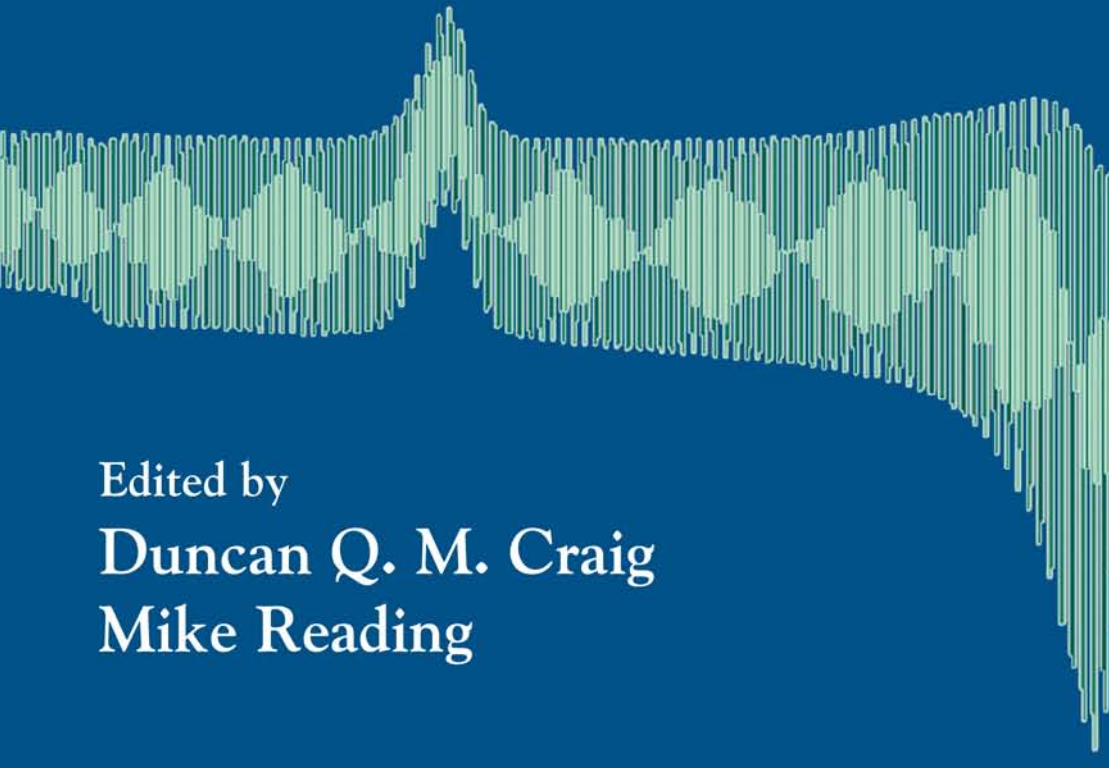
THERMAL ANALYSIS OF PHARMACEUTICALS



Edited by
Duncan Q. M. Craig
Mike Reading

CRC Press
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CRC Press
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Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an informa business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20130925

International Standard Book Number-13: 978-1-4200-1489-1 (eBook - PDF)

Preface

Thermal analysis is one of the mainstay families of techniques for the physical, and on occasions chemical, characterization of pharmaceutical materials. The long history of using thermal methods within the field, and the astonishing variety of applications to which these methods have been put, reflect the necessity of developing reliable and versatile characterization tools for the successful development of pharmaceutical products. Indeed, it is interesting to reflect that one of the key focus areas within the industry, next to drug discovery, is analytical development, an area made even more pertinent by the recent Process Analytical Technologies initiative launched by the United States Food and Drug Administration (FDA) whereby the product-to-market process may be accelerated if appropriate validation of each stage of manufacture is provided.

Given the context of the clear importance of analytical methodologies, it is perhaps useful to consider what thermal methods may and, just as importantly may not, achieve within the pharmaceutical arena. Indeed, it is possible to argue that the strengths and limitations of these methods are intrinsically linked. The first issue relates to the type of phenomenon that thermal methods may usefully study. Although there are examples of these methods yielding chemical information such as extent of cross-linking, purity, or degradation, the vast majority of applications are associated with the characterization of the physical structure and properties of materials. By "physical structure" we mean the study of the arrangement of molecules of (usually) known composition and the events associated with changes in those physical arrangements. Classically, this would include the study of melting or crystallization, although other processes such as glass transitions and associated plasticization phenomena are also widely studied. Usually, these processes are studied not because the operator is necessarily interested in the process *per se* but because that process reflects the structure of the material under ambient or user conditions, a classic example being the detection of polymorphism by studying variances in melting point. Alternatively, the thermal process may lead to the prediction of long-term behavior such as physical stability, examples including the study of glass transitional behavior in order to predict the storage conditions for which the risk of crystallization is minimized.

The second consideration is that thermal methods are extremely versatile, allowing useful characterization of almost any sample. Indeed, the methods may be used to study single or multiple component systems such as finished dosage forms, although care is required in the interpretation of data from the latter. Finally, these methods tend to be simple to use, inexpensive, and operator friendly. This is a highly pertinent practical consideration, as methods whereby absolute specialization is required may be extremely useful but are less likely to have widespread application.

As stated above, the limitations of thermal methods are effectively mirror images of these advantages. These methods involve the application or measurement of changes in heat, hence the resulting data tends to relate to temperatures of transitions or heat flow as the samples undergo such a transition. Consequently, the information gained can often only indirectly be related to the feature of interest such as crystal structure or composition. This therefore requires the operator to extrapolate this information, inevitably leading to assumptions in interpretation. Indeed, it is almost invariably the case that direct chemical or spectroscopic information is not forthcoming unless the thermal method is interfaced with a second measuring technique. This also mirrors the versatility of the approach; such versatility is possible due to the nonspecificity of the measurement. Finally, we would argue that the simplicity of measurement has in some respects proved to be a disadvantage in that thermal methods may be used as "workhorse" methods whereby they are used for simple screening, with little consideration given to the use of the methods in more sophisticated ways. A reasonable analogy comparing thermal methods with other techniques such as solid-state NMR would be learning to play the piano in contrast to a trumpet; it is possible to get a reasonable tune out of a piano with a minimum of effort or training, whereas the playing of the trumpet requires some training to avoid merely producing high-pitched shrieks. However, to play either at a high level of competence requires equivalent skill and patience for both instruments. The point being made is that the sheer accessibility of thermal measurements has arguably caused an underestimation of the level of information that may be obtained if one is willing to spend time exploring these methods in depth.

On that basis it is appropriate to outline the purpose of this book and the intended contribution that it may make to the pharmaceutical field. There are already a large number of excellent texts available in the thermal analysis and polymer fields outlining the principles and uses of these methods. There is a more limited number of (again, excellent) texts that outline the use of these methods for pharmaceutical systems, with particular emphasis on the applications of the methods. In this text we have tried to place more emphasis on the techniques themselves in terms of their use and the interpretation of the corresponding data, while at the same time writing the chapters with a strong leaning toward pharmaceutical scientists.

For example, the most commonly used thermal method is and will almost certainly continue to be differential scanning calorimetry (DSC), hence here we have dedicated three chapters to the technique covering the principles, the optimal use of the method, and pharmaceutical applications. We then include chapters on thermogravimetric analysis, modulated temperature DSC, microcalorimetry, high sensitivity DSC, thermal microscopy, thermally stimulated current, and dynamic mechanical analysis, all of which have attracted great interest within the pharmaceutical field. In all cases, these chapters combine elements of theoretical background, measurement optimization, and pharmaceutical applications. It is our profound hope that in this way we will achieve a suitable mixture of depth, relevance, and accessibility.

It is also necessary for us to define the limits of what this text is intended to cover. In the first instance, we have not attempted to provide a comprehensive review of all pharmaceutical thermal analysis studies but have instead focused on including examples that illustrate a particular point. Secondly, we have not gone into coupled

methods to any significant extent; there has been interest in using spectroscopic methods interfaced with thermal approaches and a wide range of such techniques have been explored or even commercialized. Again, we made the decision not to go into these approaches due to their highly diverse nature and our wish to focus on methods that are of most direct relevance to pharmaceutical scientists. Finally, we have not gone into the emerging raft of technologies associated with site-specific thermal analysis, such as microthermal analysis (which, perhaps ironically, the editors are themselves highly involved with at present), for the same reasons of wishing to focus on established techniques within the space available.

It only remains for us to express profound thanks to the various authors associated with the text and to the publishers for their support. Because of a range of personal circumstances this book has been longer in the making than we originally intended; unfortunately, this is far from unusual when editing books, but at the same time we do wish to thank all concerned for their patience, and we hope they and the pharmaceutical community will consider our joint efforts to have been worthwhile.

Duncan Q.M. Craig and Mike Reading

The Editors

Duncan Q.M. Craig, Ph.D., is head of pharmacy at the School of Chemical Sciences and Pharmacy at the University of East Anglia, Norwich, U.K. Previously, he worked at the School of Pharmacy, The Queen's University of Belfast, joining in 1999. There he set up the Pharmaceutical Materials Science Programme within the Drug Delivery and Biomaterials Group. He was previously a reader in pharmaceutical materials science at the School of Pharmacy, University of London.

Dr. Craig's work has involved the development of novel analytical techniques for the study of the physical properties of pharmaceuticals, with particular emphasis on thermal, dielectric, rheological, and microscopic methods. In particular, his interests lie in developing rational approaches to drug delivery system design. This has involved introducing novel techniques into the pharmaceutical arena, with his group being at the forefront of developing pharmaceutical applications for techniques such as modulated temperature DSC and microthermal analysis. He is a former editor of the *Journal of Pharmacy and Pharmacology* and the thermal analysis journal *Thermochimica Acta*. In 2003 Dr. Craig was awarded the Young Investigator Award of the Controlled Release Society, an international organization dedicated to the development of novel drug delivery strategies. He was the science chair for the British Pharmaceutical Conference 2005.

Mike Reading, Ph.D., is internationally recognized for his work on the development of novel thermoanalytical techniques. After receiving a B.Sc. and Ph.D. at Salford University and doing postdoctoral work in France (the CNRS center for calorimetry and thermodynamics, Marseilles), he worked with ICI until 1997. He left to join the IPTME at Loughborough University where he was director of the Advanced Thermal Methods Group. In 2004 he moved to the University of East Anglia to take up a chair in pharmaceutical characterization science.

As a senior research scientist with ICI Paints, Dr. Reading was involved in a wide range of materials science and analysis projects, mainly involving polymers. One outcome from his work was modulated temperature differential scanning calorimetry, which has now become a common, commercially available technique. While still at ICI, then at Loughborough University, he invented, with co-workers Azzedine Hammiche and Hubert Pollock of Lancaster University, a scanning probe microscopy technique known as microthermal analysis. This has also become a commercially available instrument that has won a number of awards for innovation. His current research interests center on using scanning probe microscopy to characterize the structure and chemical composition of samples on a small, especially nano, scale. He is developing and applying to pharmaceutical materials a variety of approaches to nano analysis including, for example, photothermal microspectroscopy.

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Contents

1 Principles of Differential Scanning Calorimetry

Mike Reading and Duncan Q.M. Craig

CONTENTS

1.1 INTRODUCTION

Differential scanning calorimetry (DSC) is the most widely used method of thermal analysis within the pharmaceutical field. The approach usually involves the application of a linear heating or cooling signal to a sample and the subsequent measurement of the temperature and energy associated with a range of thermal events including melting, crystallization, glass transitions, and decomposition reactions. There are numerous benefits associated with the method, such as the small sample size required, the wide temperature range available with most commercial instruments (typically –120 to 600°C), and the simplicity and rapidity of measurement.

To use the technique optimally, it is essential to have a sound grasp of both the principles underlying the methods and the most appropriate measurement parameters to be used for each sample. This chapter deals with the former consideration in that the basic instrument operation and the principles underlying the measurement process will be described, whereas Chapter 2 outlines the basic issues associated with the choice of experimental parameters and calibration. Chapter 3 then goes on to describe some of the principal applications of DSC within the pharmaceutical field.

1.2 COMMON FORMS OF DSC

1.2.1 Development of DSC

The basic principle underpinning DSC is that a sample is subjected to a heat signal and the response measured in terms of the energy and temperature of the thermal events that take place over the temperature range or time interval under study. The temperature profile may be in the form of heating, cooling, or an isothermal program, with heating being the most widely used approach. Consequently, although the most common use of the technique, certainly within the pharmaceutical sphere, has been to study melting responses by heating the sample at a controlled rate, many studies have also been performed on crystallization, glass transitions, and kinetic reactions such as curing. It should be borne in mind that the most common use of DSC in a global sense is for the characterization of polymers; hence, much of the theory, and indeed the hardware, has been developed with this application in mind. However, the principles involved are equally applicable to pharmaceuticals, inorganic materials, ceramics, and biological systems.

The approach involves placing the sample (usually in quantities of approximately 5–10 mg) in a metal crucible (pan) along with a reference pan (usually empty in the case of DSC but containing an inert reference material in the case of differential thermal analysis [DTA]) in a furnace and heating or cooling at a controlled rate, usually in the region of 5 to 10°C/min. When the sample undergoes a thermal event such as melting or crystallization, the temperature and energy associated with that event is assessed. As this information may be directly related to the solid-state structure, the approach is of great use for the study of pharmaceutical systems in terms of, for example, differentiation between polymorphs and measurement of glass transitions, as will be discussed in more detail in Chapter 3.

The technique is a development of the earlier method of DTA, which has now been largely (but by no means entirely) superseded by DSC. It is, however, helpful in the first instance to consider the underlying principles of DTA to gain a better understanding of heat flux and power compensation DSC.

The basic components of a DTA apparatus are a temperature-controlled furnace containing sample and reference cells and a pair of matched temperature sensors connected to recording apparatus, as indicated in Figure 1.1. The temperature sensors (usually thermocouples) are in contact with the sample and reference or their containers, and the output is amplified and recorded. DTA data may be plotted as a function of sample temperature, reference temperature (as is usually the case), or time. In both DTA and DSC, the measurement relies on the occurrence of a temperature difference between a sample and reference (ΔT) as a result of the thermal event in question.

In the case of DTA, an inert material is placed in the reference pan such that the heat capacity of the sample is approximately matched. Under these conditions, when the sample and reference are being heated at a constant rate, the DTA signal will be small when no transition is occurring. Ideally, the arrangement of the pans in the furnace is exactly symmetrical; so when the heat capacity of sample and reference are exactly the same, the temperature difference is zero.

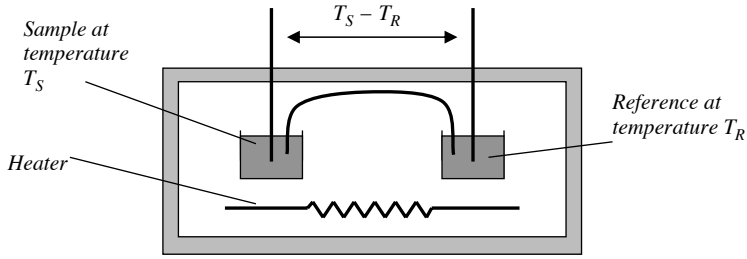

FIGURE 1.1 Typical arrangement for DTA apparatus. (Adapted from Wendlandt, W., *Thermal Analysis,* 3rd ed., Wiley-Interscience, New York, 1986.)

When the sample melts, the rate of temperature increase for the sample will be lower than that of the reference, as the energy imparted by the heating signal will be contributing to the breaking of solid–solid bonds rather than simply the raising of the sample temperature. This is illustrated in Figure 1.2.

In essence, the heat input into the sample contributes to the melting process rather than the increase in temperature, whereas the heat input into the reference continues to lead to a temperature increase. When melting is complete, the sample returns to the programmed temperature; hence, by examining the difference in temperature between the two pans, a peak is seen, as shown in Figure 1.2b.

It is clear from Figure 1.2 that the technique may easily and rapidly detect the temperature at which a particular thermal event is occurring. Indeed, current uses of the technique are based largely on the ability of the method to detect the initial temperatures of thermal processes and to qualitatively characterize them as endothermic or exothermic, reversible or irreversible, first order or higher order, etc. (2). The ability to run experiments in a range of atmospheres has also rendered the approach particularly useful for the construction of phase diagrams.

Clearly, it would be desirable if the area under the peak was a measure of the enthalpy associated with the transition. However, in the case of DTA, the heat path to the sample thermocouple includes the sample itself. The thermal properties of each sample will be different and uncontrolled. In order for the DTA signal to be a measure of heat flow, the thermal resistances between the furnace and both thermocouples must be carefully controlled and predictable so that it can be calibrated and then can remain the same in subsequent experiments. This is impossible in the case of DTA, so it cannot be a quantitative calorimetric technique. Note that the return to baseline of the peak takes a certain amount of time, and during this time the temperature increases; thus the peak appears to have a certain width. In reality this width is a function of the calorimeter and not of the sample (the melting of a pure material occurs at a single temperature, not over a temperature interval). This distortion of peak shape is usually not a problem when interpreting DTA and DSC curves but should be borne in mind when studying sharp transitions.

Differential scanning calorimetry was introduced in the 1960s as a means of overcoming the difficulties associated with DTA. Fundamentally, there are two different types of DSC instruments: heat flux and power compensation. In common with DTA, DSC involves the measurement of the temperature difference between a

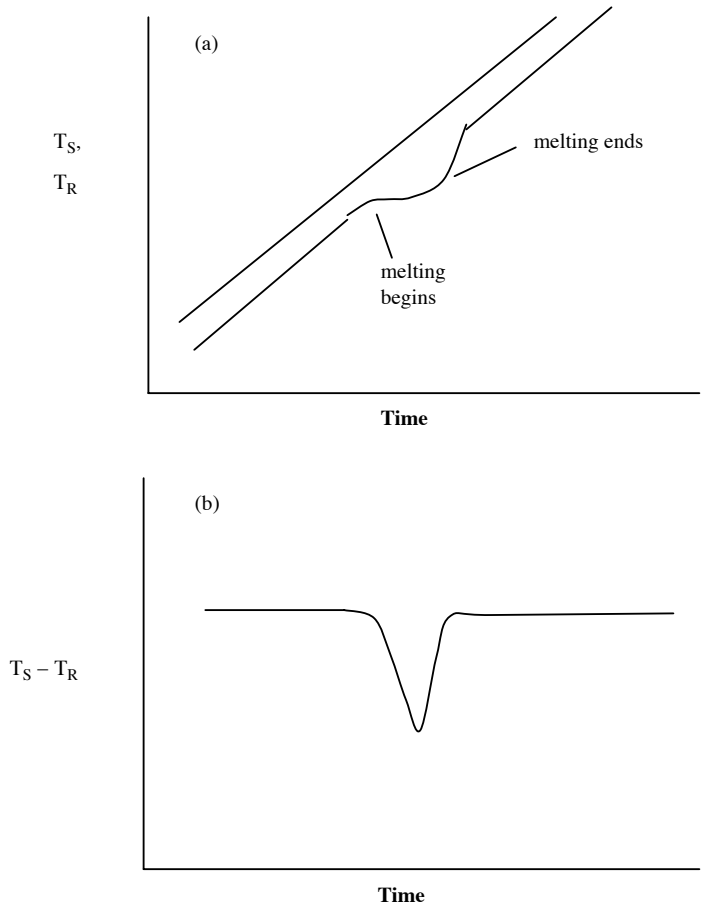

FIGURE 1.2 Typical DTA response showing (a) sample and reference temperature (TS and TR) and (b) temperature differential (TSTR) as a function of time. (Adapted from Wendlandt, W., *Thermal Analysis,* 3rd ed., Wiley-Interscience, New York, 1986.)

sample and reference. The basic innovation associated with the earliest DSC, as originally introduced by the Perkin-Elmer Co. (3,4), was that the temperature difference is kept to near-zero by placing the temperature sensors in a bridge circuit. The electrical power supplied to the sample furnace is varied so that the temperature difference between sample and reference is zero (or as close to zero as possible); hence the term *power compensation*. The reference pan is made to go through a strictly linear temperature program. The control system (ideally) forces the sample to experience the same linear temperature program. Consequently, any differences in power between this and the sample pan plus sample must be related to the sample heat capacity and the enthalpies associated with transitions. Heat flux DSC is very similar to DTA except that the sample and reference thermocouples are not placed inside the pans. Instead they are located as close as possible to the sample and reference pans as part of well-defined heat paths between the furnace and the sample

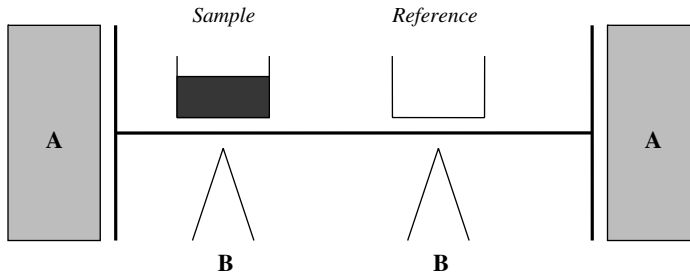

FIGURE 1.3 Schematic of a heat flux DSC. A = furnace, B = thermocouple.

and reference pans. Because of this, calibration is possible, and the heat paths are the same during subsequent experiments.

A large number of texts are available that give more details of both approaches (1,2,5–10), and only a brief outline will be given in the following text.

1.2.2 Heat Flux DSC

Heat flux DSC is the conceptually simpler of the two approaches and is represented schematically in Figure 1.3. Typically, two crucibles, one empty and one containing the sample, are placed symmetrically within a furnace with a thermocouple placed in close contact with each. The thermocouples are connected in a back-to-back arrangement such that the voltage developed from the pair is a direct measure of the temperature difference between the sample and reference. As stated previously, the cell should be designed such that the heat paths from the furnace to the sample and reference are identical, and both are also stable and well defined (usually through a metal membrane or armature that also supports the crucible). The equation for heat flow from the furnace to each crucible is then given by

$$\mathrm{d}Q/\mathrm{d}t = \Delta T/R \tag{1.1}$$

where Q = heat, t = time, ΔT = temperature difference between the furnace and the crucible, and R = thermal resistance of the heat path between the furnace and the crucible.

From Equation 1.1, it follows that the temperature difference between sample and reference is a measure of the difference in heat flow due to the presence of the sample in one of the crucibles, provided that the furnace and heat paths are truly symmetrical. Consequently, this differential heat flow is a measure of the properties of the sample, with all other influences (heat adsorption by the crucible, heat losses through convection, etc.) having been eliminated by use of the comparison with the reference. The ΔT signal requires calibration to provide a heat flow as a function of temperature, and this is usually carried out by use of standards that are usually pure metals with known enthalpies of melting and materials with known heat capacities (see Section 2.4 in Chapter 2).

A common improvement to the simple system described above is to use multiple thermocouple pairs connected in series. This increases the signal roughly in propor-

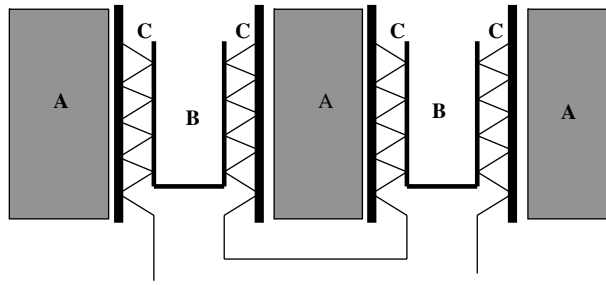

FIGURE 1.4 Schematic of a heat flux DSC with thermopiles. A = furnace, B = sample and reference crucibles, C = sample and reference thermopiles.

tion to the number of sensors used. In one configuration, illustrated in Figure 1.4, the multiple thermocouples are arranged between the source of heat and the sample with the same arrangement for the reference. The difference between the sets of thermocouples (thermopiles) at the sample and reference positions is then measured.

In heat flux instruments, it is generally the furnace that is subjected to the temperature program. Transitions in the sample are detected as a consequence of deviations from following this program. This means that the temperature profile experienced by the sample is not known in advance, although it is measured and can, therefore, be determined after the experiment. In practice these deviations from the preset program are usually small and present no practical problems of interpretation.

1.2.3 Power Compensation DSC

This type of instrument is represented schematically in Figure 1.5. The first clear difference, compared to the heat flux instrument, is that this approach uses two separate furnaces, one for the sample and a second for the reference. Both are programmed to go through the same temperature profile and the difference in electrical power supplied to the two furnaces is measured. The only difference between them should be that one contains the sample. Consequently, it is again the case that the differential signal is a measure of the sample properties, all other factors having been eliminated by the use of the reference measurement. In principle, because the quantity being measured directly is electrical power, the output requires no calibration. However, in practice, it has been found necessary to calibrate these instruments in the same way as heat flux calorimeters, using standards in order to obtain the most accurate results.

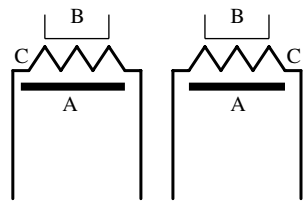

FIGURE 1.5 Schematic of a power compensation DSC. A = furnaces, B = sample and reference crucibles, C = sample and reference platinum resistance thermometers.

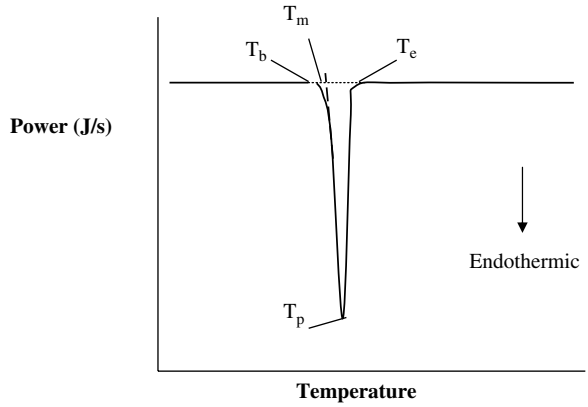

FIGURE 1.6 Typical melting endotherm for a low-molecular-weight, high-purity material.

In contrast to the heat flux approach, in these instruments it is the sample temperature that is programmed, and this should, ideally, conform exactly to the selected temperature profile. In principle, therefore, power compensation instruments provide for a better-defined experiment. In practice, however, the control system requires a finite temperature difference in order to operate and has a finite response time, so perfect control is never achieved.

Both designs of calorimeter have been commercially available for nearly 30 years without either assuming supremacy. This is because the performance of the two different types of instrument is very similar in terms of sensitivity and accuracy. The smaller furnaces of the power compensation instruments mean that they can achieve significantly higher heating and cooling rates, which is an advantage for some experiments. The heat flux instruments tend to have better baseline stability as the single furnace tends to be more robust than the two nominally matched furnaces of the power compensation design. Both instruments therefore have their advantages and disadvantages.

1.2.4 Basic Interpretation of DSC Data

DSC data is typically expressed in terms of power as a function of temperature, as indicated in the schematic diagram shown in Figure 1.6.

Examination of Figure 1.6 indicates the typical features of a simple melting response. At temperatures below the melting event, the trace shows a baseline that indicates the heat flow (power) required to raise the temperature of the sample in order to keep up with the heating program. This is therefore a function of the heat capacity of the sample *C*p as this parameter represents the energy required to raise the temperature of the sample by 1K. In terms of the DSC signal, this may be expressed via

$$dQ/dt = Cp \cdot dT/dt \tag{1.2}$$

where dQ/dt is the heat flow and dT/dt is the heating rate. In principle, therefore, the heat flow value corresponding to the baseline should yield the heat capacity of

the sample. In practice it is necessary to carefully calibrate the instrument under the conditions used for the measurement, as there are several factors over and above the heat capacity of the sample that may contribute to the baseline heat flow, including the nonuniformity of the cell and differences in mass between the sample and reference pans. The issue of accurate heat capacity measurement has been the subject of an extensive number of studies (11–15), and only a brief description will be given here. It is helpful to mention that such measurements are not common practice within the pharmaceutical sciences as yet. Given the recent interest in amorphous and partially amorphous systems that has arisen in recent years (e.g.,16–18), it is quite possible that there will be a growing interest in such measurements in the future, given the well-established wealth of information that may be obtained from heat capacity measurements of amorphous systems (9).

Traditional heat capacity measurements using DSC rely on the relationship

$$Cp = K\Delta Y/b \tag{1.3}$$

where K is the calorimetric sensitivity, ΔY is the difference in baseline values obtained in the presence and absence of sample material, and b is the heating rate. K is found by calibration with a substance of known heat capacity, with pure, industrially manufactured sapphire (Al_2O_3) being the most commonly used material. It should be noted that heat capacity will vary with temperature; hence, tables of Cp against T are available for sapphire. Heat capacity determination essentially involves three DSC scans. First, an empty-pan baseline is obtained by simply running two empty pans under the conditions to be used for the determination. Second, the experiment is repeated under identical conditions using the calibrant to obtain K, and third, the unknown is run against the reference to obtain ΔY. For more accurate measurements the experiment is run at a range of scanning speeds. As mentioned previously, this represents only the very basic means of measurement, and the texts listed previously give more detail regarding both calibration and measurement. In addition, the technique of modulated temperature DSC appears to offer several advantages with respect to heat capacity measurement, and these will be discussed in Chapter 4.

On further heating, the melting process begins. Again, however, care is required in terms of data handling. Figure 1.4 shows the response of a high-purity, low-molecular-weight material that by definition will give a narrow melting response. In practice, many materials show relatively broad melting response due either to the nature of the sample or the presence of thermal gradients within the sample pan. Similarly, many materials show multiple peaks. For example, Gelucires, which are pegylated glyceride derivatives used in controlled-release preparations, may exhibit a range of peaks due to the multicomponent nature of the material and the tendency of these components to cocrystallize into distinct structures. An example of a typical Gelucire melting peak is given in Figure 1.7.

The question therefore arises as to where the melting point should be taken from. There are a number of options: the temperature at which deviation from the baseline begins (T_b), the extrapolated onset temperature (T_m), the peak temperature (T_p), and the temperature at which the trace returns to the baseline (T_e; notation used taken

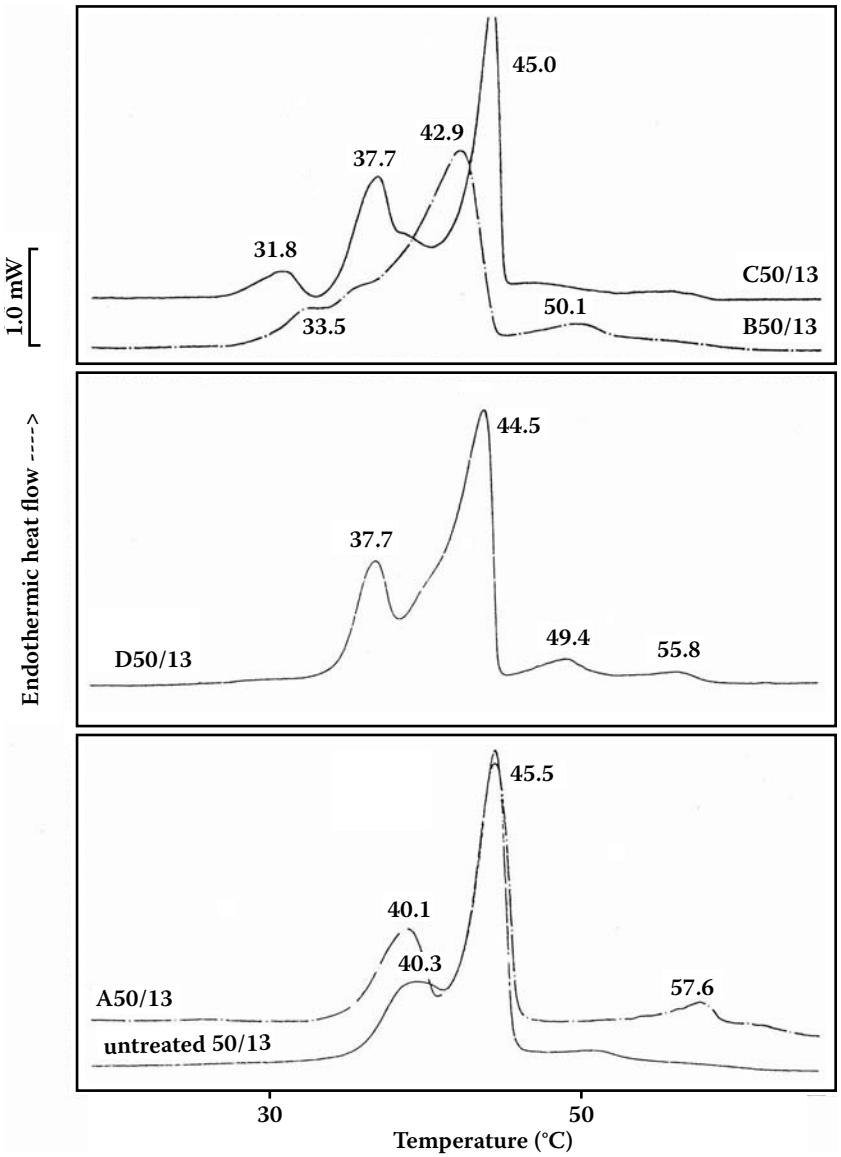

FIGURE 1.7 Melting of Gelucire 50/13. A = solvent crystallized, B = slow-cooled from the melt, C = fast cooled, D = cooled under ambient conditions. (Reproduced from Sutananta, W. et al., *Int. J. Pharm*. **110**, 75–91, 1994.)

from (8)). In the context of discussing DTA, Wunderlich (7) recommends that for samples whereby temperature gradients are small and the melting process is sharp, the extrapolated onset should be used, whereas the peak temperature should be used for materials whereby extensive peak broadening is apparent (and by implication for multiple peaks). The key consideration is that the instrument should be calibrated using the same measuring method as is to be used during the experimental run.

The area under the peak A yields the enthalpy change associated with the process according to

$$A = k'm(-\Delta H) \tag{1.4}$$

where k' is the calorimetric sensitivity (an electrical conversion factor), m is the mass of the sample, and ΔH is the enthalpy. Consequently, it is necessary to calibrate the instrument under the same conditions used as those of the experimental run and to measure the area of the enthalpic peak for the calibrant. For many experiments it is acceptable to use indium, which has a heat of fusion of 28.71 J/g. However, if events that take place at temperatures very different from the melting point of indium (156.61°C) are to be studied, it is essential to use an alternative calibrant (see Chapter 2). A further consideration is the relationship between the absolute peak area and the scanning speed. At higher scanning rates, the peaks will appear considerably larger. This may be understood with reference to Figure 1.8.

During a melting process, the heat input into the sample will be utilized to melt that material; hence a temperature differential will develop between the sample and reference as the former remains effectively isothermal during the melt. At low heating rates (T_S', T_R', A'), that lag will be relatively small at any given temperature because the reference temperature T_R' will not have increased greatly in the time period of melting owing to the slow heating rate; hence, A' will be small. For fast heating rates (T_S'', T_R'', A'') the difference between T_S'' and T_R'' will be greater

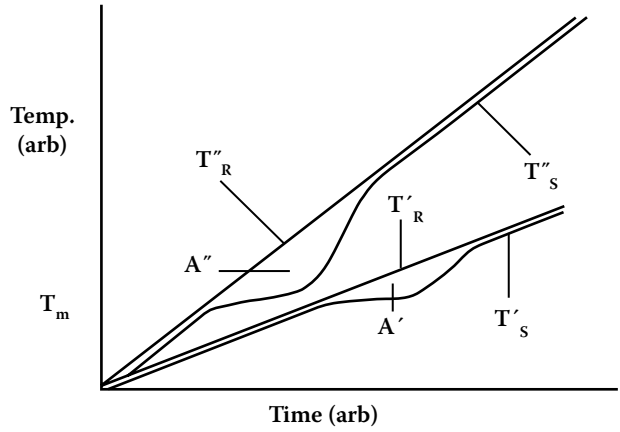

FIGURE 1.8 The effect of heating rate on signal sensitivity (see text for explanation of symbols). (Reproduced from Coleman, N.J. and Craig, D.Q.M., *Int. J. Pharm*. **135**, 13, 1996.)

during the melt; hence, A″ will also be large. Overall, therefore, lower heating rates favor greater resolution. Sensitivity is, however, improved by higher heating rates; thus any experiment must use the heating rate that gives the right balance of resolution and sensitivity.

1.3 TYPICAL RESULTS FOR COMMON TRANSFORMATIONS STUDIED BY DSC

It is now appropriate to consider the most commonly encountered types of processes that are studied by DSC and the types of results they yield.

1.3.1 Kinetically Controlled Responses

A number of processes of pharmaceutical interest are kinetically controlled, examples including crystallization, curing, and many degradation reactions. Kinetic behavior is described classically by the Arrhenius equation, which may be given in the general form

$$d\alpha/dt = f(\alpha)Ae^{-Ea/RT} \tag{1.5}$$

where α = the extent of the reaction, t = time, $f(\alpha)$ = some function of extent of reaction, A = the preexponential constant, Ea = the activation energy, R = the gas constant, and T = absolute temperature. This type of behavior is associated with the well-known energy barrier model for thermally activated processes. In this model, a material changes from one form to another more thermodynamically stable form but must first overcome an energy barrier that requires an increase in Gibbs free energy. Only a certain fraction of the population of reactant molecules have sufficient energy to do this, and the size of this fraction (and hence the total number of reactant molecules) determines the speed at which the transformation occurs. The fraction of molecules with sufficient energy is dependent upon the temperature in a way given by the form of the Arrhenius equation; thus, this must also be true for the transformation rate. The types of process that can be modeled using this type of expression include chemical reactions, diffusion-controlled processes such as the desorption of a vapor from a solid, and some phase changes such as crystallization. There will be some constant of proportionality, H', such that the rate of heat flow can be directly related to the rate of the process, viz.

$$dQ/dt = H' \cdot d\alpha/dt = H' \cdot f(\alpha)Ae^{-Ea/RT} \tag{1.6}$$

$H' \cdot d\alpha/dt$ is not the total heat flow because it neglects the contribution from the heat capacity of the material. This heat capacity can be considered to be the energy contained in the various vibrational, translational, etc., modes available to the sample. The energy contained in these molecular motions is stored reversibly, which simply means that the amount of energy taken up by them when increasing the temperature by 1°C can be entirely recovered by reducing the temperature by 1°C. This can be

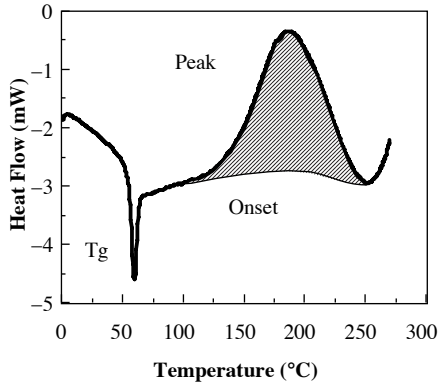

FIGURE 1.9 Example of a chemical reaction, in this case an epoxy cure, as detected by DSC, while the interpolated baseline corrects for Cp. The shaded peak is the exotherm from the chemical reaction. In this case it is proceeded by a glass transition (see chapter text).

contrasted with the enthalpy associated with, for example, a typical chemical reaction that will be either gained by the sample (endothermic) or lost (exothermic) irreversibly. Adding in the heat capacity contribution to the heat flow gives

$$dQ/dt = \beta C_p + H' f(\alpha) A e^{-Ea/RT} \tag{1.7}$$

where β = heating rate and C_p = heat capacity.

Figure 1.9 gives a typical trace for a chemical reaction showing Arrhenius kinetics. As the reaction proceeds, the heat capacity of the sample usually changes in some way. This is normally approximated with an interpolated baseline as illustrated, which then represents the βC_p contribution to the heat flow. The shaded area gives the enthalpy of the chemical reaction.

The use of DSC for studying such reactions allows the operator the possibility of obtaining not only empirical information regarding the temperature and time relationship for processes of interest but also more detailed kinetic parameters as outlined above. Clearly, the kinetic analysis may be considerably more complex when one considers non-Arrhenius behavior, and also takes into account issues such as the size and shape of the reacting species as may be the case for, for example, excipient compatibility reactions (21). Some more advanced kinetic functions are outlined in Chapter 5.

The scanning method has advantages when studying multiple stage processes that may overlap. For example, studying a higher temperature process is difficult isothermally when a lower temperature process is also present. The early part of any higher temperature isotherm will be dominated by the lower temperature process, and it may well be impossible to delineate even approximately where one process ends and the other starts. Attempts to use a lower-temperature isotherm until the first reaction is finished before proceeding to a higher temperature isotherm inevitably lead to arbitrary decisions on what exact thermal treatment to use. Scanning at multiple heating rates can give information on the kinetics of even complex behavior.

In general, simple one-stage reactions are probably best studied isothermally, whereas more complex systems are best investigated using temperature scanning.

A highly topical area within the pharmaceutical sciences for which DSC measurements may be of use for kinetic studies is in the study of recrystallization, either on cooling from the melt or from the amorphous state. Classically, such reactions are described by Avrami kinetics (22–24), given by

$$\alpha = 1 - \exp[-(Kt)^m] \tag{1.8}$$

where α is the fraction crystallized as a function of time t. K and m are constants, with the latter dependent on crystal growth morphology. The corresponding rate equation may be obtained by simple differentiation with respect to time to yield

$$\left(\frac{d\alpha}{dt}\right) = Km(1-\alpha)[-\ln(1-\alpha)]^{1-1/m} \tag{1.9}$$

This is generally referred to as the Johnson–Mehl–Avrami (JMA) equation and is frequently used for the formalization of thermal analysis crystallization data. This analysis does assume isothermal crystallization conditions and homogeneous nucleation or randomly distributed nuclei for heterogeneous growth. In addition, the growth rate of the new phase should be controlled by temperature and be independent of time. Finally, low anisotropy of the growing crystals is also assumed (25). However, Henderson (26,27) has indicated that the expression can be extended in nonisothermal conditions, whereas Ozawa (28) has proposed expressions for nonisothermal crystal growth from preexisting nuclei. A simple approach that may be easily used to yield comparative (rather than absolute) data is the Kissinger equation (29)

$$\mathrm{d}[\ln(\phi/Tc^2)]/\mathrm{d}[1/Tc] = -Ea/R \tag{1.10}$$

whereby the recrystallization peak maximum temperature (T_c) is recorded as a function of scanning rate (ϕ) to yield the activation energy E_a. Clearly, there are a number of possible approaches to analyzing kinetic data using DSC. However, caution is required by the operator in that each approach carries concomitant assumptions that may or may not be compatible with the nature of the response involved.

1.3.2 Melting and Other First-Order Phase Transitions

A first-order phase transition is defined as a process whereby the derivative of the change in free energy ΔG with respect to temperature is not equal to zero (30), i.e.,

$$(\delta\Delta G/\delta T) = (-\Delta S) \neq 0 \tag{1.11}$$

where $-\Delta S$ is the entropy change. In essence, the change in state is accompanied by a change in the temperature dependence of the free energy as the system changes from the solid to the liquid state. In practical terms the description of first order

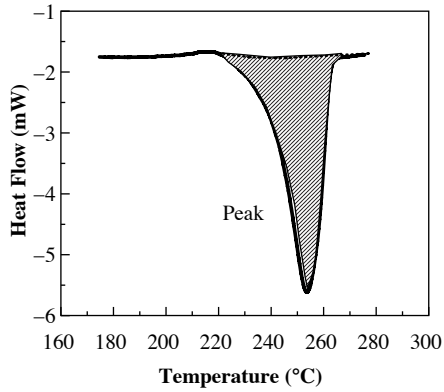

FIGURE 1.10 A typical polymer melt shown as the shaded endotherm.

indicates that the transition in question will occur at a specific temperature and will be independent of heating or cooling rate, although, as will be demonstrated, instrumental factors almost invariably result in an apparent rate dependence. The most common example studied by DSC is melting, which is characterized as a change in specific volume accompanied by a latent heat of fusion. However, other transitions such as liquid crystalline transformations may also be considered to be first order. As indicated earlier, at the melt temperature the sample will remain isothermal until the whole sample has melted. This is because a finite time is required for heat to penetrate the sample; hence, during this process the heat input contributes to the latent heat of fusion rather than increasing the temperature of the sample. The factor that determines the speed of the transition is the rate at which heat can be supplied by the calorimeter. Normally, this is fast, so the transition is very sharp with a small post-transition "tail," the length of which is determined by the speed with which the calorimeter can reestablish the heating program within the sample. Pure materials generally produce very narrow melting peaks, whereas the introduction of soluble impurities usually broadens the peak considerably by lowering the onset temperature; this phenomenon can be used to quantify the amount of impurity present in a sample.

The issue of peak broadening is also extremely important when dealing with polymeric samples. Many polymers produce a range of crystalline forms with different melting temperatures without necessarily having different internal unit cell arrangements, i.e., melting variations may be seen over and above those caused by polymorphism (described in Chapter 4). Typically, a semicrystalline polymer will comprise a distribution of crystallites with differing degrees of perfection and thus different melting temperatures. The melting transition in these materials is broad, as a succession of crystallite populations melts one after the other as the sample temperature reaches their melting temperatures. This kind of broad melting transition is illustrated in Figure 1.10. We can express this as

$$dQt/dt = \beta(C_p + g(t,T)) \tag{1.12}$$

where g(*t,T*) = some function of time and temperature that models the contribution to the heat flow from the melting process.

When the melting is rapid with respect to the heating rate, g(*t,T*) will simply be a function of temperature. This means that, in the case of the distribution of crystallites, the melting contribution to heat flow will be proportional to heating rate in an analogous manner to the heat capacity if no other process occurs. In reality this simple case is rarely encountered. This point will be discussed in more detail in Chapter 4 in terms of the use of temperature modulation. As with Arrhenius processes, a baseline can be interpolated under the peak to approximate the contribution from βC_p (Figure 1.10); hence the area under the peak is a measure of the total heat of fusion.

1.3.3 Second-Order Phase Transitions: The Glass Transition

A second-order transition is defined as a process whereby the derivative of the change in free energy is zero but the second-order derivative is nonzero, i.e.,

$$(\delta^2 \Delta G/\delta T^2) = (-\Delta Cp/T) \neq 0 \tag{1.13}$$

In this analysis the transition is defined as a step change in the heat capacity of the sample as a function of temperature. By far the most important transition that is generally considered to be second order is the glass transition, T_g. However, for completeness, other examples of second-order transitions include Curie point transitions where a ferromagnetic material becomes paramagnetic, the transition from an electrical superconductor to a normal conductor, and the transition in helium from being a normal liquid to being a superfluid at 2.2 K.

There is still considerable debate with regard to the precise meaning of the term glass transition. At first sight, the step change in C_p that occurs at the glass transition might be interpreted as a discontinuity that in turn would mean that it is a second-order transition. In fact, the transition is gradual as it occurs over about 10 degrees or more. Its position also varies with the heating and cooling rate (and with frequency in MTDSC), which reveals that it is also a kinetic phenomenon; hence, again, the process does not fit the strict definition of a second-order response.

From a phenomenological viewpoint the glass transition is seen as a change in sample flexibility over a narrow range of temperatures, with the material classically appearing brittle and glassy below the glass transition temperature (designated T_g) and more pliable at temperatures $>T_g$. The classical method of forming glasses is via cooling from the melt. For crystalline systems the cooling process results in nucleation and crystal growth at a temperature corresponding to the melting point T_m (assuming no supercooling takes place). The exothermic crystallization process results in a dramatic decrease in the free volume of the system (defined as the difference between the total volume and that occupied by the constituent molecules) as the molecules become arranged in an ordered lattice. On further cooling, less marked changes in free volume are observed as a result of heat capacity and thermal contraction effects. This is illustrated in Figure 1.11. For a glass-forming system,

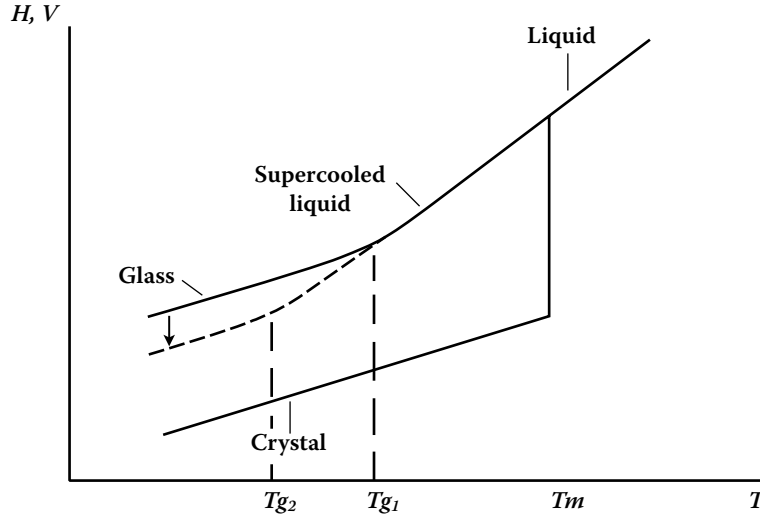

FIGURE 1.11 Schematic representation of the glass transition, comparing the behavior of systems forming glass and a crystalline solid on cooling.

however, the cooling rate may be too rapid in relation to the rate of crystallization for nucleation and growth to occur. Consequently, the system supercools and remains liquid below *Tm.* However, on further cooling, the system reaches a point whereby the molecular mobility decreases in a discontinuous manner, resulting in the system becoming "frozen" as the material assumes the material characteristics of a solid. In fact, the gross molecular conformation remains essentially the same as that of a liquid, the difference lying in a dramatic reduction in the translational and rotational motions of those molecules. The temperature at which this process occurs is cooling rate dependent, with slower rates leading to lower values for T_g, as illustrated in Figure 1.11.

There are a number of theories associated with the fundamental nature of the glass transition, but the issue remains the subject of debate within the field. One approach is to consider the transition in terms of relaxation processes. As the material is cooled in a linear fashion, at temperatures above T_g, the relaxation processes are rapid in relation to the cooling process; hence, molecular mobility remains high (relatively speaking). As the temperature lowers, the relaxation time increases up to a point whereby the rate of relaxation matches the rate of cooling. At this point and below, the large scale motions of the constituent molecules are slow in relation to the cooling program; hence, the molecular mobility relative to the time scale of the measurement is dramatically reduced and the material assumes macroscopic solid-like characteristics. Calorimetrically, this manifests itself as a reduction in the measured heat capacity.

A related explanation involves consideration of the free volume of the system, whereby this parameter is reduced to a critical value, below which free molecular motion may not take place (31–33). The glass transition may also be considered in terms of configurational entropy (34), whereby above T_g the system has addi-

tional degrees of freedom which are lost on going through the transition. The issue of the temperature dependence of the configurational entropy has been addressed by Kauzmann (35), who considered whether the glass transition could be infinitely low if the cooling rate was similarly slow. He suggested that a lower limit does indeed exist due to the thermodynamic necessity (via the third law) of the entropy for the glass being higher than the corresponding perfect crystal. This contradiction, known as the Kauzmann paradox, is resolved by there being a lower limit to the T_g, known as the Kauzmann temperature (T_k), which is typically 20 to 50 K below the experimentally derived glass transition. However, the paradox may also be resolved by considering that the extrapolation of the liquid line used by Kauzmann to predict a point at which the entropy of the glass would cross that for the crystal, is simply erroneous. The shape of the liquid line below T_g is not accessible experimentally.

In terms of the practicalities of measurement, the glass transition is essentially a change in the heat capacity of the material; hence (at least theoretically), the transition is seen as a step change in the baseline of a DSC trace (see Equation 1.2). A very simple relaxation model for the increase in heat capacity at the glass transition is given by

$$d\eta/dt = \exp[(\Delta h^*/(RT_g^2)(T - T_g)](T\Delta Cp - \eta)/\tau_g \quad (1.14)$$

where

$$\eta = \delta + T\Delta Cp, \quad (1.15)$$

δ = the excess enthalpy relative to the equilibrium value, ΔC_p = the heat capacity change at the glass transition, Δh^* = the apparent activation energy, T_g = the glass temperature, and $\boldsymbol{\tau}_g$ = the relaxation time at equilibrium at T_g.

This response is demonstrated above for Vitamin E USP (36), which is a liquid at room temperature but may form a glass on rapid cooling. In this case the step change in baseline corresponding to the glass transition is clearly visible (Figure 1.12).

However, in practice the glass transition is often superimposed by an endothermic response, as indicated in Figure 1.13 for a polylactide microsphere system (37); the change in the baseline before and after the event is clearly visible but, similarly, it is also clear that the potential for confusion with a melting endotherm is considerable. Furthermore, it is difficult to establish the exact position of the glass transition under such a peak with confidence, although methods are available whereby the T_g may be ascertained (20).

When a sample is cooled from above T_g at a given rate, it follows a given enthalpy line as shown in Figure 1.14. This then gives rise to a glass with a certain enthalpy. If a glass with a lower enthalpy than this is heated at the same rate, then an overshoot will result that gives rise to the relaxation peak seen at T_g. This is because this enthalpy must be recovered so the material can return to equilibrium above T_g. There are two common ways of making a glass with a lower enthalpy than that produced by cooling at rate $-b$. The first is to cool it at some rate slower

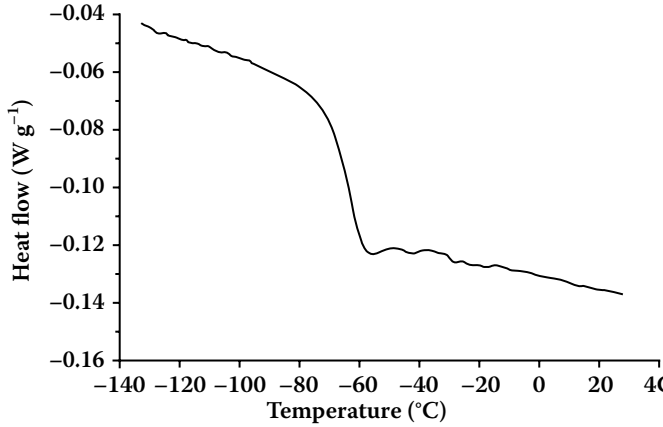

FIGURE 1.12 DSC trace for Vitamin E USP. (Reproduced from Barker, S.A. et al., *J. Pharm. Pharmcol.* **52**, 941, 2000.)

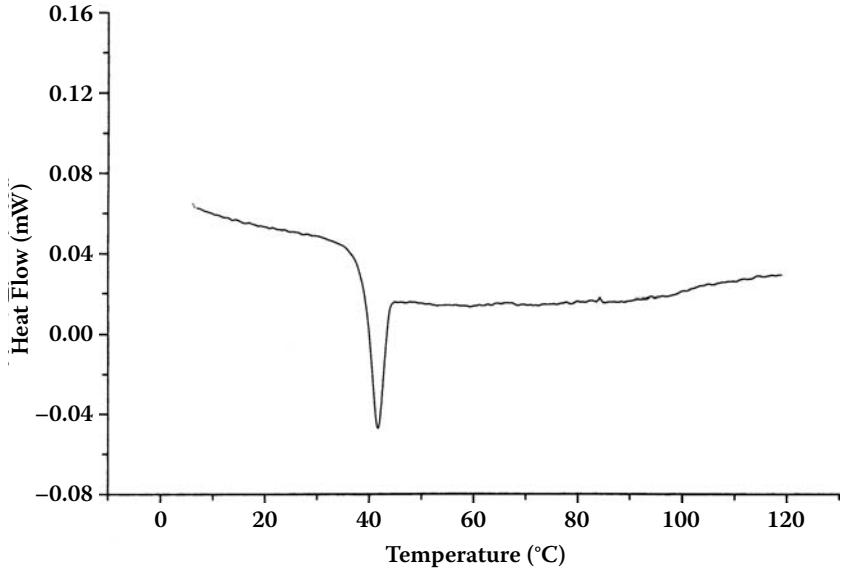

FIGURE 1.13 DSC trace of glassy polylactide microspheres. (Reproduced from Passerini, N. and Craig, D.Q.M., *J. Controlled Release* 2001, **73**, 111–115, 2001.)

than *–b*. On reheating at *b* the enthalpy peak will then be seen. The other is to cool at *–b* then anneal the sample, which will then lose enthalpy as it tries to move closer to the equilibrium line. Again, on reheating, the relaxation peak will be present. If a sample is cooled at *–b*, and then reheated at a slower rate, an exotherm will be observed before T_g as the sample loses enthalpy (anneals) as it is being heated.

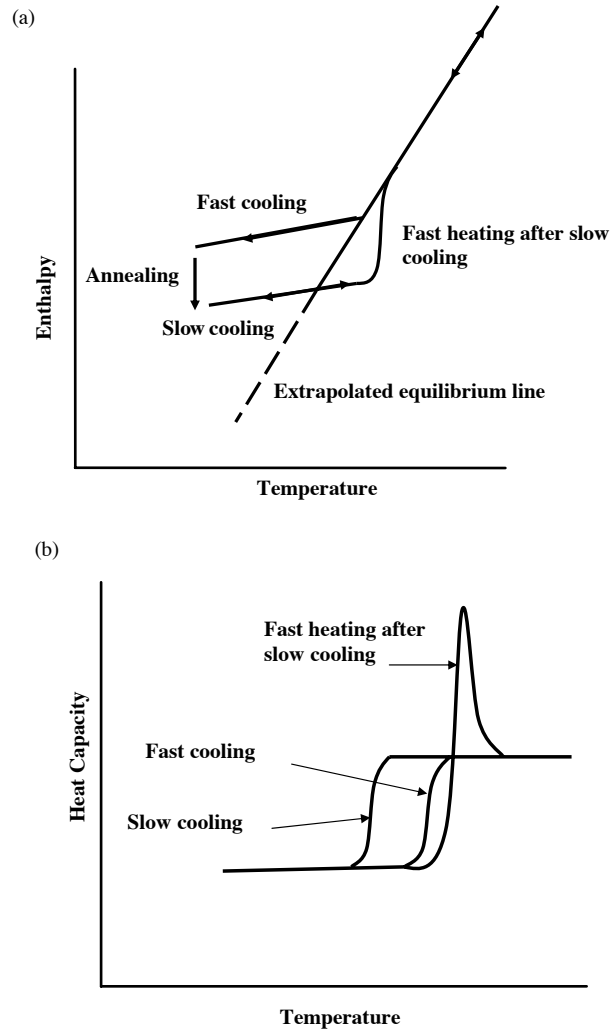

FIGURE 1.14 Schematic representation of (a) the enthalpy curve and (b) the heat capacity through T_g, illustrating the effect of cooling and heating rate.

Over and above such experimental issues, a further reason for the appearance of the endothermic peak is annealing effects. As illustrated in Figure 1.14, the glassy system is above the extrapolated equilibrium enthalpy for the liquid state, and hence there will be a tendency for enthalpic reduction as a function of time toward this equilibrium. Again, heating through T_g for such aged systems results in the appearance of an endothermic peak due to the necessity for heat input for reestablishment with the $> T_g$ enthalpy.

This time-dependent increase in the value of the enthalpic relaxation peak may in itself be used to assess the relaxation time of the system in question; this is discussed in more detail in Chapter 3.

1.4 CONCLUDING COMMENTS

This chapter has attempted to illustrate both the basic principles of DSC and, in general terms, the type of information that the method may provide. The information given here should be considered in conjunction with that imparted in the following three chapters that deal with experimental practice, pharmaceutical applications, and the new development to DSC, modulated temperature DSC. However, we believe it is essential for the principles underpinning the use of the technique to be appreciated to promote best practice when using the instrument. In particular, and without wishing to end the chapter on a negative note, it is apparent that DSC is often used as something of a black box within the pharmaceutical sciences, as illustrated by, for example, the common practice of not labeling the *y* (power) axis when presenting DSC data and the frequent omission of calibration information. However, the important point to be emphasized in the present context is that DSC represents a highly versatile and reliable approach for the study of a wide range of systems and problems. The following chapters will take this principle further by illustrating both the issues associated with making good measurements and the ways in which information may be extracted for the study of pharmaceutical materials in particular.

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2 Optimizing DSC Experiments

Trevor Lever

CONTENTS

2.1 INTRODUCTION

A differential scanning calorimeter (DSC) measures the heat flow to or from a sample, usually as the sample is heated. Any change that can affect the heat flow characteristics within the DSC or the sample will therefore affect the data produced by the instrument. This chapter explains the variables that can affect the heat flow signal measured by the DSC and why it is important for the operator to understand them. This chapter is intended to be complementary to both the operator's manual (for whatever instrument is used) as well as the many texts on DSC theory, with the focus being on the practical aspects of making good DSC measurements.

To understand and appreciate the effect that each of the experimental factors have upon the final DSC trace, it is useful to have a basic understanding of the heat flow and heat transfer processes occurring within the DSC during an experiment. The specific heat flow path will vary from one type of DSC design to another, but some general rules will apply. As this topic has been covered in more detail in Chapter 1, it is considered helpful to revisit some of the very basic concepts to provide a context for explaining the influence of experimental parameters.

In a typical experiment the DSC records the heat flow into, or out of, the sample as a function of temperature or time. In the absence of any transition (e.g., melting), the heat flow recorded can be represented as

$$\mathrm{d}Q/\mathrm{d}t = \mathrm{d}Q/\mathrm{d}T \cdot \mathrm{d}T/\mathrm{d}t \tag{2.1}$$

where $\mathrm{d}Q/\mathrm{d}t$ is the heat flow, $\mathrm{d}Q/\mathrm{d}T$ is the heat capacity, and $\mathrm{d}T/\mathrm{d}t$ is the heating rate. In other words,

$$\text{Heat Flow} = \text{Heat Capacity} \cdot \text{Heating Rate}$$

When a sample undergoes a thermal transition, such as melting, this may be considered as either a gross change in heat capacity of the sample or as an extra term f (T,t) that can be added to Equation 2.1 to cover these kinetic events:

$$\mathrm{d}Q/\mathrm{d}t = \mathrm{d}Q/\mathrm{d}T \cdot \mathrm{d}T/\mathrm{d}t + \mathrm{f}\,(T,t) \tag{2.2}$$

or

$$\text{Heat Flow} = \text{Heat Capacity} \cdot \text{Heating Rate} + \text{Kinetic Events}$$

As no universal "heat flow meter" exists, it is necessary to make differential measurements by measuring the heat flow between the sample and an inert reference. The magnitude of the heat flow will be governed by the thermal resistance of the system, and the difference in temperature between the sample and reference

$$dQ/dt = (T_R - T_S)/R \tag{2.3}$$

where T_R and T_S are the reference and sample temperatures, respectively, and R is the thermal resistance between reference and sample.

From these equations it can be seen that key quantities that can affect the measured heat flow signal in a DSC are:

- The heating rate
- The heat capacity
- Kinetic events (e.g., melting or degradation)
- The thermal resistance between the sample and reference
- The temperature difference between the sample and reference

These variables must be understood and controlled to obtain quality DSC data, that is, data that are both reproducible and representative of the sample's properties.

Some of these variables can be controlled, or at least influenced, by the operator. The heating rate is clearly a variable over which the operator has control. The operator can only influence others, such as the thermal resistance of the DSC. For example, by changing the purge gas to one that has higher thermal conductivity, heat transfer is improved.

In a typical DSC experiment, a weighed sample is encapsulated in an aluminum pan. This is then placed into the DSC together with a reference pan. The sample and reference are then heated in a controlled environment, and the heat flow difference between them is recorded. Similar experiments are made with standard materials in order to obtain calibration constants so that quantitative temperature and heat flow data may be obtained in subsequent experiments. The variables and issues arising from this simple description of a typical DSC experiment can be split into three categories: equipment, sample, and experiment. These areas are described in more detail later.

2.2 EQUIPMENT

Besides the DSC, there are other pieces of equipment and ancillaries that need to be maintained and calibrated to ensure that accurate DSC data are produced.

2.2.1 Analytical Balance

The analytical balance that is used to weigh out the sample is often the limiting factor in regard to the accuracy of the heat flow signal produced by the DSC. The balance should be checked and calibrated daily against a known traceable reference weight. Also, the balance should be accurate enough for the amount of sample to be weighed and to provide the quantitative enthalpy data required.

A 5-digit balance should be considered as a minimum requirement when weighing samples in the 10 to 20 mg range, a 6-digit balance for 1 to 10 mg samples, and a 7-digit balance for samples less than 1 mg. Balances should be kept clean. Sample pans should also be cleaned with a brush prior to loading on to the balance to ensure that any sample that may have adhered to the outside of the pan is removed.

2.2.2 Purge Gas

Most DSC experiments on pharmaceutical materials are carried out in an inert atmosphere, usually nitrogen. Helium, which has a higher thermal conductivity, can be used if the thermal resistance of the DSC needs to be reduced. This has the effect of increasing the resolution of transitions that are close to each other in temperature.

Helium should also be used as a purge gas in DSCs that use a liquid nitrogen cold-finger system for subambient operation. This is because the liquid nitrogen coolant temperature is below the dew point of the nitrogen purge gas. A drawback to using helium over nitrogen as a purge gas is that it takes considerably longer for the DSC system to reach equilibrium and stabilize after the cell has been opened to the air. This is because the difference in thermal conductivity between helium and air is much greater than the difference in thermal conductivity between nitrogen and air.

2.2.3 Purge Flow

A constant purge of gas through the DSC ensures that any volatile products evolved during the DSC experiment are swept away from the measuring sensor. It also ensures a nonoxidative and constant environment around the sample area, which helps in maintaining day-to-day baseline reproducibility.

A change in the flow rate of the gas used to purge the DSC can have several effects. First, it is possible that it will change the temperature and enthalpy calibration. The magnitude of this variation will vary from one type of DSC design to another as some instruments preheat the purge gas prior to its entering the DSC cell. Second, for experiments where a volatile substance is evolved from the sample when it is heated, the DSC peak shape will be affected by the speed at which the volatile substance is removed.

A slow decrease in the flow rate into the DSC will be observed if cylinders are used that are fitted with single-stage regulators, as the output pressure will decrease as the cylinder slowly empties. This effect may be minimized by the use of two-stage cylinder regulators or, ideally, the use of calibrated mass flow controllers, which will remove this variable from the experiment altogether.

2.2.4 DSC

2.2.4.1 Temperature Calibration

In any DSC experiment where the sample is heated, the sample and its surroundings are not in thermal equilibrium. The sample temperature will be slightly lower than that of the furnace temperature. The transfer of heat between the furnace, the sample,

and the reference is not instantaneous and depends upon the heat transfer characteristics of the particular DSC design. Consequently, a correction is required so that accurate transition temperatures are measured from the DSC heat flow data. This introduces the concept of "thermal lag" within the system. In fact, there are a number of thermal lags to be considered: the lag between the furnace and the bottom of the sample pan, the lag between the bottom of the sample pan and the sample, and then the thermal lag throughout the sample. Various methodologies exist to compensate for one or all of these thermal lags. Temperature gradients within the sample can be minimized, for example, by using small samples and pans with good heat transfer characteristics and slow heating rates. However, the thermal lag can never be removed and so must always be calibrated for.

Temperature calibration requires that traceable standards, with known transition temperatures, be run under exactly the same conditions as those to be used when running samples. The observed DSC heat flow transition temperature for the standard is then compared to the known value and a correction is applied, usually through software. The most common temperature calibration standards used in DSC are the melting points of pure metals such as indium, lead, and tin. These metals are available in high purity and with well-known melting points. Few organizations provide these materials with any melting point certification or traceability, one exception being the U.K. Laboratory of the Government Chemist (LGC).*

This temperature calibration does not take into account thermal lag (and therefore temperature gradients) within the sample, one of the arguments put forward to support the use of organic materials to temperature-calibrate a DSC for pharmaceutical measurements. However, the poor availability of pure and certified organic temperature standards of sufficient accuracy is a powerful argument against using such materials.

Temperature calibration should be performed over the temperature range of interest. Surprisingly, many laboratories (and published papers) still settle for a single-point temperature calibration (invariably, indium [156.6°C]) and assume that the temperature calibration of the instrument is linear over the entire temperature range. Probably, this is not the case. At least two temperature calibration points should be made, and these should embrace the temperature range of interest. It is also common to see an operator calibrate with two materials (indium and some other higher melting point metal such as lead [327.5°C] or tin [231.93°C]) and then analyze samples with transitions in the ambient to 100°C temperature range. It is recommended that one temperature calibration point should be close to room temperature and, additionally, one below room temperature, if subambient measurements are made.

The effect of heating rate on the DSC heat flow signal will be considered in more detail in Subsection 2.4.2. However, it is useful to consider this parameter in terms of calibration protocols. Figure 2.1 shows the onset temperature of the melting peak of indium at seven different heating rates. As the heating rate increases, the thermal lag between the furnace and the sample increases. From Figure 2.1 it can

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