Investigation of the Ageing of Ball Milled Sugars and Sugar Alloys.

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Summary

The ageing of molecular alloys, formed via the ball milling of a binary system of two molecular crystals, was investigated using temperature modulated differential scanning calorimetry (TMDSC). It was shown that, over time, the thermal behaviour of the ball milled material can change depending on the post-milling time point for the analysis. It is also apparent that variability can arise with a change in the total mass of material in the milling vessel and also between different batches of the same material.

Introduction

The affinity of amorphous material to form a crystalline state can be problematic with regards to active pharmaceutical ingredients (API). Stabilising the vitreous form by blending with an excipient with a higher T_g could prove advantageous. In this form, an API may have increased bioavailability. Solid-state vitrification and alloy formation between a binary mixture of an excipient and an API may prove to be advantageous. The enhanced stability of this amorphous state should therefore be investigated. The mechanical milling process induces structural transformations of the material and drives it to a state of non-equilibrium [1]. TMDSC has previously been used to study ageing, grinding, heating, and the formation of molecular alloys [1,2,3,4]. However, an investigation into the changes which occur in the thermal properties of the materials immediately after ball milling appears to be unreported. The relaxation of this non-equilibrium state was monitored using TMDSC. The binary system of sucrose and anhydrous trehalose was investigated. In addition, the effect of the duration of the ball milling process is also reported on the sugar, maltose monohydrate. This mirrors some previous work reported on lactose monohydrate [4].

Experimental

100mg and 50mg of material were milled in a ceramic lined, oven dried, ball-milling vessel. The milling of the materials was performed at room temperature, under an atmosphere of nitrogen. The material was in a 1:1 mixture by weight of sucrose and anhydrous trehalose. The milling duration was 2.5 hours on a RETSCH oscillating ball mill. After the milling procedure, small samples of the materials were taken (1-5mg) and analysed by TMDSC at given time intervals. The samples were equilibrated at 30ºC for 5 minutes after which the temperature was raised to 240ºC at a rate of 5ºC/min with a temperature modulation of ±0.796ºC every 60 seconds.

Solid-state, 13C CP-MAS NMR measurements were made on a Bruker 500MHz spectrometer. The NMR analysis was done in a series of alternating experiment types. Acquisitions alternated from a short 15 second delay time and a longer 300 second delay time. The shorter delay time shows the shorter relaxations associated with increased molecular motion involved with amorphous materials. The longer acquisition time of 300 seconds gives a better indication of the ordered crystalline structure present which has in comparison a longer T1 relaxation time.

Maltose monohydrate was treated in a similar way to the binary mixture. During TMDSC analyses, the material was equilibrated at 0ºC after which the temperature was raised to 210ºC at a rate of 5ºC/min. The modulation overlay was identical at ±0.796ºC every 60 seconds. This temperature program was chosen to include the most important thermal events and also remain below the melting and later decomposition temperature of the maltose monohydrate sample. The milled samples are referenced against the un-milled raw starting materials. This gives an indication of the changes in the thermal behaviour of the materials caused by the milling process.

Results

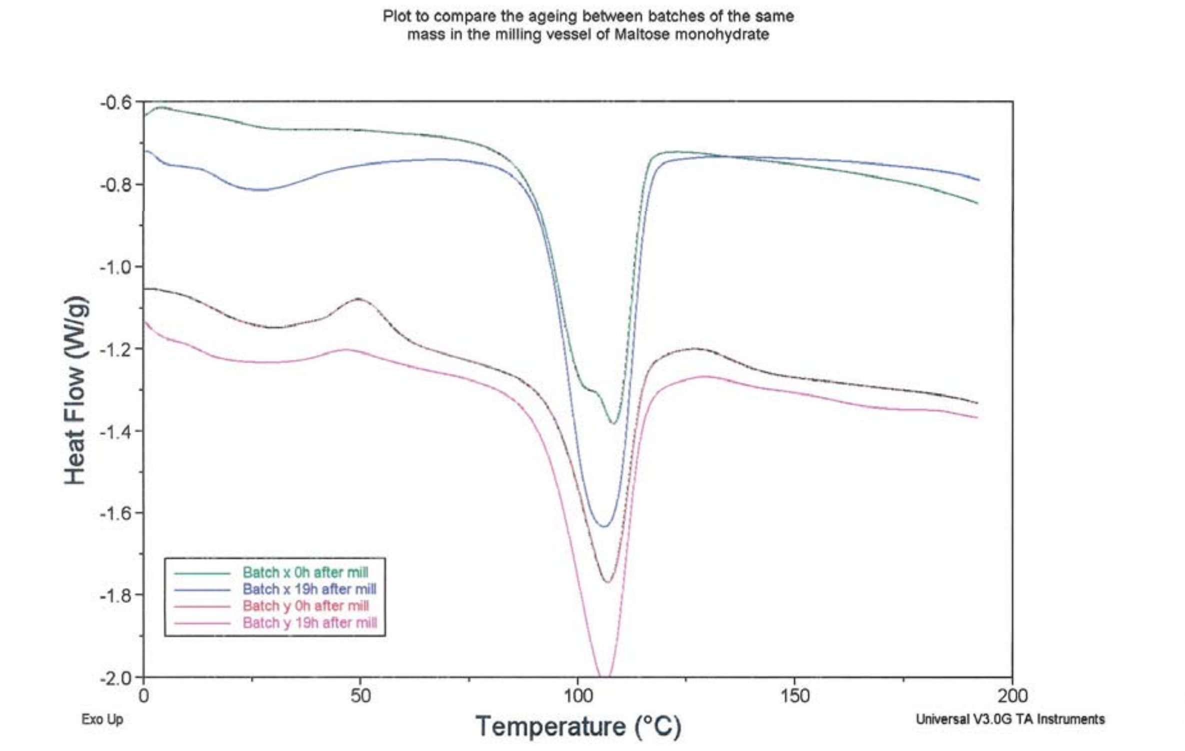

Fig 1. Batch variability between 50mg samples of Maltose monohydrate milled for 2.5 hours

Fig 1 shows the variability associated with the procedure. After 19 hours post milling time, an exothermic event at 50ºC evolved in Batch Y, which was not apparent in batch x. A distinctive peak shape was also noticeable in the initial analysis of Batch X at approximately 110ºC. This was not present in the initial analysis of batch y.

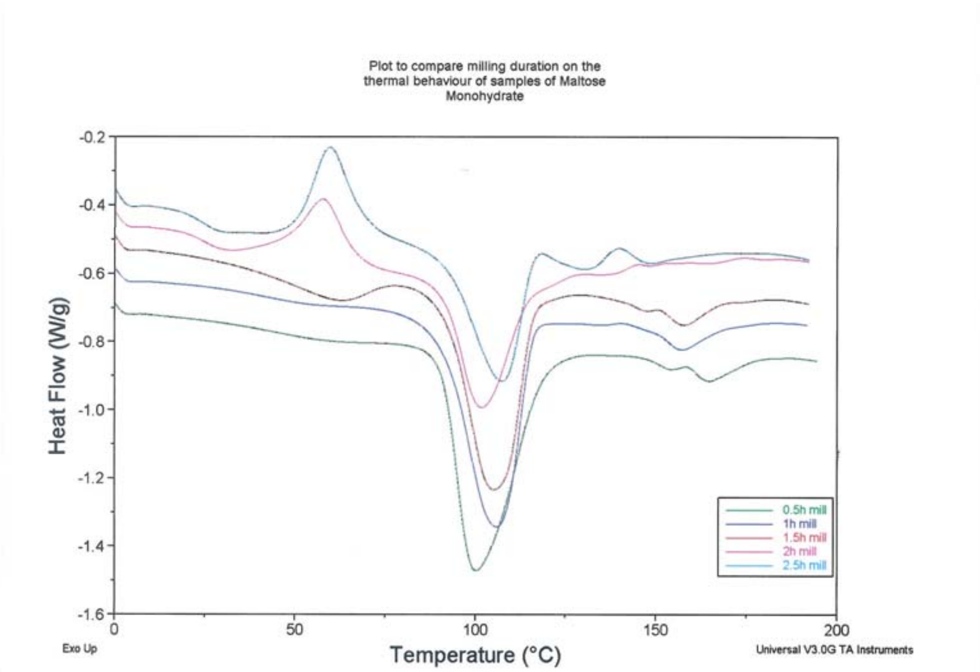

Fig 2. Effect of the duration of ball-milling on the thermal properties of maltose monohydrate.

As the duration of the ball milling is increased, thermal events appear to be modified to a greater degree (Fig 2). In the region at approximately 60ºC, an exothermic event evolves and becomes more pronounced with the extent of ball milling. In addition, the endothermic event at 100ºC becomes less pronounced and shallower with increased milling duration.

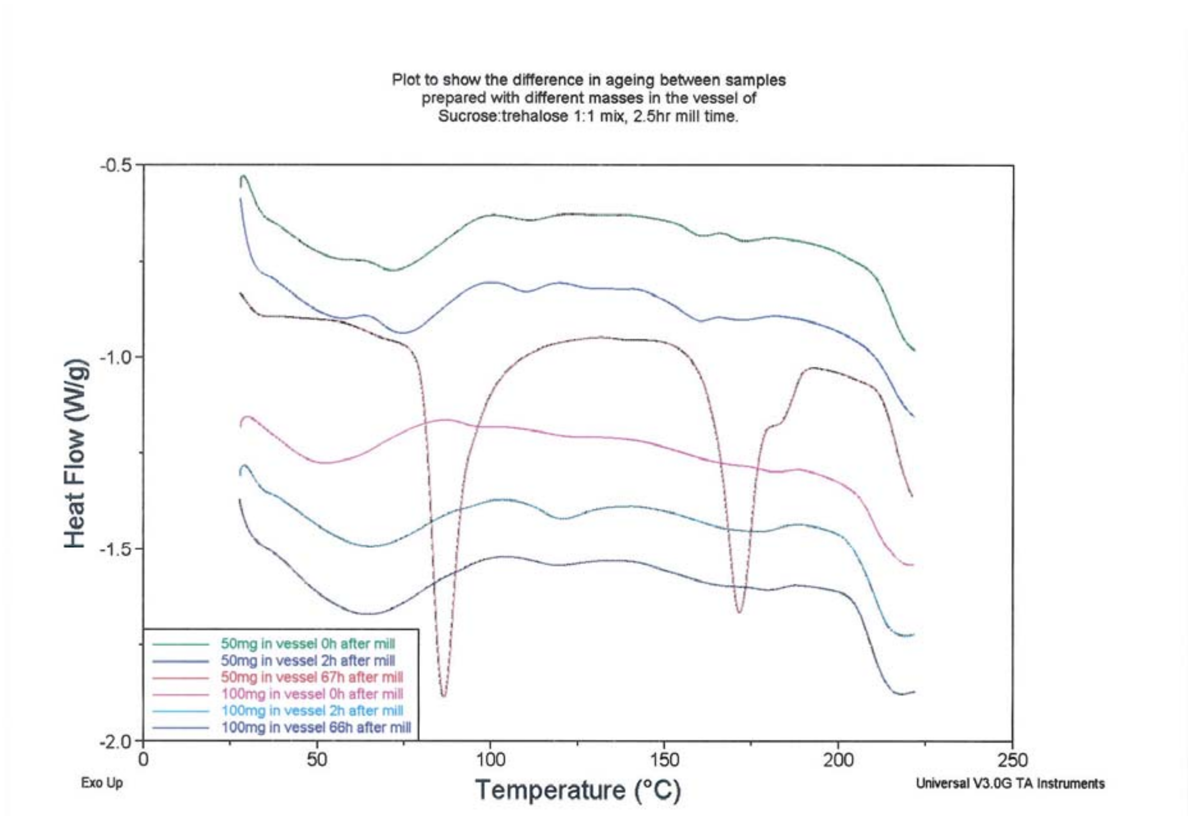

Figure 3. Plot comparing different masses of material in the milling vessel

Fig 3 compares two masses (50mg and 100mg) of a 1:1 mixture of sucrose and anhydrous trehalose. This shows considerable variation in the thermal behaviour of the materials depending on the mass of material used in the milling vessel. The smaller batch of material shows more pronounced thermal behaviour. After 67 hours post milling time, two large endothermic peaks evolve at 90ºC and 170ºC. These peaks do not evolve in the larger batch of material.

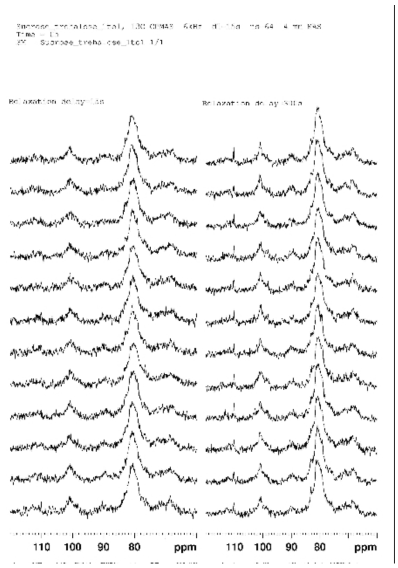

Figure 4. Solid state NMR of sample of 1:1 mixture of sucrose:trehalose milled for 2.5 hours and left to age in the NMR instrument. Short relaxation 15s relaxation on the left, long 300s delay on the right. Time zero at the bottom.

A solid state NMR analysis was performed on the sucrose:anhydrous trehalose mix. The short relaxation on the left hand side shows 4 broad indistinct peaks, which show no change in intensity, sharpness or shift with time. These solid state NMR results show, as expected, broad peaks due to the increased content of amorphous materials in the samples. However, the peaks at 110ppm and 80ppm on the long relaxation time appear to show an increase in sharpness and intensity with time. The long-delay acquisition series shows narrow signals that are indicative of a crystalline material with a long T1 relaxation, these sharp signals are not observed in the short-delay series.

Discussion

All of the TMDSC traces show changes in the thermal behaviour of the ball milled materials compared to the original raw material. Numerous factors such as the duration of ball milling, the quantity of material processed and post milling analysis time seem to affect the thermal transitions observed. The duration of ball milling obviously needs to be optimised on an individual basis to ensure complete alloy formation. The quantity of material can have an affect on the efficiency of the mixing process in the ball milling vessel, leading to compaction at the ends and therefore inefficient mixing. Batch variability may also be due to sampling problems caused by compaction.

Conclusion

It is well known that ball milling at room temperature has the ability to structurally change molecular materials and consequently change their thermal behaviour. However, the thermal behaviour of these materials has been shown to vary quite significantly with post-milling time, the quantities of material processed and even between batches of the same material. It is therefore important to understand how these factors affect the stability and analysis of ball milled materials. Care must be taken to ensure that the quantity of material has been optimised for the vessel and that efficient sampling can be achieved if compaction occurs during milling. As previously reported, the duration of ball milling is also important to ensure good alloy formation. However, it is equally important to ensure that the ball milled material has been investigated for ageing phenomena as this can have quite a drastic effect on the observed results.

Acknowledgements

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