APPLICATION NOTE

Dynamic Mechanical Analysis

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The Application of Mesh Material Pockets in DMA Analysis of Amorphous and Crystalline Lactose Powders

Introduction

Lactose is a very important pharmaceutical excipient used in tablet and inhalation products. It is prone to forming amorphous regions on processing however, and it can be problematical to characterize amorphic material in a sample. Differential Mechanical Analysis (DMA) with material pocket is a method which can be used to accurately determine very low levels of amorphous content in lactose (Royall 2005, Mahlin 2009), due to the high sensitivity of DMA to glass transitions. The material pocket facilitates the analysis of lactose in the powder form, resulting in a very powerful tool for the analysis of mixtures of crystalline and amorphous lactose.

DMA works by applying an oscillating force to the material and the resultant displacement of the sample is measured. From this, the stiffness can be determined and the modulus and tan δ can be calculated. The modulus is a highly useful measure of the materials properties. When an oscillating stress is applied to a material in the DMA, the material becomes deformed, or strained. The amplitude of the deformation is measured, and the ratio of the applied stress and the resultant strain is termed the modulus. When a material goes through a transition such as a melt or recrystallization, that involves a dramatic change in the materials stiffness, a step-change will be observed in the modulus value. This indicates that the material has become stiffer (recrystallization) or less stiff (melting), and is a useful indicator of the materials structure during heating. In a viscoelastic material, there will be two components to the modulus, one in phase with the applied stress (the storage modulus), and one out of phase (the loss modulus). The ratio of the in phase and out of phase components of the modulus describes the damping properties of the material, and is termed tan δ. If tan δ is plotted against temperature a glass transition will normally be observed as a peak since the material will absorb energy as it passes through the glass transition.

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A problem with this technique for the analysis of the thermo-mechanical properties of lactose is that both amorphous and crystalline forms of lactose may contain moisture. When heated this may lead to complex observations in thermal and more specifically DMA studies. When crystalline lactose mono-hydrate is heated it releases water, which may affect the mechanical changes observed as a function of temperature. Because of the disordered structure of amorphous lactose, it has a tendency for sorption of water. This can affect the thermo-mechanical behaviour observed for amorphous lactose, specifically the observation of more than one glass transition due to the plasticising effects of water. DSC analysis of the glass transition of semi-crystalline lactose shows a dehydration event that occurs prior to the glass transition of amorphous lactose (Saunders 2004). Previous DMA material pocket experiments (Royall 2005) have shown this dehydration event occurring, indicated by a peak in modulus response, prior to glass transition. It would appear, however, that when the DMA experiment is carried out using a solid material pocket, the sample is unable to fully dehydrate due to being sandwich between two solid steel plates. In this application note we explore the use of an alternative material pocket construction, using Dutch Twilled steel mesh (Warren 2012). The Dutch Twilled mesh has small pores which facilitate the movement of water in and out of the sample. We carry out a direct comparison between Dutch Twilled and solid material pockets for the analysis of crystalline and amorphous forms of lactose, using the PerkinElmer DMA 8000.

Experimental

Crystalline α-lactose monohydrate was obtained from Sigma-Aldrich® (Batch no.056K0718). Amorphous lactose was made by preparing a 10% (w/w) lactose solution in ultrapure water (HPLC gradient grade Fisher Scientific, Ltd., Leicestershire). This solution was spray dried using a 191 Büchi mini spray drier (Büchi Laboratoriums, Technik AG, Switzerland) to obtain amorphous lactose (Hogan and Buckton 2000).

All DMA analysis was carried out using a PerkinElmer DMA 8000 instrument. Solid steel material pockets were obtained preformed from PerkinElmer (Seer Green, U.K., Part No. N5330323). Dutch Twilled mesh was obtained from G. Bopp Ltd. (MM10344 wire cloth). The Dutch Twilled pockets were fabricated from Dutch Twilled mesh cloth to the same size parameters as the solid steel pockets.

Both pockets were treated identically during the experimental procedure. The pocket was scored across the mid-point, and folded in half to an angle of approximately 60 ˚C (Figure 1). Approximately 50 mg of lactose was accurately weighed into the pocket. The pocket was then folded in half, crimped closed to form a sandwich approximately 0.5 mm wide, reweighed, and clamped into the DMA. The pocket was loaded in a single cantilever bending mode, with one end of the pocket clamped to a fixed support and the other end clamped to the drive shaft. All the clamps were tightened using a torque wrench to a force of 5 N. This meant that one end of the pocket was held stationary, while the other end was subjected to an oscillating displacement by the driveshaft. This resulted in the pocket being deformed in an oscillating, bending motion in and out of plane, subjecting the lactose powder in the pocket to a horizontal shear. The sample was subjected to heating from 20 ˚C to 230 ˚C at a heating rate of 2 ˚C/min, while undergoing a dynamic displacement of 0.05 mm at 1, 10 and 30 Hz. The force was automatically controlled between 1 N and 10 N to achieve the target displacement. The modulus was calculated from the actual measured dynamic displacement amplitude.

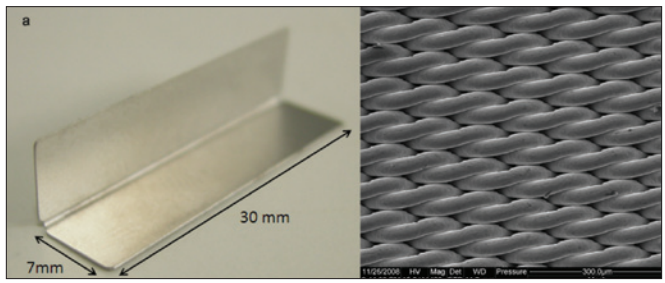

Figure 1. A) The solid steel material pocket, folded in half ready for sample loading. B) A scanning electron microscopy image of the mesh pocket material (400x magnification) showing detail of the pores in the mesh material.

Results

Figure 2 shows the data obtained using a solid steel material pocket for crystalline and amorphous forms of lactose. The crystalline lactose shows a clear dehydration peak (A) resulting from the rearrangement of structure following loss of water followed by a large drop in modulus resulting from the melting of the crystalline lactose (B). Amorphous lactose shows a highly complex DMA trace when analysed using a solid pocket. Two separate glass transitions are observed (C and D) before the material undergoes recrystallization followed by melting (E). The first glass transition (C) is much smaller than the second glass transition (D). It was hypothesised that the solid material pocket would not allow all of the moisture content to evaporate from the amorphous lactose sample, as while water could evaporate from the exposed edges of the sample, the lactose in the center of the pocket would retain some moisture content.

Therefore, the glass transition of the material at the center of the pocket will be plasticized by water and occur at a lower temperature to the dry lactose at the edges of the pocket. This results in two separate glass transitions being observed (the plasticized transition from 70-90 ˚C, followed by the main transition at 120-130 ˚C), limiting the ability with which amorphous content may be measured by measuring the glass transition.

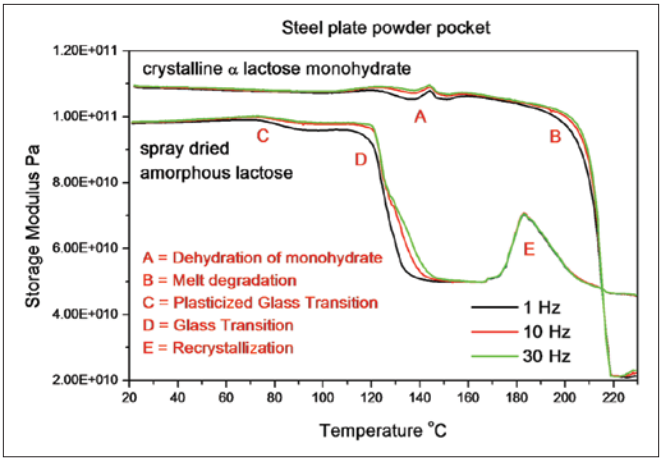

Figure 2. A comparison between amorphous and lactose monohydrate characterized using the plate design for the powder sample holder in the DMA.

Figure 3 shows the data obtained for the same amorphous and crystalline lactose samples analyzed in a Dutch Twilled mesh pocket. The Dutch Twilled mesh has small (~4 µm) pores (Figure 1) in its weave, which means that while the sample is held in the pocket, water vapor and other volatiles are free to move in and out of the sample. In Figure 3 the observed modulus is an order of magnitude smaller than that seen with the solid pocket in Figure 2 as the mesh pocket is less stiff than the solid material pocket (the main contribution to the modulus value in a material pocket experiment comes from the pocket itself, rather than the material contained within the pocket, but the transitions observed result from the material held in the pocket). The crystalline lactose data in Figure 3 does not show any dehydration peak, unlike the crystalline lactose in the solid material pocket (Figure 2 A), indicating that in the mesh pocket the lactose dehydration is not associated with a large change in structure within the lactose. As with the solid pocket, the crystalline lactose in the Dutch Twilled mesh pocket undergoes a clear melt transition.

The amorphous lactose in Figure 3 shows a single glass transition (B), with no indication of any plasticized glass transition at a lower temperature. This suggests that the lactose in the Dutch Twilled mesh pocket has been able to fully dehydrate prior to undergoing its glass transition, in a manner facilitated by the pores in the Dutch Twilled mesh. The observation of a single glass transition would in theory allow for more sensitive detection of amorphous content within crystalline lactose, and vice versa, using DMA, although it should be noted that the lower mechanical strength of the mesh pocket results in a poorer signal-to-noise ratio than is achievable with the solid steel pocket.

Both the mesh pocket (Figure 3C) and the solid steel pocket (Figure 2E) show a pronounced recrystallization peak (170-190 ˚C) in the mechanical response of amorphous lactose to temperature. This is as a result of the large increase in the stiffness of the lactose within the pocket when it undergoes recrystallization. In the mesh pocket the recrystallization peak is more pronounced relative to the glass transition, so in the mesh pocket it may be more obvious when small amounts of amorphous material are present, due to the relative size of the recrystallization peak. This could result in a greater sensitivity towards small amounts of amorphous content.

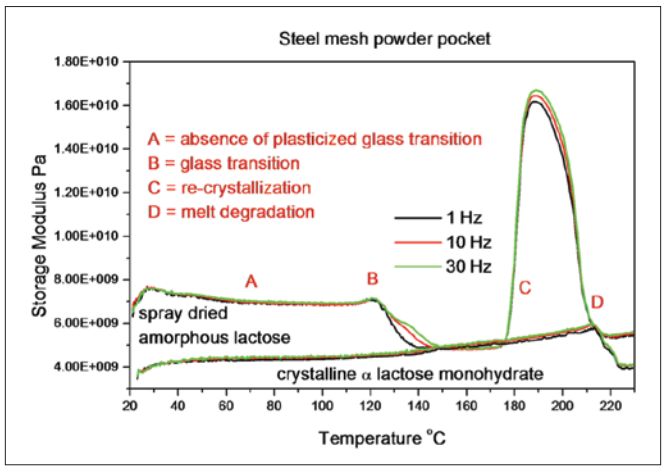

Figure 3. A comparison between amorphous and lactose monohydrate characterized using the mesh design for the powder sample holder in the DMA.

Conclusions

The data presented in this application note show the comparison between material pocket technology made from solid steel and Dutch Twilled steel mesh for the analysis of amorphous content in lactose. The solid steel material pocket has previously been shown to be a highly sensitive method for the detection of amorphous content in lactose by measuring the glass transition of the amorphous material. The sensitivity of the method, however, is limited by the presence of a small glass transition at a lower temperature than the main transition, due to the plasticizing effect of small amounts of water that is trapped in the lactose. Prior to going through the glass transition the lactose undergoes a dehydration event, but in the solid steel pocket it is unable to fully dehydrate. The pores in the Dutch Twilled mesh pocket allow the water from freely evaporate from the lactose, meaning that only a single glass transition is observed. Thus, the Dutch Twilled material pocket provides a more reliable result than the solid steel material pocket due to the Dutch Twilled materials greater permeability to volatiles being released by the sample.

References

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