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Applications of modulated differential scanning calorimetry in preformulation studies

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Abstract

Characterization of the thermal properties of active pharmaceutical ingredients is critical in the selection of appropriate physical forms for development and defining proper manufacturing, handling and storage conditions of those chemical entities. Modulated differential scanning calorimetry (MDSC) has proven to be an effective tool in the thorough characterization of thermal behavior of compounds in preformulation studies. Selected applications of MDSC for various preclinical compounds are presented, thereby demonstrating the utility of this analytical method in the determination of glass transitions, characterization of desolvation and degradation processes as well as in the study of polymorphic transformations and crystallizations. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Modulated differential scanning calorimetry (MDSC); Glass transition; Desolvation; Degradation; Polymorphic conversions; Preformulation

1. Introduction

Differential scanning calorimetry (DSC) has been a widely utilized thermal technique within the pharmaceutical disciplines of preformulation and formulation. DSC may be used qualitatively and quantitatively to characterize heat flows associated with thermal events and obtain information on physical and or chemical transformations as a function of temperature or time [1–5]. Although DSC is an invaluable analytical tool, the technique does suffer from limitations with respect to its ability to delineate complex transitions into individual contributing components. Many thermograms contain complex transitions with overlapping events, which may potentially be resolved by decreasing the heating rate and sample size at the expense of sensitivity. Therefore the DSC analyst is often forced to compromise between resolution and sensitivity. These limitations can lead to difficulties in the understanding and interpretation of thermal events.

Alternatively, modulated temperature DSC (MDSC) offers a solution to overcome many of the aforementioned analytical limitations. MDSC differs from conventional DSC wherein the sample is subjected to a more complex heating program incorporating a sinusoidal temperature

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modulation accompanied by an underlying linear heating ramp. Whereas DSC is only capable of measuring the total heat flow, MDSC provides the total heat flow, the non-reversible (kinetic component) and the reversible (heat capacity component) heat flows. MDSC is growing in interest as witnessed by a review published by Coleman and Craig [6], which outlines the basic principles governing DSC and MDSC and potential applications of MDSC to formulation aspects of pharmaceutical development. Craig and Royall [7] have described practical considerations and limitations with respect to defining experimental parameters in MDSC. MDSC has been used in formulation studies to measure the glass transition of lyophilized bovine somatotropin/sucrose mixtures to determine the influence of drug:excipient ratio on the glass transition value [8]. In this particular application, MDSC proved advantageous in separating out the glass transition from enthalpic relaxation phenomenon. Application of MDSC in measuring the glass transition using Saquinavir as a model drug has been demonstrated with emphasis on the effects of experimental parameters [9].

The purpose of this publication is to showcase some of the applications of MDSC to various compounds within the preformulation area where the technique has added significant value in the thermal characterization of drug substance and enhanced interpretation of thermal events arising from multiple origins.

2. Experimental

MDSC experiments were performed using a Model 2910 Modulated DSC and a TA 2100 Thermal Analyst Controller (TA Instruments, New Castle, DE, USA). Samples were sealed in aluminum DSC pans and subjected to an underlying heating rate of either 2 or 3°C min^{-1} and the temperature was modulated at an amplitude of ± 1°C s^{-1}. All compounds were supplied by DuPont Pharmaceuticals and were used as received. Compounds studied may represent current or potential clinical development candidates, therefore the structures and therapeutic information are proprietary in nature and not disclosed.

3. Results and discussion

3.1. Glass transitions

The determination of glass transitions (Tg) of pharmaceutical products, excipients and active drug substance is critical to considerations of proper handling, manufacture and storage conditions of these materials. The Tg represents the temperature below which the molecular mobility of a glassy amorphous solid is dramatically reduced and above which the amorphous material takes on a 'rubbery' character with increases in the number and magnitude of molecular motions [10]. Given that increased molecular mobility can lead to increased chemical reactivity and the propensity for a metastable amorphous material to crystallize over time, amorphous solids should be handled and stored well below the glass transition temperature, which makes accurate determinations of the Tg imperative in preformulation and formulation development.

Often the presence of extraneous thermal events such as enthalpic relaxation or moisture loss can confound the measurement of the Tg. The utility of MDSC in these situations has been shown for polymer blends and nylon [11] and in formulation applications [7]. Enthalpic relaxation originates from thermally induced atomic or molecular rearrangement at the glass transition, which results in structural relaxation towards equilibrium [12]. An example of this phenomenon is seen in Fig. 1 in which the enthalpic relaxation is observed at 107.2°C in the total and the non-reversing heat flow signals and the underlying glass transition can be seen in the reversing signal. Above the glass transition, the molecular mobility increases and crystallization of the drug substance occurs, as witnessed by the presence of a major exothermic event above 190°C.

Moisture in amorphous material can act as a plasticizer and therefore may have profound lowering effects on values for the glass transition. Furthermore, the loss of moisture upon heating typically results in broad endotherms that may not allow facile determination of the glass transition by DSC since a preconditioning heating step is required before the glass transition can be

determined. Fig. 2 shows a MDSC thermogram for a polymeric drug substance that contains residual moisture. The volatilization of water upon heating results in an extremely broad en-

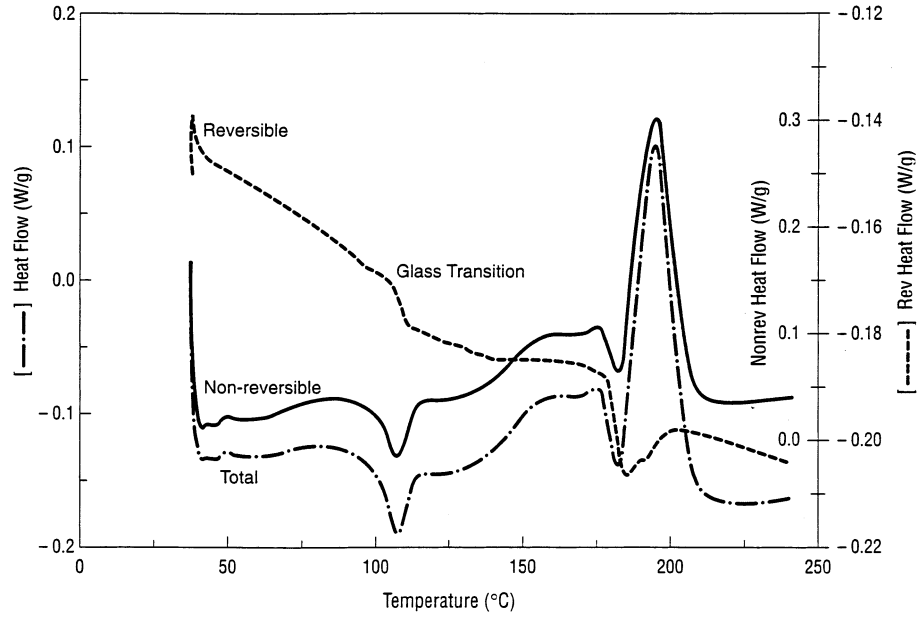

Fig. 1. Modulated DSC thermogram separates the enthalpic relaxation at 107.2°C (shown in the non-reversible signal) from the glass transition (shown in the reversible signal).

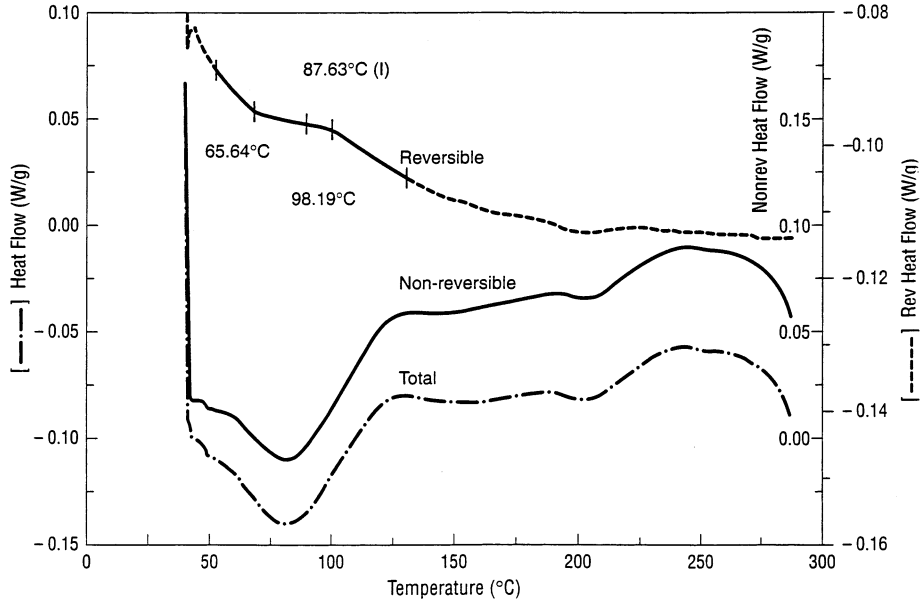

Fig. 2. Modulated DSC thermogram of a polymeric drug substance illustrating the loss of moisture in the broad non-reversible endotherm and the underlying glass transition in the reversible signal.

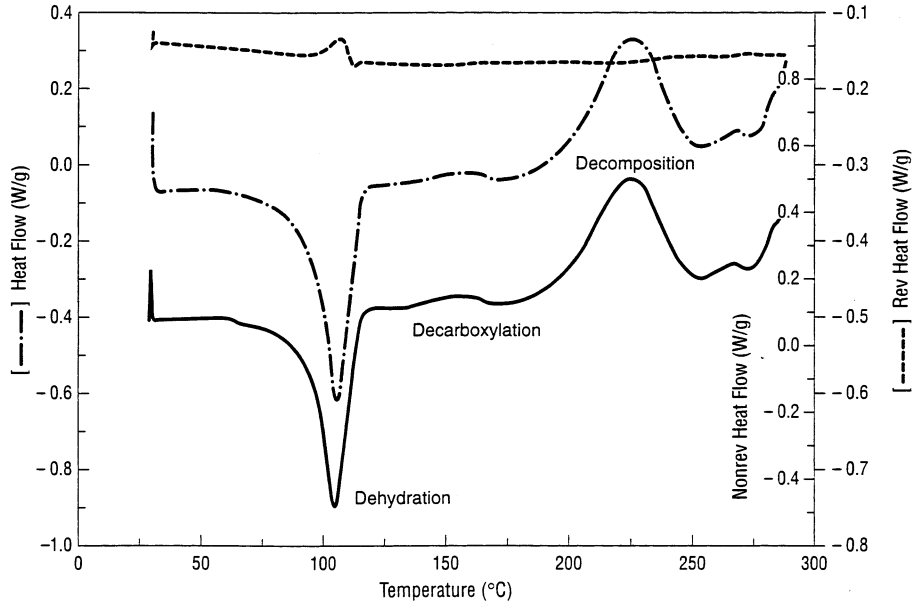

Fig. 3. Modulated DSC thermogram of a drug substance undergoing multiple non-reversible events including dehydration at 105.5°C, decarboxylation at ~150°C and further decomposition above 200°C.

dotherm from 50 to 125°C, which overlaps the glass transition at 87.6°C. Furthermore the plasticizing effect of water renders a broad glass transition spanning from 65.6 to 98.2°C. The use of conventional DSC to measure the Tg of this compound requires the sample to be subjected to a heat/cool/reheat cycle that results in the acquisition of a glass transition on material that has a significantly altered water content. Given the plasticizing effect of water and the fact that the Tg is lowered in the presence of water, determination of Tg by conventional DSC may misrepresent the Tg giving artificially high values in the absence of water and therefore MDSC may give a more meaningful value of Tg.

3.2. Desolvation and degradation

The ability of MDSC to discriminate non-reversible processes from those which are at equilibrium (reversible) is a useful aid in the characterization of thermal events. Examples of non-reversible processes include, but are not limited to desolvation, crystallization phenomena, and decomposition. An example of a complex thermogram showing multiple non-reversible processes is shown in Fig. 3. The compound was initially received as a stable dihydrate, and the release of the water of hydration from the crystal lattice is observed in the total and non-reversing signals at 105.5°C. The sensitivity of MDSC allows the detection of broad non-reversible exotherm at ca. 150°C, which corresponds to the decarboxylation of the compound. Finally, a major non-reversible exotherm attributed to further decomposition was observed at 222.9°C. Fig. 4 illustrates yet another example of decomposition in which the high energy exotherm at 216°C represents a non-reversible thermally induced cleavage of a hydroxamic acid functional group.

Frequently melting of drug substance is accompanied by decomposition. MDSC is capable of deconvoluting overlapping melting and decomposition processes as shown in Fig. 5 where the total heat flow signal shows inadequate resolution of the melt endotherm and the decomposition exotherm. Separation of the events by MDSC clearly shows the reversible endothermic melt component at 198.4°C and the non-reversible decomposition exotherm at 200.1°C.

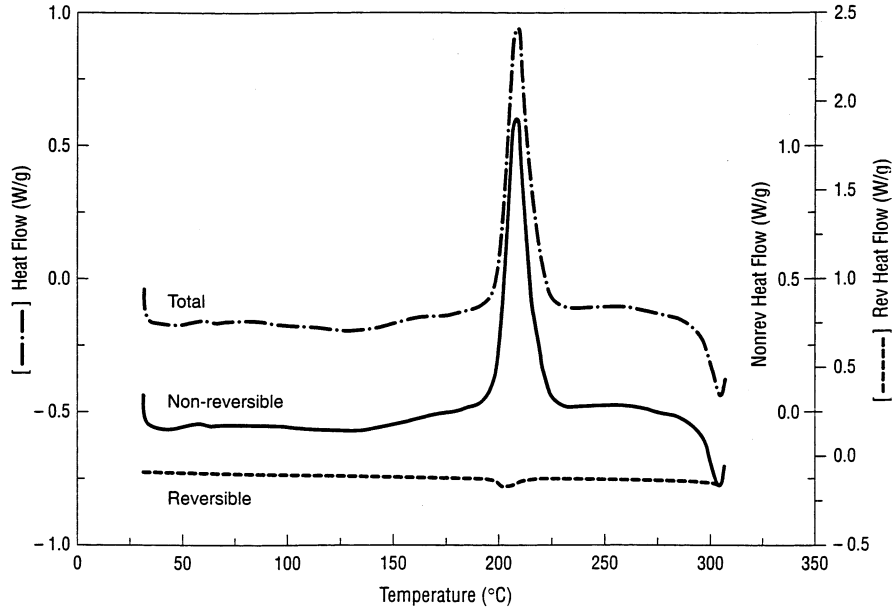

Fig. 4. Modulated DSC thermogram of a thermally labile drug substance. The exotherm occurring at 222.9°C corresponds to thermally induced cleavage of a hydroxamic acid functional group on the molecule.

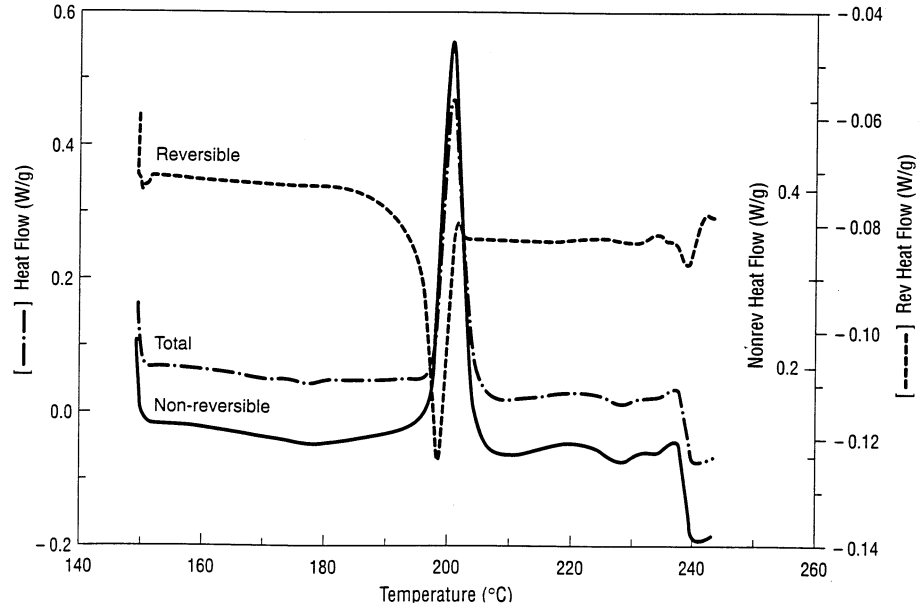

Fig. 5. Modulated DSC thermogram of a drug substance exhibiting overlapping melting with decomposition. The melt endotherm is seen in the reversible signal and can clearly be resolved from the decomposition exotherm in the non-reversible heat flow.

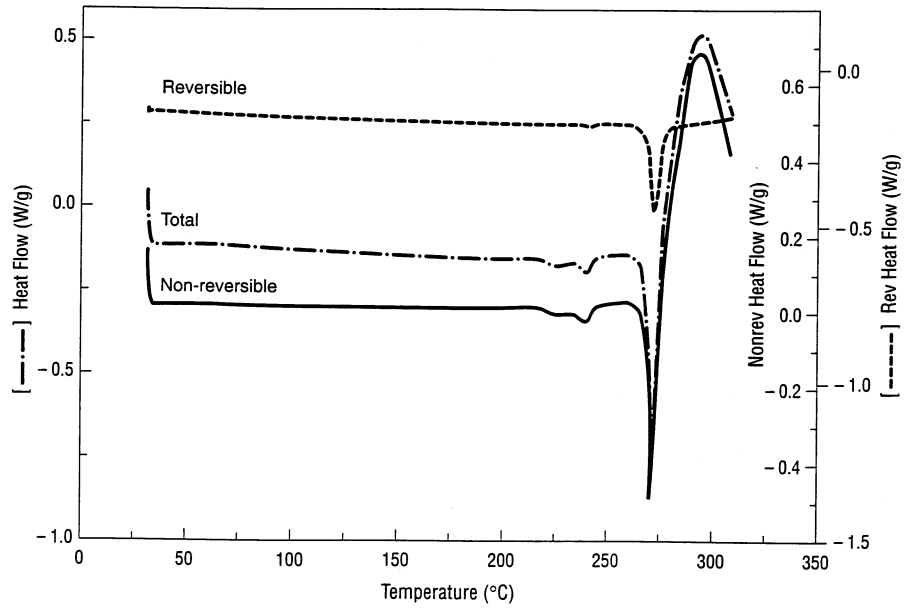

Fig. 6. Modulated DSC thermogram of losartan, which initially undergoes a non-reversible solid-solid polymorphic conversion, shows an endothermic melt transition in the reversible signal and finally decomposes as seen in the non-reversible exotherm.

3.3. Polymorphic transformations

Although X-ray powder diffraction is generally required for confirmation of different crystalline forms, MDSC has been a useful tool along with hot stage microscopy to provide insight into various types of polymorphic transformations.

The solid–solid polymorphic interconversion of losartan occurs in the absence of melting and has been previously reported [2]. The MDSC thermogram for this compound is shown in Fig. 6, where the kinetically controlled molecular reorganization is responsible for the broad endotherm at 237.4°C seen in the non-reversible heat flow and virtually no reversible transition is observed. In addition to the polymorphic conversion, decomposition after melting of the compound is also observed as an exotherm at 270.5°C in the non-reversing signal.

Another type of a polymorphic conversion is illustrated in Fig. 7 in which the transformation occurs via a melt followed by recrystallization. The endotherm present at 175.8°C in the reversing signal represents the initial melt prior to the non-reversible recrystallization exotherm at 177.3°C. The presence of an endotherm coinciding with the initial melt was also observed in the non-reversing heat flow. While this occurrence is quite common in MDSC, the cause for the signal is not widely understood by those using the technique, but maybe due in part to initiation of the polymorph recrystallization upon initial liquification (melting) of the material.

4. Conclusions

The utility of MDSC in a preformulation setting has been demonstrated by the various examples discussed in this paper. Modulated DSC has been useful in the characterization of glass transitions of amorphous drug substances, which is essential in defining the handling and storage limitations for these materials. The application of MDSC to study non-reversible processes, such as desolvation, degradation and polymorphic conversions has been valuable in the defining these kinetic processes for potential development candidates and permits thorough characterization of thermal behavior at the preformulation level. The

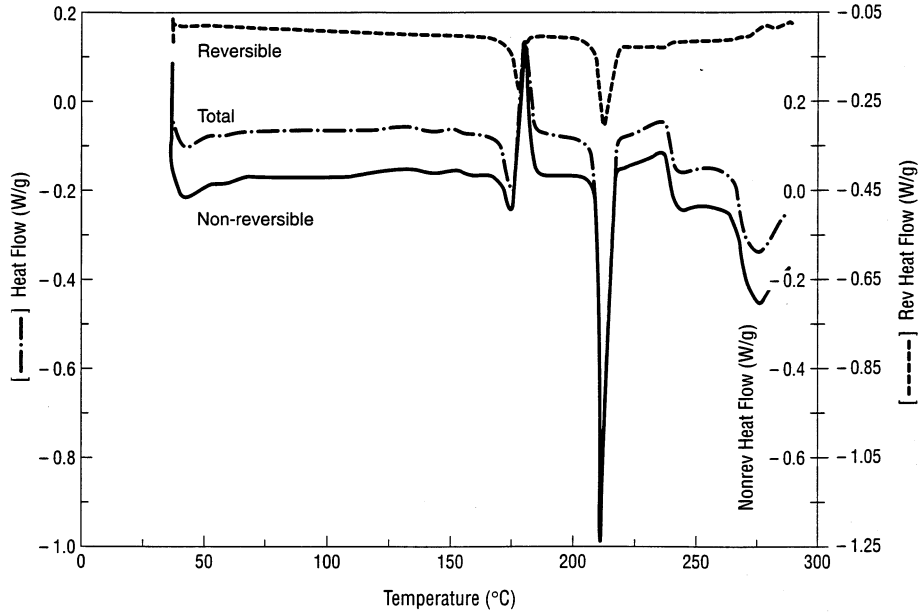

Fig. 7. Modulated DSC thermogram of a polymorphic drug substance that melts, as seen by the reversible endotherm at 175.8°C, with recrystallization following in the non-reversible signal at 177.3°C.

study of polymorphism and identification of the most thermodynamically stable form is of particular importance in preformulation activities. MDSC has allowed the study of recrystallization phenomenon and together with hot stage microscopy and X-ray powder diffraction MDSC provides a valuable tool to obtain information on the nature of such transformations.

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