A Comparison of DSC Techniques to Increase Sensitivity in Pharmaceutical Amorphous Content Studies

Introduction

Amorphous content has been of great interest in pharmaceutical formulations for many years as it is often a critical factor in the performance of pharmaceutical end products. In addition to the amorphous content having an impact on the bioavailability of the active pharmaceutical ingredient (API), amorphous materials tend to easily absorb small molecules such as solvents and water, which can greatly impact the dissolution properties and shelf-life of the pharmaceutical end product. X-ray diffraction (XRD), Raman spectroscopy, micro-calorimetry, gravimetric vapor absorption (GVA) and differential scanning calorimetry (DSC) are the techniques most commonly used to determine amorphous content, each having their own advantages and disadvantages.

DSC is commonly used due to its high sensitivity compared to XRD and its faster experiment times than micro-calorimetry or GVA. One of its biggest challenges, however, is amorphous content needs to be detected in real world samples, where content can be very low. In addition, new areas of research are focused on the effects of the physical processing of crystalline pharmaceutical ingredients and how the processing generates amorphous content which, in turn, affects product performance. There are several ways in which the sensitivity of DSC measurements can be improved, for example by increasing the sample size, removing interferences in the data and increasing the scanning rate. In this paper we review different approaches and directly compare the results of Modulated Temperature DSC and HyperDSC®.

Measuring heat-flow

DSC measures the heat-flow into or out of a material when it is heated, cooled or kept at a constant temperature. The signal from the DSC measurement is heat-flow and it can be calculated by multiplying the sample mass by the sample specific heat capacity and the heating rate. The equation is written as:

$Q=m*Cp*\beta$.
Where Q is heat flow
m is sample mass
Cp is sample specific heat capacity
β is heating rate.

Therefore, an increase in the sample mass or the heating rate will, in turn, increase the heat-flow signal.

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Increasing sample weight

Increasing sample weight will give a bigger heat flow signal as shown in Figure 1. Different size indium samples from 1 mg to 30 mg were heated at 10 ˚C/min. As the sample weight increased, the melting peak also increased. However, the sample size is limited by the volume capacity of the DSC sample pan. Especially with low density pharmaceutical samples, it is sometimes difficult to pack enough sample into the DSC pan. In addition, large amounts of sample may not always be available, e.g. expensive drug candidates.

HyperDSC

HyperDSC is a one of the latest DSC analysis techniques that utilizes the fundamental property of the DSC measurement in that the sensitivity is directly related to the temperature ramp rate. It requires a DSC instrument with an extremely fast response time and very high resolution. In contrast to most heat flux DSC instruments, the HyperDSC uses a double-furnace design which incorporates two ultra-light-weight furnaces with very low thermal inertia and the fastest possible DSC response time. It allows very fast linear heating and cooling scanning, up to 500 ˚C/min.

Modulated Temperature DSC (MT-DSC)

MT-DSC is a method that uses a temperature program different from the traditional constant heating rate ramp. It may either employ a sinusoidal oscillating temperature program, or a temperature program with a series of heat and hold. The resulting heat flow signal can be processed into two signals. One is the “reversing signal”, which represents thermodynamic events like glass transition. The other one is the non-reversing signal, which represents some kinetic events like evaporation and curing. By separating non-reversing signal from reversing signal, modulated temperature DSC can remove signal interferences from non-interest sources, such as enthalpy relaxation from the Tg of the amorphous material.

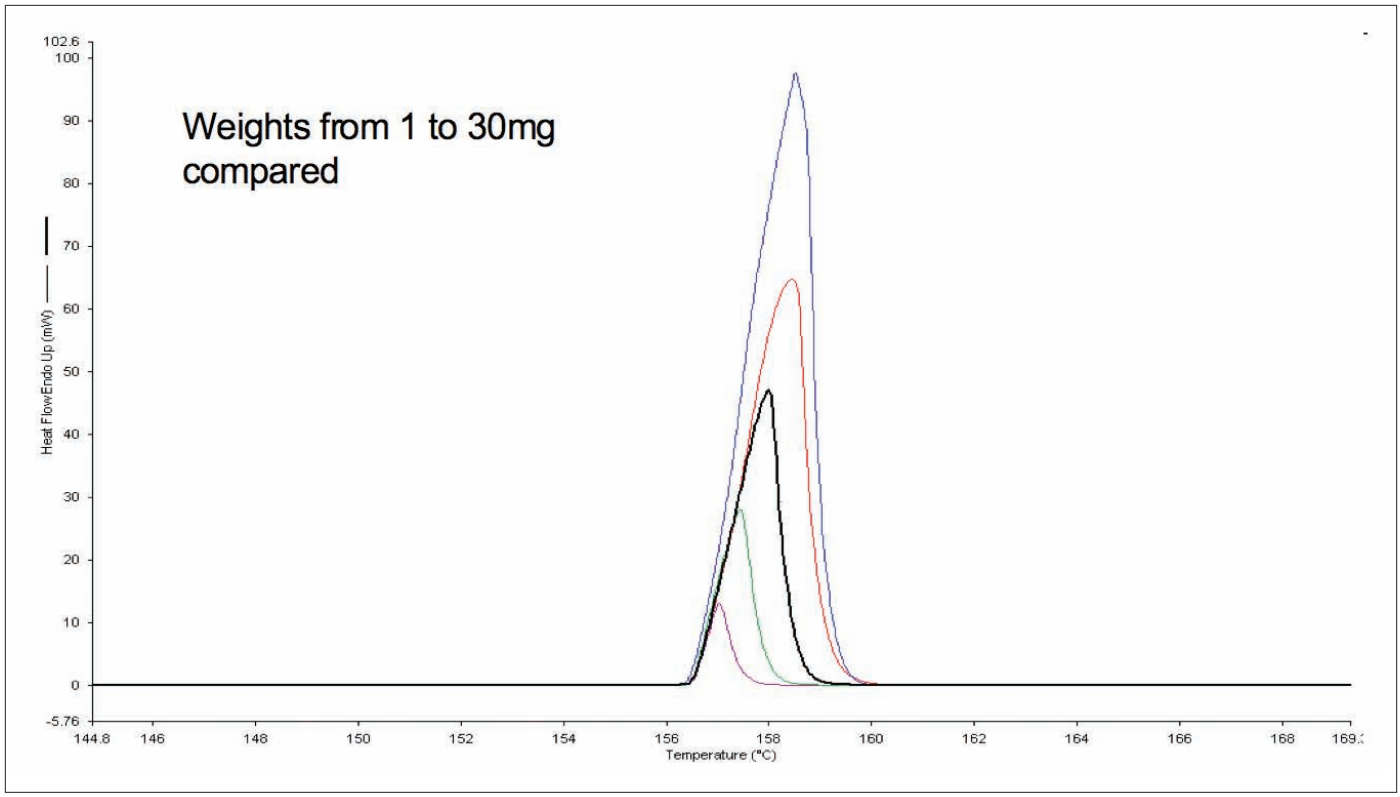

Figure 1. The melting peak for a standard of indium run using varying weights of sample. Note, the initial melt temperature shows minimal change despite the change in mass.

Polyvinylpyrrolindone (PVP)

PVP is an amorphous material often used as a binder in pharmaceutical tablet formulations. It is a hydroscopic material and as water is adsorbed its glass transition temperature will lower. PVP is often mixed with a diluent (e.g. lactose) in the actual formulation and the content of PVP can be 5% w/w or less. The Tg information is important to the formulation study as the glass transition has a significant effect on the physiochemical stability of the material.

Sample preparation

In order to test the capability of detecting Tg of PVP in mixture, samples of PVP with increasing amounts of lactose were prepared. The level of PVP ranged from 5% to 50%.

Results

MT-DSC was found to be able to detect the Tg of PVP at 40%, but not at 30% and as shown in Figure 2. However, HyperDSC at a rate of 200 ˚C was sensitive enough to detect the Tg at 5% of PVP, as demonstrated in Figure 3. The apparent step change of Tg in the 5% PVP sample further indicated that even lower levels of PVP can be detected.

The Tg measured is the same as that of pure PVP and the step change at Tg lowers with the decreasing PVP content. This confirms that the measured transition is from PVP. The fact that HyperDSC can be used to study the Tg at a level low enough to relate to that present in an actual formulation offers the potential to understand more clearly how the Tg of PVP can affect the physical properties of a formulation.

MT-DSC typically uses slow underlying scanning rates which may take a long time. As in this study for a heat scan from 0 ˚C to 150 ˚C, the MT-DSC took 75 minutes, while fast scan DSC took only 45 seconds. Also, the cooling time from 150 ˚C to 0 ˚C on the double-furnace DSC is much shorter than on the single furnace, heat flux DSC due to the furnace size. Overall, the fast scan on the double-furnace DSC saves a lot of experimental time and the productivity is improved dramatically.

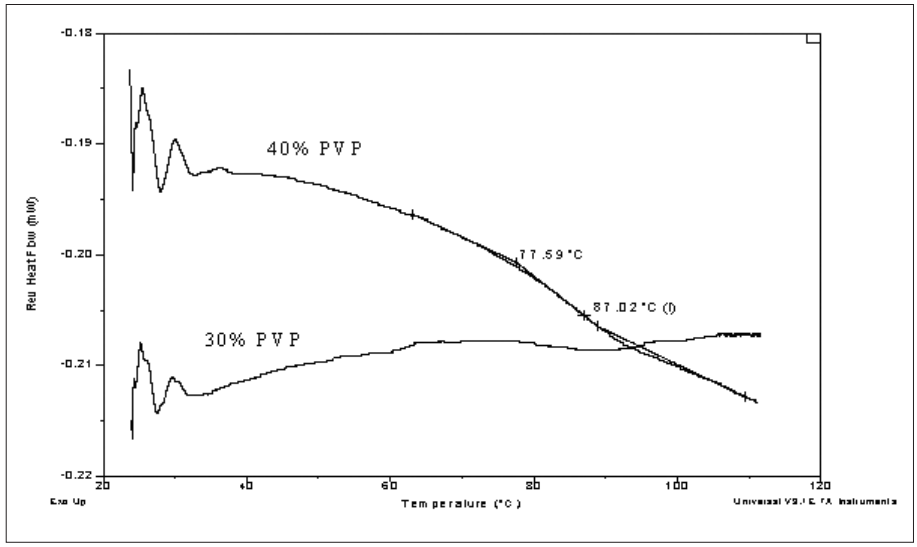

Figure 2. Reversing heat flow curves for PVP/lactose mixtures obtained using MT-DSC (data from work published by Buckton, 2005 and used with permission).

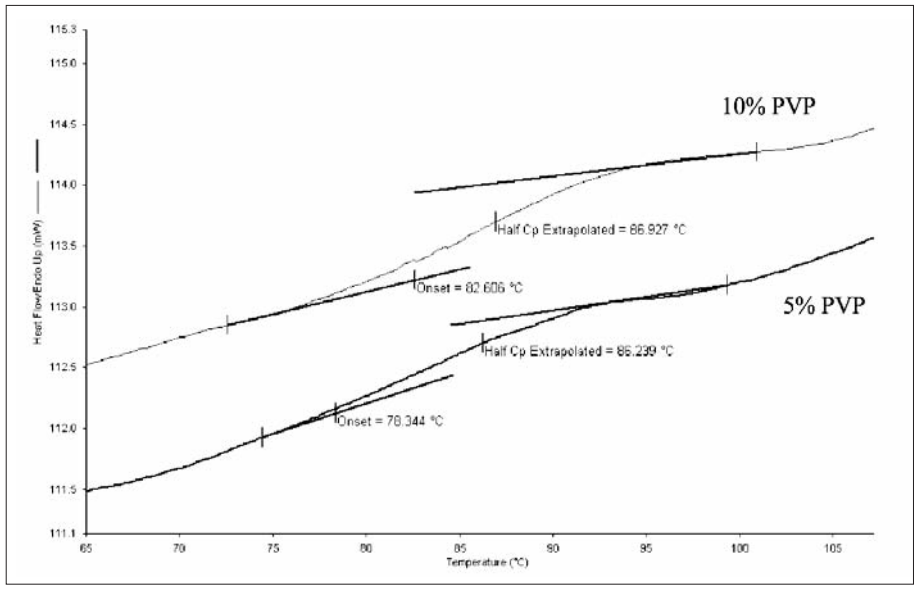

Figure 3. Heat flow curves for PVP/lactose mixtures obtained using HyperDSC by PerkinElmer (data from work published by Buckton, 2005 and used with permission).

Summary

This study compared HyperDSC by PerkinElmer with MT-DSC for an application relevant to the pharmaceutical industry. HyperDSC provides a dramatically higher level of sensitivity than MT-DSC. This allows the detection of very low levels of amorphous content in actual formulations, which often are undetectable by conventional and modulated temperature DSC. The high speed associated with HyperDSC increases the throughput and makes it an ideal screening tool.

Table 1. Summary of results for PVP/lactose mixtures.

Sample	Modulated Temperature DSC or MT-DSC		HyperDSC	
	Tg at half CP (°C)	Step change at Tg (J/g)	Tg at half Cp (°C)	Step change at Tg (J/g)
100% PVP	81	0.27	88	0.43
50% PVP	82	0.13	*	*
40% PVP	87	0.12	*	*
30% PVP	ND	ND	*	*
20% PVP	ND	ND	86	0.10
10% PVP	ND	ND	87	0.05
5% PVP	ND	ND	86	0.02

ND: not detected. * Not tested as 20% w/w/ PVP was detected.

Reference

1. R.D. Saklatvala, M.H. Saunders, S. Fitzpatrick and G. Buckton; J. Drug Del. Sci. Tech., 15 (4), 257-260, 2005.

Acknowledgment

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