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UTILIZATION OF DSC FOR PHARMACEUTICAL CRYSTAL FORM QUANTITATION

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Abstract

The existence of multiple crystal forms in a drug substance poses interesting development challenges as the material is taken from discovery through formulation, manufacture and market. There are a number of factors why drug substances under development are screened for presence of multiple crystal forms. Different crystal forms may exhibit varied performance properties including bioavailability and solubility, as well as, differences in physical properties such as morphology and melting point. These properties can affect the design of the manufacturing processes for the bulk drug substance, the formulation and the performance of the drug product.

This paper will focus on the application of differential scanning calorimetry (DSC) for the quantitation of pharmaceutical crystal forms. Feasibility studies were conducted on several pharmaceutical drug substances which were known to have multiple crystal forms, to determine if quantitative, semi-quantitative or limit of detection tests could be developed. The conclusion from these studies is that polymorphic crystal systems comprised of either close, or melting with decomposing, endotherms, competing transitions, or that contain sample contaminants, may not be optimum candidates for quantitation by DSC. Conversely, crystal systems that contain polymorphs that exhibit well-resolved endothermic or exothermic transitions, for either solvated *vs.* unsolvated species or both unsolvated, may be excellent candidates for crystal form quantitation by DSC.

Keywords: crystal forms, dsc, pharmaceuticals, polymorphs, quantitation

Introduction

Thermal analysis encompasses a number of different techniques (DSC, TG, DEA, TMA, DMA, micro-TA, temperature modulated DSC, micro-calorimetry, thermal microscopy, hyphenated thermal techniques, etc.,) used to study a broad range of materials such as polymers, ceramics, composites, proteins, explosives, pharmaceuticals, etc. The pharmaceutical industry has widely utilized DSC to study a number of solid-state properties including: purity [1, 2], optimization of dissolution parameters [3], amorphous materials [4–7], dispersions [8], excipient particle size studies [9], evaporation [10], excipient compatibility [11–15], encapsulation [16], salt selection [17–18], dosage form studies [19–20] and characterization of poly-

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morphs as part of a multi-disciplinary approach [21–26]. In addition, a number of studies have discussed the application of DSC and other thermal analysis techniques for the investigation of the thermal behavior of crystal systems [27–35].

Crystal forms or polymorphs are materials that can be crystallized in more than one lattice structure in the solid-state. Since crystal forms may exhibit different properties (e.g. melt transitions, dissolution, bioavailability, morphology, etc.), the generation of a drug substance under development containing a mixture of crystal forms can cause significant challenges for crystal form selection, process scale-up and development. Since delays associated with the resolution of these development issues can affect project timelines, a comprehensive understanding of not only the physical properties of the material is required, but also the relationship between the identified crystal forms. This understanding is required not only to minimize the development time, but also to ensure that the most stable and/or most appropriate crystal form or salt of the drug substance has been selected.

Since crystal forms can exhibit varied physical properties, these differences can be detected using a number of analytical techniques. If the technique proves successful in differentiating between these crystal forms, they may be utilized for the quantitation, e.g.: XRD [36–38], IR [39–41], IR/XRD [42–43], Raman [44], solution calorimetry [9, 45–46] and DSC [47].

The goal of this paper is to illustrate that not all pharmaceutical compounds are appropriate for crystal forms quantitation using DSC. Some examples in this paper will show good likelihood of success for the development of a DSC quantitation method, when pure materials are used and when the transitions of interest are unobstructed, while other examples will show that a quantitation method may not be developed due to the presence of completing transitions and sample inhomogeneity (decomposition products, impurities).

Experimental

Experimental parameters

DSC curves were collected using a TA Instruments 5000 series controller with a 2920 differential scanning calorimeter. Samples were weighed into DSC auto-sampler pans, and the mass accurately recorded. The samples were heated at a ramp rate of 10°C min^{-1} (unless otherwise stated) in an open pan configuration to temperatures spanning the transitions of interest, but no higher than 300°C. A nitrogen purge rate of 25 mL min^{-1} was utilized for all experiments. Cell constant, baseline, and two-point temperature calibrations were conducted at the 10°C min^{-1} ramp rate.

Materials

Proprietary Bristol-Myers Squibb drug substances were utilized in these case studies.

Mixture sample preparation

Mixtures of the crystal forms were prepared by weighing one crystal form into open DSC auto-sampler pans, with the second crystal form being weighed directly on top of the first, without the aid of mixing or compression. A total mass between <1 mg to ~25 mg was used for each of the experiments. X-ray powder diffraction was utilized to make an assessment of the polymorphic purity of the drug substances.

Results and discussion

Case study A - monohydrate and anhydrous crystal forms - quantitation is possible

The drug substance utilized in case study A exhibits two crystal forms, a monohydrate and an anhydrous form. The monohydrate form melts with volatilization near 115°C. The TG and DTG curves show that the temperature corresponding to the maximum mass loss correlates to the 115°C melt endotherm. Measurement of this mass loss once the dehydration is complete near 150°C indicates a volatile loss of 3.3%. The anhydrous form melts near 160°C. The TG and DTG curves show a mass loss of 0.5% when the volatilization is complete at 150°C. Figure 1 presents an overlay of typical DSC curves for these two forms. Hot stage microscopy confirmed the melt transitions.

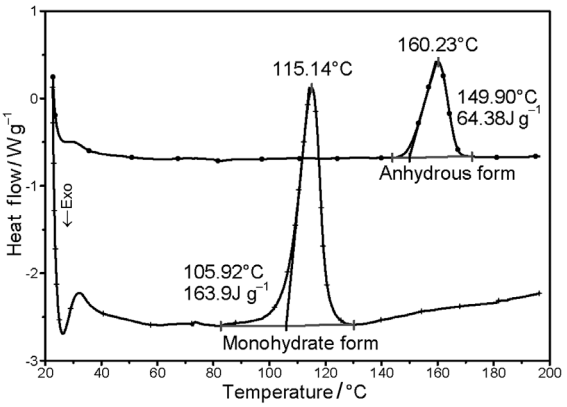

Fig. 1 Case study A overlay of the DSC curves for the monohydrate (bottom) and anhydrous (top) crystal forms

The characterization of the thermal properties of this drug substance indicated that at elevated temperatures the monohydrate crystal form converts to the anhydrous crystal form. Since additional studies indicated the monohydrate form possessed the superior physical properties required for continued development (i.e. solubility and stability), the monohydrate form was selected for development. The chemical process to generate this drug substance included a conversion step from the anhydrous

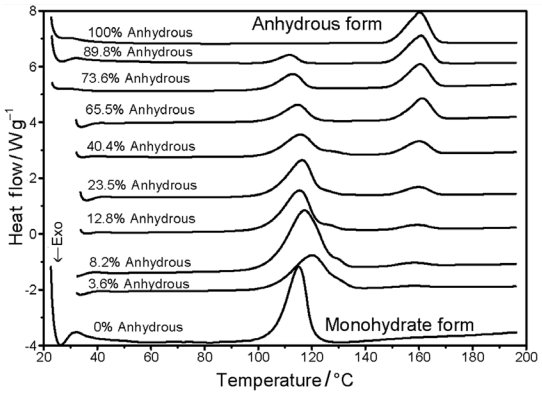

Fig. 2 Case study A overlay of the DSC curves from the quantitation feasibility study to determine the presence of the anhydrous form in the monohydrate crystal form

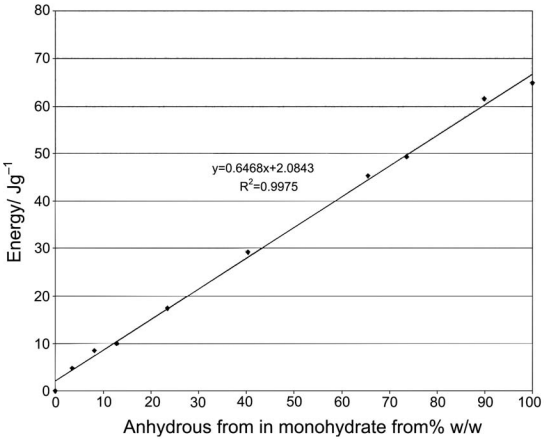

Fig. 3 Case study A data plot from the quantitation feasibility study to determine the presence of the anhydrous form in the monohydrate form

form to the monohydrate form, so it was desirable to develop a method to monitor the completion of the form conversion. Since DSC instrumentation was available to the process scientists, the development of a DSC quantitation method for the two forms was initiated.

Mixtures of the two crystal forms were prepared over the range of 0 – 100% *w*/*w* anhydrous form. Four mixtures were made below the 15% *w*/*w* anhydrous form concentration, since this was the greatest area of interest. An additional six mixtures were prepared over the remaining range, 15 to 100% *w*/*w* anhydrous form. Figure 2 presents an overlay of the DSC curves collected from the feasibility study. The DSC curve corresponding to 3.6% *w*/*w* anhydrous form (2nd from bottom) indicates the presence of a very small endotherm (4.8 J g^{-1}) whose maximum is near 160°C, which corresponds to the

Table 1 Case study A data plot from the quantitation feasibility study to determine the presence of the anhydrous form in the monohydrate form

Anhydrous in monohydrate/% *w*/*w*	H_f at 160°C/J g^{-1}	Theoretical H_f at 160°C/J g^{-1}
0	0	0
3.6	4.8	2.3
8.2	8.5	5.3
12.8	10.0	8.3
23.5	17.4	15.2
40.4	29.2	26.2
65.5	45.3	42.4
73.6	49.3	47.7
89.8	61.5	58.2
100	64.8	64.8

melting of the anhydrous crystal form. As the concentration of the anhydrous form is increased (from 8.2% through 100%) an increase in the heat of fusion energy for the 160°C endotherm is clearly observed. A broadening of the monohydrate melt transition near 115°C is observed in many of the curves, due in part to the time lag that may have existed in the DSC pan as the heat traversed the large mass of material that was often utilized in this study to achieve the required concentrations.

The heat of fusion data collected from this series of experiments is plotted as a function of percent anhydrous content in Fig. 3, while the individual data points are listed in Table 1. The correlation coefficient of the best-fit line shown in Figure 3 is 0.9975, indicating a linear correlation between the heat of fusion energy and the % *w*/*w* anhydrous form.

If one assumes, based on the X-ray powder diffraction pattern where no amorphous halo is observed, that the material is 100% crystalline, then an estimation of the heat of fusion for each concentration can be calculated using 64.8 J g^{-1} for the H_f of the anhydrous form. The most right column in Table 1 presents the theoretical heat of fusion values for the anhydrous form. When these calculated values are compared to the experimental values, the experimental values are always higher than the calculated heat of fusion values. This suggests that the assumption of 100% crystallinity may be incorrect, since the presence of low concentrations of amorphous or partially crystalline material below the detection limit of the XRD, could crystallize into crystalline material, therefore shifting the heat of fusion values. These calculated heat of fusion values are off ~2-3% which is below that the DSC detection limit determined in this study.

Based on this single set of data, DSC appears to be a suitable technique for the detection of the anhydrous form in the monohydrate down to approximately 4% *w*/*w* anhydrous form. It should be noted that these studies were conducted to determine the feasibility of developing a DSC method. Additional experiments are required to optimize

several experimental parameters including: pan configuration, sample quantity, appropriate mixing of crystal forms prior to analysis, temperature ramp rate, etc. Once these experimental parameters are optimized, a follow-up data set could be generated from which a limit of detection or minimum quantifiable limit and reproducibility values could be generated. This applies to all the case studies in this paper.

Case study B – two crystal forms that melt with decomposition – quantitation not possible

The drug substance utilized in case study B crystallizes in two crystal forms; a higher melting form I, which melts with decomposition near 187°C, and a lower melting form II, which melts with decomposition near 184°C. TG and hot stage microscopy studies confirmed this thermal behavior. Figure 4 presents an overlay of typical DSC curves for these forms.

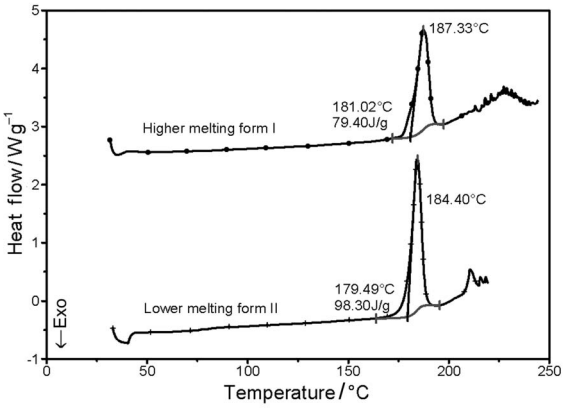

Fig. 4 Case study B overlay of the DSC curves for the higher melting form I (top) and the lower melting form II (bottom)

A quantitation method was investigated to determine if DSC could assist in identifying the presence of crystal form II in crystal form I for lab scale-up batches. Mixtures of the two crystal forms were prepared for DSC analysis by varying the concentrations of the lower melting form II in the higher melting form I over the approximate range of 0 to 100% *w*/*w*. The DSC curve in Fig. 5 represents a mixture of approximately 60% lower melting form II in higher melting form I. The transitions observed include the melt with decomposition maximum for the higher melting form I at 188.8°C and the shoulder whose maximum is at 185.5°C, which represents the melt with decomposition of the lower melting form II. The 60% lower melting form II mixture was the lowest concentration of form II in form I in which a shoulder was observed. Analysis of the mixtures prepared in this case study indicated that no baseline resolution between the two melt/decomposition transitions was achievable.

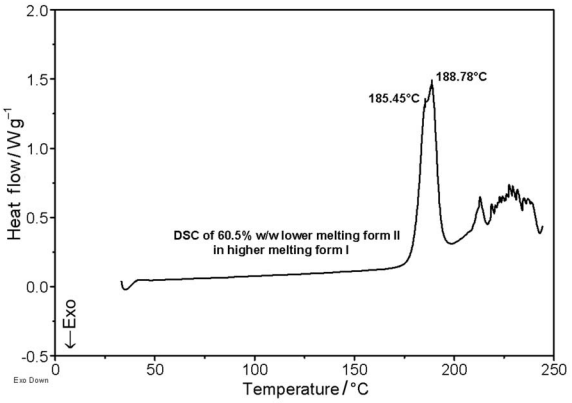

Fig. 5 Case study B DSC curve for a 60.5% *w*/*w* mix of the lower melting form II in the higher melting form I

Since these two crystal forms had similar melt with decomposition maxima, DSC could not provide adequate peak resolution to facilitate the development of a method to quantitate the undesired crystal form. In this case, DSC is not an appropriate quantitation method and an alternate technique, such as X-ray powder diffraction (XRD) and Raman spectroscopy, may be more appropriate for development of a quantitation method. Initial studies did observe differences between the two crystal forms using these techniques.

Case study C – two close melting crystal forms – quantitation not possible

The compound studied in case study C is a drug substance intermediate that can be isolated in two different unsolvated crystal forms; a high melting form that melts near 114°C, and a lower melting form that melts near 104°C. TG and hot stage micros-

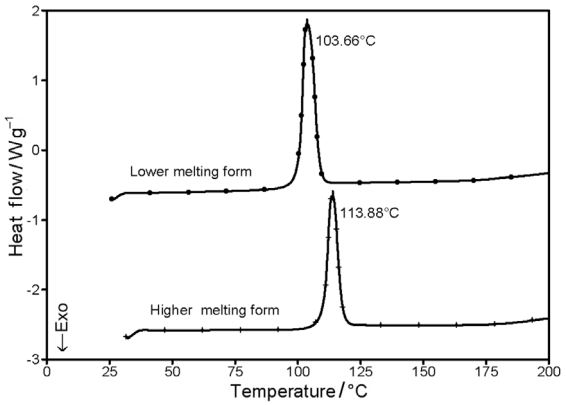

Fig. 6 Case study C overlay of the DSC curves for the two different unsolvated crystal forms; a high melting form (bottom) and the lower melting form (top)

copy data confirmed this behavior. Typical DSC curves representing the low and high melt crystal forms are presented in Fig. 6.

Since there was interest in using available instrumentation as an in-process control tool to rapidly identify the crystal form of the synthesized intermediate, studies were conducted to determine if DSC could differentiate between the two crystal forms. Since the DSC curves representing the two pure crystal forms each indicated single melt endotherms, with a 10°C difference between the two maxima, the development of a DSC quantitation method appeared feasible. Initial studies were conducted using mixtures of ~50% *w*/*w* of the two crystal forms. Data collected at a 50°C min^{-1} temperature ramp rate indicated poor baseline resolution of the two melt endotherms. Subsequent studies conducted to separate the two endotherms using both 10 and 5°C min^{-1} temperature ramp rates were unsuccessful in significantly improving the baseline resolution. While utilization of the 5°C min^{-1} heating ramp rate did improve the baseline resolution to a small degree, it did not improve the separation adequately to continue with the development of a DSC quantitation method. An overlay of curves obtained from these heating rate studies is presented in Fig. 7. An investigation into use of lower heating rates, such as 1°C min^{-1}, was not explored since it did not appear that adequate baseline resolution could be achieved at that

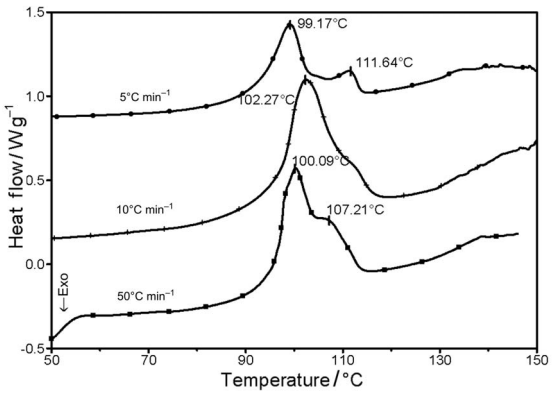

Fig. 7 Case study C overlay of the DSC curves collected for ~50% mixtures of the lower and higher melting crystal forms at different heating rates

ramp rate, and that an alternate analytical tool may be more appropriate for a crystal form quantitation method.

Case study D – mixture of 2:1 and 1:1 complexes – quantitation possible

The drug substances utilized in case study D were 1:1 and 2:1 (complex:drug) complexes of a bulk drug with L-phenyl alanine. Initial crystallization experiments on un-complexed material generated amorphous material. Subsequent experiments aimed at generating complexes to increase solution stability were successful in syn-

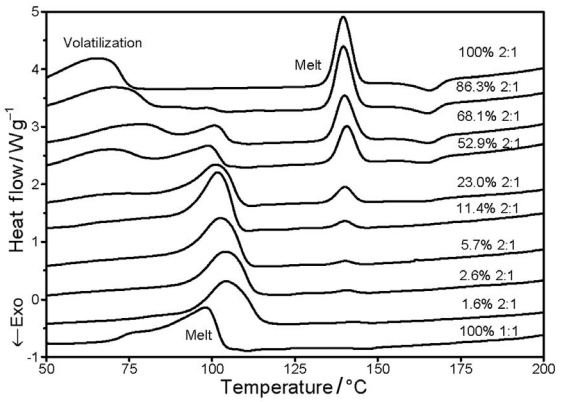

Fig. 8 Case study D overlay of the DSC curves from the quantitation feasibility study to determine the presence of the 2:1 complex in the 1:1 complex

thesizing 1:1 and 2:1 complexes that were crystalline. A quantitation method was requested to determine the presence of low levels of the 2:1 complex in the 1:1 complex, since presence of the higher molecular mass 2:1 complex impurity could cause problems for HPLC purity assays. DSC was one of the analytical techniques examined to monitor the presence of the 2:1 complex, since the manufacturing for this drug substance possessed this equipment in their laboratories.

The top and bottom curves in Fig. 8 provide typical DSC curves of the pure 2:1 complex and 1:1 complexes, respectively. These show the distinct differences in their thermal behavior. The 1:1 complex curve (bottom) exhibits a melt and volatilization endotherm near 100°C, while the 2:1 complex curve (top) exhibits a volatilization endotherm near 65°C, a melt endotherm near 140°C, an exothermic transition near 166°C, followed by decomposition. Hot stage microscopy and TG confirmed the melt and volatile transitions.

To determine if DSC was an appropriate technique for determining the presence of low levels of the 2:1 complex in the 1:1 complex, a series of mixtures were prepared for analysis. Four mixtures were prepared containing <10% *w*/*w* 2:1 complex in the 1:1 complex and an additional six mixtures were prepared covering the 10-100% *w*/*w* range.

An overlay of the DSC curves collected from the samples representing the mixtures of 2:1 in the 1:1 complex studied is presented in Fig. 8. Several trends can be observed as the concentration of the 2:1 complex increases in the mixtures: 1) an increase in the energy in the 65°C volatilization and 140°C melt endotherms, 2) an increase in the energy of the 166°C exothermic transition, and 3) a decrease in the energy of the 100°C melt and volatilization endotherm. The 2:1 complex provides three separate and characteristic thermal events that could potentially be used for its quantitation.

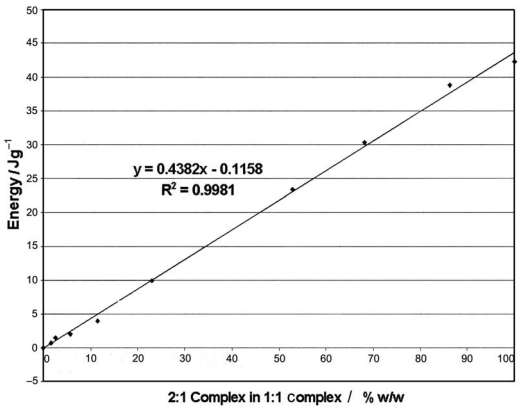

Fig. 9 Case study D data plot from the quantitation feasibility study to determine the presence of the 2:1 complex in 1:1 complex using the 140°C endotherm heat of fusion data

Table 2 Case study D data from the quantitation feasibility study to determine the presence of the 2:1 complex in the 1:1 complex

2:1 complex in 1:1 complex/ % *w*/*w*	H_f at 140°C/J g^{-1}	H 166°C/J g^{-1}
0	0	0
1.6	0.7	0
2.6	1.5	0
5.7	2.0	0
11.4	4.0	0
23.0	9.9	0.6
52.9	23.4	3.7
68.1	30.3	5.4
86.3	38.8	8.0
100	42.3	8.5

Since the 140°C melt endotherm represented a single well resolved transition, it was evaluated first to determine its sensitivity for the detection of the 2:1 in the 1:1 complex. The heat of fusion data collected from the 140°C melt endotherm for these mixtures is plotted *vs.* the % *w*/*w* 2:1 in the 1:1 complex in Fig. 9. The data points plotted are listed in Table 2. The results from this study indicates a linear correlation between the composition of the mixture and the heat of fusion (r^2 =0.9981), suggesting that DSC is capable of detecting the presence of the 2:1 in the 1:1 complex. A detection of < 2% *w*/*w* is easily achieved.

The energy data collected from the 166°C exothermic transition of the mixtures was also evaluated and is presented in Fig. 10 and Table 2. Due to the low energy as-

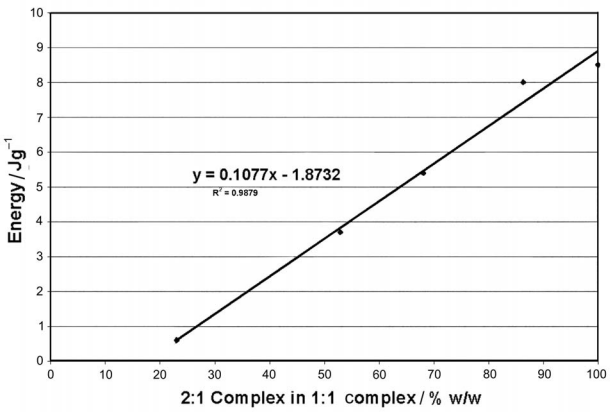

Fig. 10 Case study D plot from the quantitation feasibility study to determine the presence of 2:1 complex in 1:1 complex using the 166°C exotherm energy data

sociated with this transition, no differences were observed for mixtures containing less than 23% *w*/*w* 2:1 complex. The mixtures containing greater than 23% *w*/*w* 2:1 in 1:1 complex were plotted and indicated a linear relationship between the energy at this transition and the % *w*/*w* 2:1 in 1:1 complex ($r^2 = 0.9879$). Although a correlation between the 166°C exothermic transition and the ratio of 2:1 complex was demonstrated, a thorough understanding of the identity of this transition should be known prior to generation of quantitation values.

No observations were noted during hot stage microscopy experiments above the melt temperature to identify this exothermic transition. To characterize this transition further, other second tier characterization techniques, such as variable temperature X-ray diffraction, isothermal and/or quench cooling DSC, and additional hot stage microscopy studies, would be required. Previous characterization of salts and complexes of bulk drugs exhibiting exothermic transitions following a melt, indicated the crystallization of the bulk drug substance from the molten/decomposed material, rather than the salt or complex. Further investigation is required to determine if compound D exhibits similar behavior.

Conclusions

The case studies presented in this paper probe a number of important factors affecting the applicability or inapplicability of DSC as a crystal form quantitation technique. The conclusion from these studies is that crystal systems containing polymorphs, which exhibit either close melting or melting with decomposing endotherms, overlapping transitions, sample contaminants, etc. may not be good candidates for quantitation by DSC. Conversely, crystal systems that contain polymorphs which exhibit well resolved endothermic or exothermic transitions, for either

solvated *vs.* unsolvated species or both unsolvated, may be excellent candidates for crystal form quantitation by DSC.

Although differential scanning calorimetry is a valuable tool to aid in the characterization and quantitation of pharmaceutical crystal forms, the applicability of this technique must be identified and then the method optimized. Prior to the development of a limit of detection, semi-quantitation or full quantitation DSC method, both the physical properties of the material, and the thermal behavior of the crystal forms that comprise the crystal system, must be understood. Once this information is collected, analytical techniques may be evaluated to determine which technique is the most appropriate. DSC may not always be the most appropriate assay for crystal form quantitation, however its presence in industrial laboratories is an advantage in its utilization for crystal form quantitation. The factors for selection of an alternate technique for quantitation may be due to a variety of reasons that may be related to: the properties of the material (e.g. decomposition, crystallinity, poor transition separation, etc.), or to issues regarding the development of the assay, (e.g. availability and cost of instrumentation, method development time, experience of the scientist, etc.).

Sample parameters that should be optimized when the DSC limit of detection, semi-quantitation or full quantitation method is developed, include particle size, sample pan configuration, mixing of forms, morphology, sample quantity in DSC pan, hygroscopicity, amorphous content, etc. This optimization ensures that the selection of the most appropriate technique and sample parameters are selected.

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