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Summary of Lecture Transcripts

Turning DSC Charts of Polymorphs into Phase Diagrams: A Tutorial Paper†

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Abstract:

A DSC chart can be turned into a phase diagram generally only with the aid of other experimental information, such as solubility measurements or slurrying experiments. There are several ways of presenting phase behaviour diagrammatically. It is shown how to produce a phase diagram and how to avoid some of the potential errors of the experimental measurements.

Introduction

The selection of the appropriate polymorph for development and ultimate manufacture and the subsequent consistent production of that polymorph are of prime importance, particularly in the pharmaceutical industry. The proper understanding of a polymorphic system and most particularly of its behaviour, involves drawing at least a rough phase diagram, possibly in the form of a so-called semischematic phase diagram, initiated by the Innsbruck school.[1,2] An essential element in the construction of any phase diagram, whether a quantitatively accurate one or a schematic one, is the use of DSC traces. For an accurate diagram, the enthalpies and temperatures of the true thermodynamic solid−solid and solid−liquid transitions are needed, plus the determination of heat capacities over a range of temperatures. Ideally this will require the use of adiabatic calorimetry,[3,4] although measurements can also be made by DSC.[5] It is a thesis of this paper that a schematic phase diagram is sufficient for all ordinary working problems, and so refinements such as heat capacity (C_p) differences fall outside the scope of this presentation. For a schematic diagram, the enthalpies as well as the transition temperatures are important, because these can be used to determine the relationships, monotropic or enantiotropic, between the phases, using Burger's rules.[1]

A great curiosity is that none of the texts on thermal analysis examined by the author actually sets out in detail how this process of turning DSC traces into phase diagrams can be achieved. In fact, a reliable phase diagram cannot generally be drawn without the addition of other information, which can be obtained from solubility and slurry equilibration measurements. Even the message of the preceding sentence is difficult to find in the literature. The object of the present tutorial paper is to enable an analyst or development chemist, faced for the first time with such a problem, to carry out the process of turning experimental thermodynamic and thermal data into a useful phase diagram. This diagram then presents a compact overview of the polymorphic system and may enable further insight into, and understanding of, the choice of the preferred crystalline form for development. It can also lead to understanding of the outcome of crystallisation, at least in respect of the stability of the damp isolated form and its behaviour.

Discussion

A phase diagram is a thermodynamic representation, whilst a DSC run is a dynamic experiment relying on kinetics. Thermodynamics tells you what the system can do, or should do, but not what it does. The very existence of a metastable polymorph is due to the triumph of kinetics over thermodynamics. In the case of melting, the transformation process normally occurs so rapidly that the melting point can hardly ever be exceeded. However, instrumental factors such as rate of heat flow into the sample can produce a delay in the recording of the melting point. The solution to this problem is to apply a slower temperature ramp-up during the DSC experiment. Since the onset temperature changes less with change of heating rate than does the peak temperature,[6] it is a more reliable indicator of the true melting point. There are occasional reports in the literature of the occurrence of delayed melting.[7] In conducting many melting point measurements by a variety of techniques, one occasionally notices slow melting. However, for all practical purposes, the measurement of a melting endotherm at a heating rate of 5 or 10 °C per minute nearly always gives a sufficiently true measure of the thermodynamic melting point for ordinary use.

The same is not true of solid−solid transformations. There is always a hysteresis between the temperature of transformation on heating and that on cooling.[8] The smallest interval known

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(1) Burger, A.; Ramberger, R. *Mikrochim. Acta* **1979**, *II*, 259–271.
(2) Griesser, U. J.; Burger, A.; Mereiter, K. *J. Pharm. Sci.* **1997**, *86*, 352–358.
(3) Westrum, E. R.; McCullough, J. P. In *Physics and Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds.; Interscience: New York, 1963; Vol. 1.
(4) Gaisford, S.; O'Neill, M. A. A. *Pharmaceutical Isothermal Calorimetry*; Informa Healthcare: New York, 2007.
(5) McNaughton, J. L.; Mortimer, C. T. *Differential Scanning Calorimetry*; Perkin-Elmer: Norwalk, CT.
(6) Charsley, E. L.; Laye, P. G.; Palakollu, V.; Rooney, J. J.; Joseph, B. *Thermochim. Acta* **2006**, *446*, 29–32.
(7) Wunderlich, B. *Thermochim. Acta* **2007**, *461*, 4–13.
(8) Mynukh, Y. *Fundamentals of Phase Transitions, Ferromagnetism and Ferroelectricity*; First Books: New York, 2001.

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to the author is that of D,L-norleucine around 118 °C. The interval recorded by DSC is unlikely to be less than a few degrees, but that is more a reflection of the heat inertia of the apparatus than of actuality. By hot-stage microscopy for which arbitrarily slow heating can be applied to a minute sample, the smallest difference between heating and cooling transformations that we have observed reaches 0.6 °C (typically 117.6 and 118.2 °C, but this can vary slightly between crystals, or even within different parts of the same crystal). Some trigger (probably a crystal defect) is needed to initiate the transformation. The change of structure is very slight, involving only a chain rotation and end of alkyl chain slippage.[9] Both the structures are of similar energy, and the energy barrier is small; thus, the facile transformation is understandable.

By contrast, the thermodynamic transition point of the change for sulfathiazole III to sulfathiazole I lies at 94.5 °C as determined by Milosovich,[10] and at 95.5 °C by the author. The transformation seen in DSC never occurs at less than about 120 °C but can lie anywhere between 120 and 175 °C, the latter being the melting temperature of Form III.[11] Many crystals will not transform at all but will melt first. Although this is extreme behaviour, it is not rare. The thermodynamic transition point between α- and γ-glycine has been reported[12] to be at 165 °C, but experimentally it can be observed anywhere between 165 and 210 °C. Further examples are tabulated by Kawakami.[13] Therefore, when evaluating a solid−solid transition observed in a DSC trace, it is necessary to determine that lower temperature at which the thermodynamic transition point lies.

Slurry Transformation. One means of doing this is by slurry transformation. Slurry transformation offers the opportunity of determining the thermodynamic transformation point, as well as giving some indication of the likely rate of transformation in the presence of solvents. A slurry of the compound, preferably as a mixture of the forms in a suitable solvent, is maintained at a given temperature. The solid product is analysed at intervals to determine the change of polymorphic composition. The mixture will gradually transform to the more stable form. The most suitable solvent will be one in which substantial solubility is shown,[14] but care must be taken to avoid solvents which are potential solvate formers. The experiment is repeated at different temperatures until the thermodynamic transition point is bracketed. Near the transition point, the rate of transformation may be very slow, because of the lack of thermodynamic driving force, which is proportional to the difference in Gibbs free energy between the polymorphs. At the transition point, this is theoretically zero. If the Gibbs energy curves of the two polymorphs lie very close together over a wide temperature range, no transformation may be observed within a reasonable time. It may not be possible in such cases to determine the transition point, but only a range within which it must lie. This is uncommon, but not unknown, as in the example of RG 12525.[15] The comforting side of this situation is that because the polymorphs show similar solubility over a wide temperature range, the problem of possible interconversion is unlikely to occur.

Solubility Measurements. These also allow the thermodynamic transition point to be estimated. The more stable polymorph has the lower solubility—this is a thermodynamic necessity. In practice, the value of the measured solubility of a polymorph may not be a good estimate of the thermodynamic solubility, because the accurate determination of solubility is an undertaking fraught with difficulty. In a monodisperse powder, the true solubility is approached asymptotically. In the average polydisperse sample, the largest particles dissolve last, so the approach to equilibrium is even slower. A calculation is provided by Mullin[16] to show that an increase in particle size from 1 to 10 μm in the case of lead chromate will increase the time of dissolution from 7 h to 30 days. It is not usually appreciated that the lower the solubility, the slower the equilibration. The conversion of the metastable polymorph to the stable form can obscure true differences in solubility, as can the formation of hydrates or solvates, ionisation or chemical reaction. It is important to check for the integrity of the solid during the dissolution process. The method of determining the true solubility of a metastable form in the face of polymorphic conversion is to keep adding more of the metastable form until a plateau of the solubility can be measured. The particular need for high purity of the sample in this case will be understood. The use of dissolution rates as a substitute for solubility measurements brings a further set of problems.[17] The main issue concerns the necessity for similar surface areas of the samples, as dissolution rate is proportional to both solubility and surface area. Surface areas are difficult to measure accurately. The use of intrinsic dissolution certainly reduces but does not eliminate the problem, since there is no opportunity to assess the true surface area or particle anisotropy during the dissolution.

Provided that the solubility ratio between polymorphs is not very large or that the solubilities are not so high as to produce solutions lying well beyond the region of ideal behaviour, then the solubility ratio must be the same in any solvent at a given temperature. Hundreds of examples of the solubility of polymorphs have been reported in the literature, but in many cases the reported solubility ratios do not agree, even within a paper, illustrating the warning just made about the difficulty of determining accurate solubilities. In the pharmaceutical literature, Nordstom and Rasmuson[18] have provided the most convincing set of solubilities known to the author. Comparison of the solubility of the polymorphs of *m*-hydroxybenzoic acid in four solvents at nine temperatures is possible from their figures. The ratios differ little with temperature, and vary between 1.21 and 1.33 overall. For individual pairs of measurements at low concentration the typical variation (i.e., error) can

(9) Coles, S. J.; Griesser, U. J.; Hursthouse, M. B.; Pitak, M.; Threlfall. T. L. *Cryst. Growth Des.*, accepted for publication.
(10) Milosovich, G. *J. Pharm. Sci.* **1964**, *53*, 484–487.
(11) Lagas, M.; Lerk, C. F. *Int. J. Pharm.* **1981**, *8*, 11–24. Herein is quoted a lower value of 105° for the transition. However, there was and remains considerable confusion in the literature over the distinction between the polymorphs of sulfathiazole; thus, by no means is it certain that the transition reported is from Polymorph III to Polymorph I.
(12) Park, K.; Evans, M. B.; Myerson, A. S. *Cryst. Growth Des.* **2003**, *3*, 991–995.
(13) Kawakami, K. *J. Pharm. Sci.* **2006**, *5*, 982–989.
(14) Gu, C.-H.; Young, V.; Grant, D. J. W. *J. Pharm. Sci.* **2001**, *90*, 1878–90.
(15) Carlton, R. A.; Difeo, T. J.; Powner, T. H.; Santos, I.; Thompson, M. D. *J. Pharm. Sci.* **1996**, *85*, 461–467.
(16) Mullin, J. W. *Crystallisation*, 2nd ed.; Butterworth: London, 1972; p 166.
(17) Threlfall, T. *Analyst* **1995**, *120*, 2435–2460.
(18) Nordstom, F. L.; Rasmuson, A. C. *Eur. J. Pharm. Sci* **2006**, *28*, 377–384.

amount to 5%. All the measurements were carried out at least in duplicate, and every care was taken with the analysis. It is difficult to imagine that more accurate values could be obtained without extraordinary experimental effort. Since the solubility difference[19] between polymorphs is often quite small and inevitably drops towards zero as the transition point is approached, the applicability of solubility in isolation for the determination of transition points and overall phase diagrams is likely to be limited.

Phase Diagrams. There are several possible ways of presenting a phase diagram. The simplest representation is probably the plot of solubility against temperature, Figure 1. This can be determined in principle by measuring the solubilities of the two forms over a wide range of temperature. In practice this is hardly ever a practical proposition, for the reasons just mentioned, but particularly because of the conversion of the metastable form at higher temperatures. Stability is represented on this diagram as the downward pointing axis; thus, at any temperature the most stable form is represented as the lower of the two curves. The more stable of the forms at lower temperature becomes the less stable at higher temperature. At the transition point, the forms are equisoluble and equistable. The higher-melting form is referred to as 'Polymorph I' and the lower-melting form as 'Polymorph II' throughout this discussion.

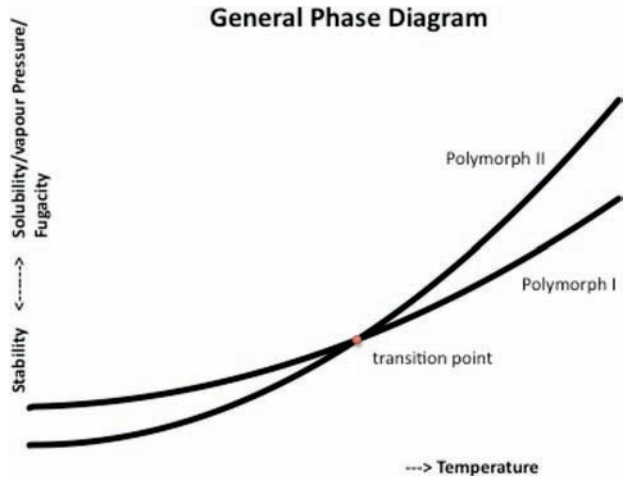

Figure 1

When the liquidus curve (which can only be obtained from vapour pressure measurement, not from solubility determination) is added to the diagram, the coincident points of this curve and the solubility curves represent the melting points of the two dimorphs, Figures 2, 3, and 4.

It is usual to consider the two possible theoretical possibilities within this phase diagram: that in which the fictive transition point lies above the melting point of the lower melting of the two forms, Figure 2, and that in which the transition point lies below the melting points, Figure 3. These are respectively referred to as monotropic and enantiotropic relationships between the dimorphs. It can be seen that these are merely regions within Figure 1, the extent of each region being determined largely by the position of the melting curve on the abscissa. For practical purposes, there is a third important case,

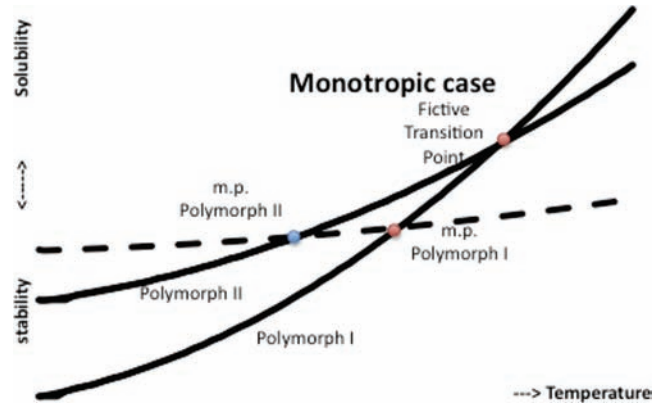

Figure 2

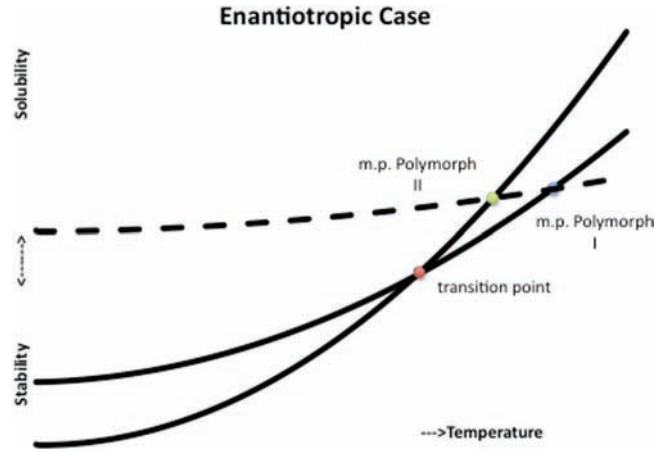

Figure 3

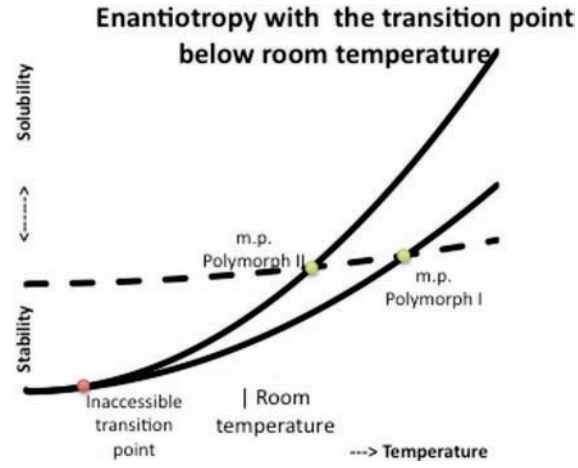

Figure 4

that shown in Figure 4, which represents an enantiotropic relationship but in which the transition point lies below working temperatures, that is well below room temperature. This matters, because the system may be determined to be enantiotropic, but the expected reversal of stability between the forms does not occur within accessible temperatures. In Figure 4, the transition point is labelled 'inaccessible', for this is often the case. For example, facilities may not be available to reach the required temperature. Even if facilities do exist, the transition at low temperature may be so slow that it will not be observable. There is one further variation of theoretical interest, namely that for which the transition temperature lies below absolute zero.

(19) Pudippedi, M.; Serajuddin, A. T. M. *J. Pharm. Sci.* **2005**, *94*, 929–939.

Conventional wisdom, derived from consideration of crystals held together solely by van der Waal's forces, would deny such a possibility. However, for hydrogen-bonded structures, it is a possible occurrence. For practical purposes, it is of no consequence. For the monotropic case, the curve for one solid form lies above the other at all temperatures, so that one of the dimorphs is always less stable than the other. Consequently, transformation can occur in only one direction in the solid state. In the case of enantiomorphism, the direction of transformation can be altered by adjusting the temperature.

Although presented as solubility on the abscissa, the underlying thermodynamic factor is fugacity, and so the axis could equally well be labelled from a theoretical perspective as vapour pressure. Rarely are vapour pressures measured, because of the underlying difficulty of doing so. The liquidus curves shown in all the diagrams are merely representational lines passing through the melting points: the accurate phase diagram referred to in the introduction would involve such a determination.

The curves can be formally linearised by plotting the logarithm of solubility against reciprocal temperature. The resulting phase diagram is generally referred to as the van't Hoff plot, because the axes derive from the van't Hoff equation, $\ln S_1/S_2 = \alpha \cdot 1/T$, where S_1 and S_2 are the solubilities and T is the temperature (Figure 5).

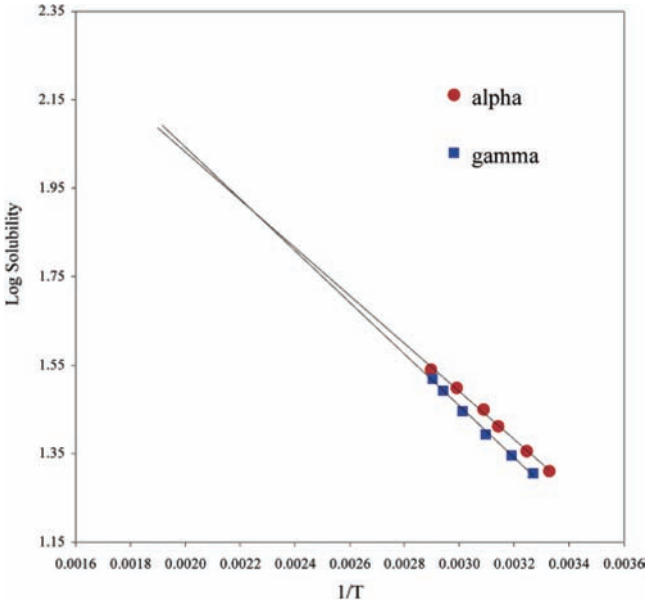

Figure 5

The van't Hoff plots are generally used to extrapolate measured solubilities in an accessible region, for example between 20 and 50 °C, in order to determine the transition point in a less accessible region. The inaccuracies of this procedure are generally not appreciated. Burger[20] has stated that the resulting estimated transition temperature could be in error by tens of degrees. It is easy to see, by drawing the 5% error bars suggested earlier, that for close and nearly parallel lines the temperature might be in error by more than 100 °C if a long extrapolation is involved. The value of the van't Hoff equation for the determination of transition points is matched only by its propensity to error, and the sole justification for its use is that it may be the only procedure available.[21]

When nonlinear plots are observed, it is usually the case that both lines are curved, and curved to a similar extent, which suggests that the underlying problem is connected to the molecular structure rather than the crystal structure. It is probably most frequently caused by conformational change with temperature or with a change of association in solution. Following a suggestion due to Burger,[20] it is possible to linearise curved van't Hoff plots, with a view to obtaining better extrapolations to the transition point. However, the previous warnings still apply. As an example, the transition point between polymorphs I and III of acetazolamide has been determined as 93 °C by the van't Hoff procedure, above 118 °C by slurrying, and below 148 °C by DSC.[2] It is highly probable, therefore, that the true value lies between 118 and 148 °C.

Urakami et al.[22] have suggested an alternative and quicker way of estimating the transition points. In essence the solubilities of the dimorphs are measured at only one temperature, and the slopes of the solubility curves are determined from the enthalpies of dissolution at that temperature. The danger in such a procedure is easily seen by consideration of the probable error bars associated with each of these measurements. In effect, one pair of measurements has been substituted for the many which are present in the usual van't Hoff plot.

An alternative but equivalent representation is the plot of Gibbs energy against temperature, Figure 6. The relationship between the abcissae on each of the diagrams is given by $\Delta G = RT \ln S$. This accounts for the difference in shape of the curves, as compared with those in Figures 1−5. As previously the more stable of the dimorphs is determined by the lower lying of the two solidus curves. The enthalpy (ΔH) curves have been added to this diagram to aid in the discussion of Burger's rules.[1]

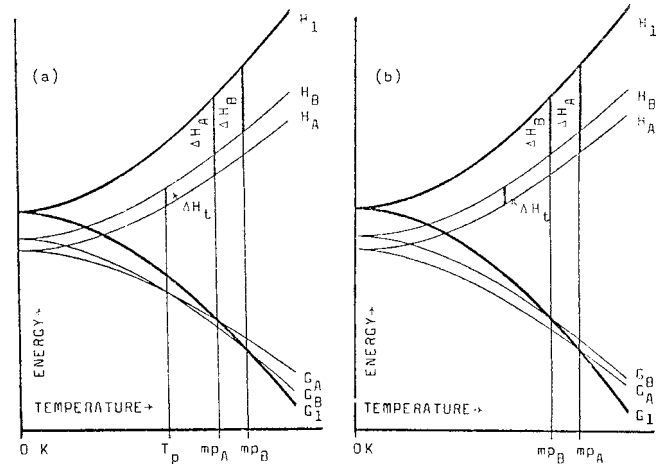

Figure 6

Burger's Rules. The Heat (Enthalpy) of Transition Rule states that if an exotherm is observed, no transition lies below that temperature. If an endotherm is observed, then the transition point must be at, or below, the observed endotherm.

(20) Burger, A. *Acta Pharm. Technol.* **1982**, *28*, 1–20.

(21) This is not an original sentence: it is an adaptation of one given by Fowler, F. W. In *Modern English Usage*, 2nd ed.; OUP: Oxford 1965. of the limitations of analogy as a logical process.

(22) Urakami, K.; Shono, Y.; Higashi, A.; Umemoto, K.; Goto, M. *Chem. Pharm. Bull.* **2002**, *50*, 263–267.

The Heat (Enthalpy) of Fusion (Melting) Rule states that if the higher melting of the two polymorphs has the lower enthalpy of fusion, then the relationship is enantiotropic. Conversely, if the higher melting of the two polymorphs has the higher enthalpy of fusion, then the relationship is monotropic.

Referring to the energy/temperature plots of Figure 6, $H = G + T\Delta S$. Therefore when $T = 0$ K, $H = G$ and the curves meet. H is the integral of the specific heat capacities, C_p, which must be positive, therefore the H curves slope upwards with temperature. G is the negative summation of the entropies, and S is again related to C_p. ΔS must be positive, therefore the G curves must slope downwards. The curves must diverge, and detailed analysis shows that they must diverge increasingly with temperature.

As the stability at 0 K of forms decreases, the rate of divergence between the ΔG and ΔH curves will increase. This follows from the relationship between stability, bond strength, vibrational frequency, and C_p, in which C_p may be regarded as a consequence of the intermolecular friction.[23] Therefore the G curves cross once if at all, whilst the H curves never cross. Burger's Heat of Transformation rule can be ascertained by concentrating on the H curves and seeing what happens on going from H_A and H_B and vice versa, remembering that this is only possible by lowering the free energy, i.e. ΔG must be positive. Hence, those processes which are exothermic on raising the temperature are spontaneous ones. Spontaneous processes are necessarily irreversible, so this transition will be irreversible at or below that temperature. The reverse applies to endothermic processes. Burger's Heat of Fusion rule depends on H_A and H_B being approximately parallel so that the difference in C_p does not obscure the differences in the heats of transition. Burger's rules are for the interpretation of the experimental observations, not a substitute for them. The Heat of Fusion rule should be used only if the transition cannot be measured. Some authors have presented more accurately drawn phase diagrams.[24,25] It will be noticed that the true curvature is very slight and is exaggerated in the drawings of ΔG against temperature in Figure 6.

DSC Charts. The next task is to establish the overall relationship between the polymorphic forms by means of the DSC traces. A polymorph screen will have already established the existence of distinct forms by a selection of methods including thermomicroscopy, DSC, XRPD, IR and Raman spectroscopy and perhaps solid-state NMR spectroscopy and single crystal X-ray diffraction. Of these, only DSC and thermomicroscopy will indicate anything about the phase and stability relationships. In this account, only the question of true polymorphism will be considered, unencumbered by hydration, and for simplicity the discussion will be restricted to the case of dimorphs. The understanding of this case will allow the extension of these same principles to more complex thermal behaviour. There are only 4 basic types of DSC traces which are likely to be obtained from a dimorphic system, in the absence of decomposition at or below the melting point. These are illustrated and discussed in detail below.

Basic Case 1, Figure 7.

For one polymorph, an endothermic solid−solid transition is observed followed by melting. Only an endothermic event (melting) is observed for the other polymorph at the same temperature as that for the melting on the first trace. If the second trace contains a further event—exotherm or endotherm—or

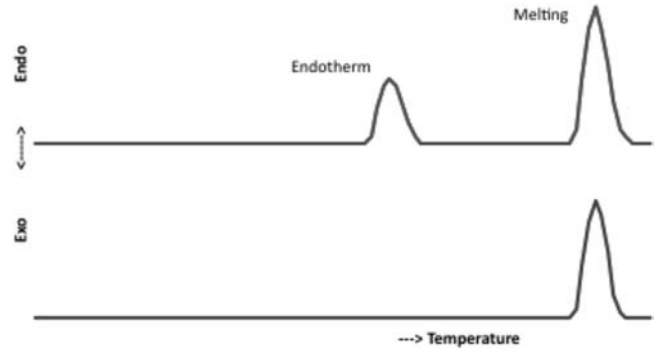

Figure 7

if the observed melting lies at a different temperature to that of the first trace, then clearly at least three forms are contributing to the thermal events. These or further complexities lie outside the scope of the present paper, although the principles of the interpretation are those laid out here. It is also the case that the enthalpy of melting (J/g) must be the same for the two traces. The enthalpy of melting is the area under the melting event divided by the mass of sample. In most modern instruments this is calculated automatically. Such calculations involve a choice of the appropriate baseline under the melting curve; it will be assumed here that the baseline is sensibly flat, and that there is no dispute about the choice of baseline or the accuracy of the resulting enthalpy measurement. To determine that the interpretation of the two thermal events is correct, a thermomicroscopic study is recommended. This will show the solid-state transition and the melting but of course without the possibility of enthalpy measurements. Although it would seem intuitive that the earlier endotherm cannot be a melting, a possible interpretation could be that it represents a transition to a liquid crystal, and the later one is due to the melting/clarification of the liquid crystal to the anisotropic liquid, for example. Hence, the importance of examining the behaviour under the microscope.

The information from the DSC traces is unambiguous, namely that there must be an enantiotropic relationship between the two forms. However, it is possible, though not very likely, that the transition point is below room temperature rather than above it. The checks that should be carried out, apart from hot-stage microscopy to ensure that the thermal events are correctly identified, are either solubility measurements or slurrying experiments at room temperature. It is possible that the attainment of equilibrium by either technique is slow. This will especially be the case if the transition point lies near room temperature, as the driving force for transition will be very small. A transition point near room temperature may render a solid-state presentation of a pharmaceutical impossible, if transformation occurs readily or is catalysed strongly by moisture. In the case of a transition near room temperature, it will be necessary to repeat the slurrying experiments over a range of temperature to ensure that the transition point is correctly located.

Case 2, Figure 8.

For one polymorph, the DSC trace shows an exothermic solid−solid-state transition followed by a melting endotherm. Only an endothermic event (melting) is observed for the other polymorph. The remarks above, with reference to the absence

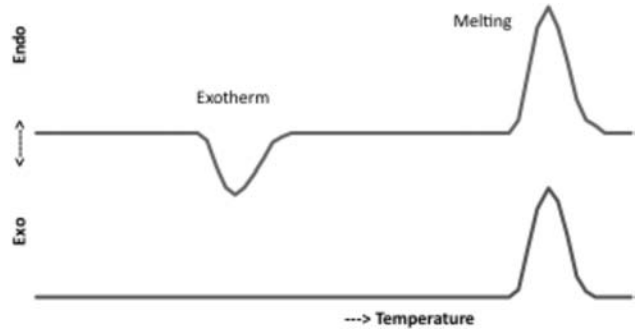

Figure 8

of other events, and the same temperature and enthalpy of melting apply also here.

The interpretation is ambiguous as to whether an enantiotropic or monotropic relationship exists between the two forms—either there is a transition point above the experimentally observed transition, or there is a monotropic relationship. The latter is overwhelmingly more likely. One possible way of distinguishing between them is by running the DSC traces at faster rates. If the exotherm of the slower runs turns into an endotherm at a higher temperature in the faster runs, then the relationship is enantiotropic, and the transition temperature lies between the temperatures of the observed endotherm and exotherm. The reason for this behaviour is that the relative stability of the two forms has reversed in passing the transition temperature. The use of very high heating rates, attainable on some modern instruments, may even allow the solid−solid transition to be bypassed, and the melting event of the first polymorph to be observed. Hot-stage microscopy is again desirable to check that the thermal events have been correctly identified. To distinguish the monotropic from the enantiotropic case requires solubility measurements at a high temperature. From a practical point of view, these are difficult to perform. Solubility or slurrying experiments at room temperature may supply the most useful information as to the stable form and its useful range of stability. In principle, the stability relationships around the melting point can be determined from Burger's rules. In practice, this may give unclear results because of small enthalpy differences and the difficulty of their accurate measurement. van't Hoff extrapolation from low temperatures is likely to be unreliable. In those cases for which the transition temperature or fictive transition temperature is very close to the melting temperature, it will clearly be exceedingly difficult to produce measurements sufficiently reliable to provide confidence in the conclusion. However, this case is exceedingly rare, and the consequences of placing a transition point a degree below, rather than a fictive transition point a degree above, the melting point is of no practical consequence, however intellectually untidy such a thought might appear.

Case 3, Figure 9.

In the case of Figure 9, for the first trace, melting is accompanied by, or immediately followed by, recrystallisation to the other polymorph which subsequently melts. Only an endothermic event (melting) is observed for the other polymorph at the same temperature as that of the final melting on the other trace.

This case is ambiguous as to whether an enantiotropic or a monotropic relationship is present. The same comments as to the relative frequency of these possibilities apply as in case 2 above.

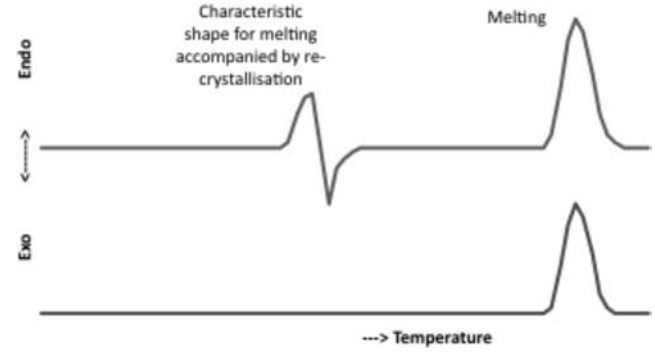

Figure 9

DSC experiments at different rates are likely to be rewarding in this case. The approach of the sample to the melting point often loosens the intramolecular straightjacket of the crystalline state, so that the solid−solid transition can often be seen when using a slow heating rate prior to the melting, which is then unaccompanied by the recrystallisation phenomenon. This changes the behaviour into that of Figure 7 or Figure 8. On the other hand, more rapid heating rates may allow the recrystallisation process to be bypassed and permit the DSC traces to be dealt with as case 4, below. A problem with the melting/recrystallisation event is that it is not possible to separate out the enthalpies associated with the separate events, thus preventing the confident application of Burger's rules. Solubility or slurry measurements can confirm the room temperature stability relationship between the polymorphs. An apparent monotropic relationship could actually be enantiotropic with a transition point far below room temperature. It is again a purist's approach to know this, but for practical purposes it is of no consequence. The convergence or divergence of the solubility curves over a temperature range will probably allow a clear-cut distinction in the case of a transition point lying only a little below room temperature. If the instrument allows for operation below room temperature, then the confidence in the monotropic/enantiotropic case can be extended to the lower temperature limit of the instrument. Nevertheless the possibility of a transition below that cannot be eliminated, unless the divergence of the curves clearly points to a transition above the melting point.

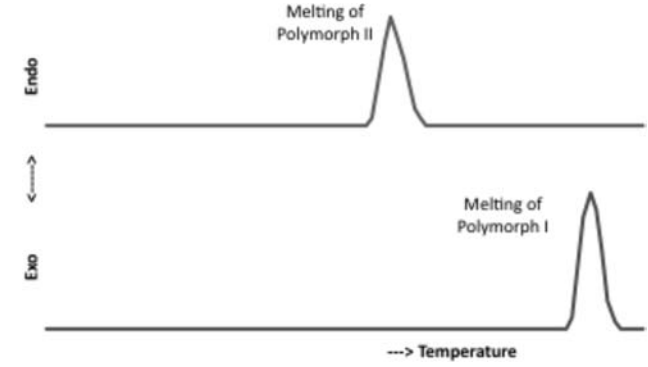

Figure 10

Case 4, Figure 10.

In Figure 10, Only a melting event is seen in the run from each sample with no interconversion.

The enantiotropic case can be distinguished from the monotropic case by the Enthalpy of Fusion rule. If the higher-melting sample has the higher heat of fusion, then the samples are monotropically related. If the higher-melting sample has the lower heat of fusion, they are enantiotropically related. The result is clear when the enthalpies are substantially different, and the melting points are reasonably close, for example within 20 °C of each other. This is the case for the vast majority of dimorphic pairs. The reason for this caveat is that if the melting points are a long way apart, and the heat capacities of the two forms are different, a discrepancy could arise. The Entropy of Fusion[26] rule is then better, but determination of the relative stabilities by solubility or slurrying at room temperature will suffice to establish the case. However, the fact that no conversion is observed on heating implies a large energy barrier, suggesting that room temperature conversion is likely to be slow. For this reason, slurrying at a higher temperature is recommended.

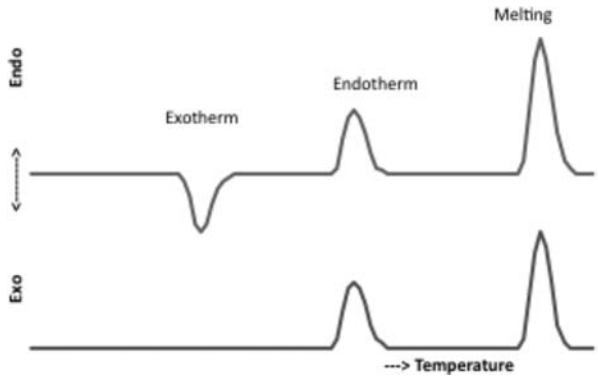

Figure 11

Complex case, Figure 11.

It should be emphasised that the case in Figure 11 is rare, and is included only as a warning that thermal behaviour sometimes produces more solid−solid transitions than the number of species present. In this case, the form that is less stable at room temperature transforms monotropically below the transition point to the more stable form. Upon passing the transition point it becomes the less stable form, and then transforms back to its original form, which is now the more stable form, which subsequently melts. It would be expected that specimens of the other dimorph would transform endothermically at similar temperature to the upper traces, so giving the lower trace. Running the DSC at a faster rate will probably change the behaviour to that of Case 1. Other problematic behaviour could include multiple transition points due to individual crystals with different defect concentrations leading to a multitude of transition temperatures. This is uncommon, but has been reported for acetazolamide[2] and for sulfathiazole,[27] although the issue was not recognised in the latter case. Although not mentioned earlier, it is nearly always worthwhile to run the DSC traces of a polymorphic system in cooling as well as in heating mode. If the heating is stopped after the first endotherm is seen and the sample cooled, the ease of reversibility of the transition may become apparent. In the case of an exotherm, cooling and reheating will indicate whether the supposed product of the transformation is in fact the one produced. A further check on this can be made by variable-temperature Raman or infrared spectroscopy, or XRPD. However, these techniques can be time-consuming, and thermal vibration at higher temperature causes deterioration of the traces. High temperature infrared spectra are also subject to thermal emission effects.

Examples of all the types of traces shown in the figures are available in the literature. Urakami *et al.*[22] usefully presented pharmaceutical examples of the four sorts of traces shown in cases 1−4 above, collected in one paper. Acetazolamide polymorphs A and B behave like case 1. Seratrodast polymorphs I and II behave like Case 2. Carbamazepine polymorphs III and I behave as Case 3, and indomethazine α and γ forms, as Case 4. Other literature examples are: Case 1, zanoterone[28] forms I and III; Case 2, tegafur[29] α and β; Case 3, flurbiprofen[30] polymorphs I and II, zanoterone[28] polymorphs I and V; Case 4, metazachlor[31] polymorphs I, II, III and IV. Some of these are taken from complicated polymorphic systems, but often a metastable form will simply transform to the highest melting form without the involvement of any other form, as shown in these cases. There are many other examples of straightforward DSC traces of polymorphs in the pharmaceutical literature.

Conclusions

DSC traces can be converted into phase diagrams, usually with the help of supplementary information from slurrying experiments or solubility measurements. Various phase diagrams can be drawn, but they are all thermodynamically equivalent. An appreciation of the thermodynamic basis of DSC charts will always help in understanding those charts and in converting them into phase diagrams. In most practical applications, a schematic phase diagram is nearly always sufficient. It may not matter if the thermodynamic transition point cannot be accurately located, for example if it lies outside working temperatures. Knowledge of the approximate location of a transition point suffices in the majority of cases.

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