s^{-1}, a broad exothermic signal followed the dehydration−melting peak (Figure 7B), corresponding to the recrystallization of the melt into Form 1.[11] Still upon heating, an endothermic signal is observed at 250−260 °C, corresponding to the melting of Form 1. When the heating scan rate is decreased to 10 K·s^{-1}, the crystallization peak becomes narrower and closer to the dehydration−melting peak (Figure 7C).

For comparison purpose, the three DSC curves in Figure 7 give the Cp variation as a function of the temperature. For that, a normalization of the heat flow by the heating rate has been made.

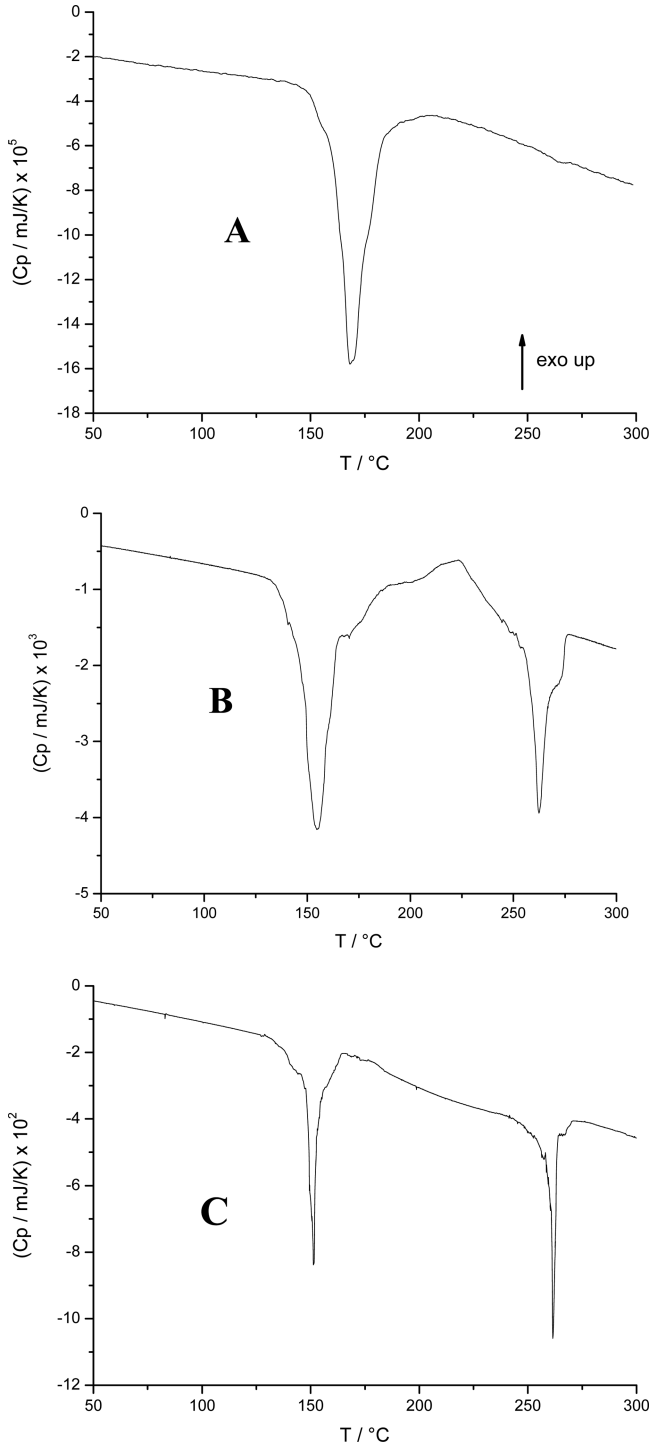

Figure 7. DSC curves of prednisolone sesquihydrate. Scan rate: (A) 1000, (B) 100, and (C) 10 K·s^{-1}.

CONCLUSION

By applying very high heating and cooling rates with a FDSC device on products that used to degrade upon melting, we have shown that it is now possible to obtain their glassy state, which is not possible with conventional thermal analysis techniques. In a pharmaceutical preformulation context, the knowledge of such thermodynamic data is very useful to predict solid-state behavior of this class of substances during pharmaceutical operations. Moreover, the possibility to obtain glasses of substances that normally degrade upon melting, should be of interest to characterize them by other analytical techniques.

The glass transition point determined by FDSC agrees very well with the one calculated from the Beanan−Kauzmann rule ($T_g \approx 2/3T_m$). The consistency of the experimental and calculated results tends to prove that the glasses obtained by FDSC are actually composed of nondegraded molecules.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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