Organic Process Research & Development **2000**, *4*, 384−390

Crystallisation of Polymorphs: Thermodynamic Insight into the Role of Solvent

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Abstract:

Dependent on the conditions, crystallisation of polymorphs from solvent may be under kinetic or thermodynamic control. In the latter case the nature of the solvent will be immaterial in respect of the polymorph produced. The conditions under which each of these factors may apply are analysed in detail. The transition point between two dimorphs may not present a sharp divide in which crystallisation above and below the transition temperature produces the high melting and the low melting polymorph, respectively. It is shown that even in those cases where the choice of solvent appears to be critical this may be a secondary effect related to the concentration attainable in that solvent at a certain temperature rather than a specific effect dependent on solvent−solute interaction. A corollary to these considerations is the necessity to determine solubility curves and metastable zone widths in order to be able to control polymorph crystallisation.

Introduction

There are numerous accounts in the literature of the effect of conditions and of additives on the growth rate of crystals forming from solution and of the consequent variation in crystal habit, face perfection, and crystal size distribution.[1] This knowledge in some cases allows control of the crystalline product in these respects.[2] By contrast less has been written about the rational control of different polymorphs[3] and even less from the point of view of understanding the general factors underlying the observed results. Most of the accounts which purport to address this latter issue prove on close examination to be plausible deductions from a limited set of specific experimental observations, but unrelatable to the general problem of the interaction between thermodynamic and kinetic factors and of the relative importance of nucleation, early crystal growth and subsequent transformation. This state of affairs is all the more surprising because of the high profile enjoyed by polymorphism and related solid-state phenomena[4,5] in recent years in the area of pigments, explosives, electronics, food, agrochemical, and, above all, in the pharmaceutical industry, in which regulatory controls necessitate the close examination of all products under development for their solid-state behaviour.[6]

Experiments reported in the literature for crystallisation of polymorphs are frequently unrepeatable. Detailed comparison of the stated polymorphic outcomes of crystallisation of much investigated substances often reveals the lack of consistency between accounts. The author recently undertook to crystallise 20 well-known pharmaceutical polymorphic pairs, using apparently well-described recipes, often from well-respected groups, but failed to obtain the expected outcome in respect of the form obtained in 10 of these cases. Others have recently encountered the same problem with respect to one of these compounds, carbamazepine.[7] This is not a criticism of the veracity of previous work but a reflection of the complexity of polymorph behaviour, a matter which is often overlooked. For example it appears no longer possible to crystallise sulphathiazole I reliably from *n*-propanol[8,9] which has been a standard method for half a century. Other sulphathiazole polymorphs also cannot be prepared reproducibly by direct crystallisation, despite intensive investigation and thus need to be prepared by maturation or solvate decomposition routes.[10] The sheer confusion surrounding the reported polymorphs of mannitol has been recently highlighted and clarification of its polymorphic behaviour attempted.[11] A major part of the problem of repeating the literature on the preparation of polymorphs would appear to stem from the widespread but erroneous belief that the solvent is the unique determinant of the polymorphic outcome, so that other essential parameters such as concentration, cooling rate, and temperature of nucleation are not recorded. The object of this paper is to indicate the circumstances under which the solvent will not and cannot affect the polymorphic outcome and circumstances under which it may do so.

Discussion

Instinctively, it would be expected that slow crystallisation from dilute solution would produce the form stable at the temperature of nucleation and crystallisation, whereas rapid crystallisation from concentrated solution in which the kinetics could dominate would generate metastable forms. Whilst there may be some tendency for solutions to behave in this way, the effects of solution concentration are more

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Published on Web 09/15/2000

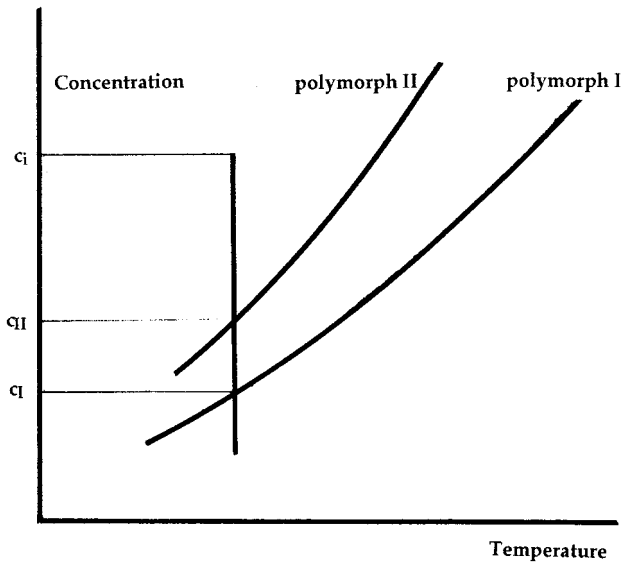

Figure 1. **System of two polymorphs. Solution at point of spontaneous nucleation with initial supersaturation $(c_i - c_I)/c_I$ with respect to polymorph I and supersaturation $(c_{II} - c_I)/c_I$ of polymorph II with respect to polymorph I. After Cardew and Davey.[10]**

complicated than the above simplistic description would suggest, as has been shown by Cardew and Davey.[12] They analysed theoretically the effect of crystallisation of a simple dimorphic system at a constant temperature, illustrated in Figure 1. By consideration of the supersaturation of the initial solution with respect to the two forms and by making reasonable assumptions about the interfacial tension they were able to derive relative nucleation rates. They were also able to formulate equations describing the relative growth rates. Three types of behaviour were recognised, dependent on the total variation of nucleation and crystal growth rate. These were (a) the more stable form would crystallise preferentially at all concentrations, (b) the less stable form would crystallise preferentially only at high concentrations, (c) the less stable form would crystallise preferentially only at intermediate concentrations. Presumably, this intermediate concentration could be moved at least marginally towards the lower concentration region by a suitable choice of parameters. Hence, there is the whole range of possible behaviours with concentration in respect of the polymorphic expectations. Cardew and Davey describe the system as monotropic, because of their subsequent considerations of the transformation kinetics, but it is in fact completely general, and indeed the diagram as drawn could represent an enantiotropic situation.

The system discussed applies either to an evaporative crystallisation which has reached a given concentration or to a cooling crystallisation which has reached a given temperature (most probably room temperature) and then begins to crystallise. To generalise the analysis and to make it more applicable to common practice it is necessary to consider a solution being cooled through the nucleation and crystallisation temperature. This is set out for an enantiotropic dimorphic system in Figure 2, using the desirable nomenclature in which polymorph I is the high melting form and polymorph II is the low melting one.[4] This representation is capable of subsuming the monotropic case by altering the temperature scale so that the transition point X lies below absolute zero or above the melting point of either of the forms. Indeed enantiotropic systems in which the transition point is far removed from room temperature behave for all practical purposes as monotropic systems. For clarity the initial diagram has been restricted to the dimorphic case, as a trimorphic or polymorphic representation would have rendered the diagram unintelligible. No issue of the general principles to be discussed is lost thereby, but some further considerations relating to solvate formation and highly unstable monotropic forms are presented in Figures3 and 4.

Let us now consider the effect of cooling hot, undersaturated, solutions of various concentrations, A, B, C, D, E, F, and G as shown in Figure 2.

(A) If a solution of initial concentration A is cooled, it will reach saturation and then pass through the metastable zone to a point A1 at which it will spontaneously nucleate and crystallise. If the rate of cooling is controlled so that the combined regime of cooling and desaturation due to the crystallisation does not take the concentration to the left of the solubility curve of polymorph II (and it cannot lie to the right of the solubility curve of polymorph I), the crystalline product must consist entirely of polymorph I at this stage (A2), having followed the path from A1 to A2. The product could be filtered off, or it could be cooled further, relying on the massive area of crystal surface of polymorph I and of nuclei of polymorph I in solution to bring down the rest of the product as polymorph I. Provided that the transformation of I → II is not rapid, this procedure will reliably produce polymorph I. If under these circumstances, polymorph I does transform to polymorph II, then there is no polymorphism issue as only polymorph II can be obtained and kept.

The ratio of the solubility of two polymorphs in any solvent is a constant at any given temperature, provided the solutions are ideal, as this solubility ratio is a thermodynamic invariant, being a measure only of the relative thermodynamic stability (Gibbs energy) of the polymorphs at that temperature.[4,13] Therefore, the result of changing the solvent will only be to transform the concentration axis linearly. If the solutions are non-ideal, then the concentration axis will need to be re-scaled in a nonlinear fashion. The temperature axis and the diagram itself will remain precisely the same. The result remains the same for any solvent. The solvent plays no part in the polymorphic outcome other than in determining the numerical values on the ordinate.

(B) When a solution of concentration B is cooled to B1 and seeded with polymorph I, it will behave exactly as described under A above. The difference between A and B is that B cannot reach the spontaneous crystallisation zone of polymorph I before passing into the metastable zone of polymorph II. Thus, for any solution crystallising within the area jkXn of the diagram, between the solubility curves for

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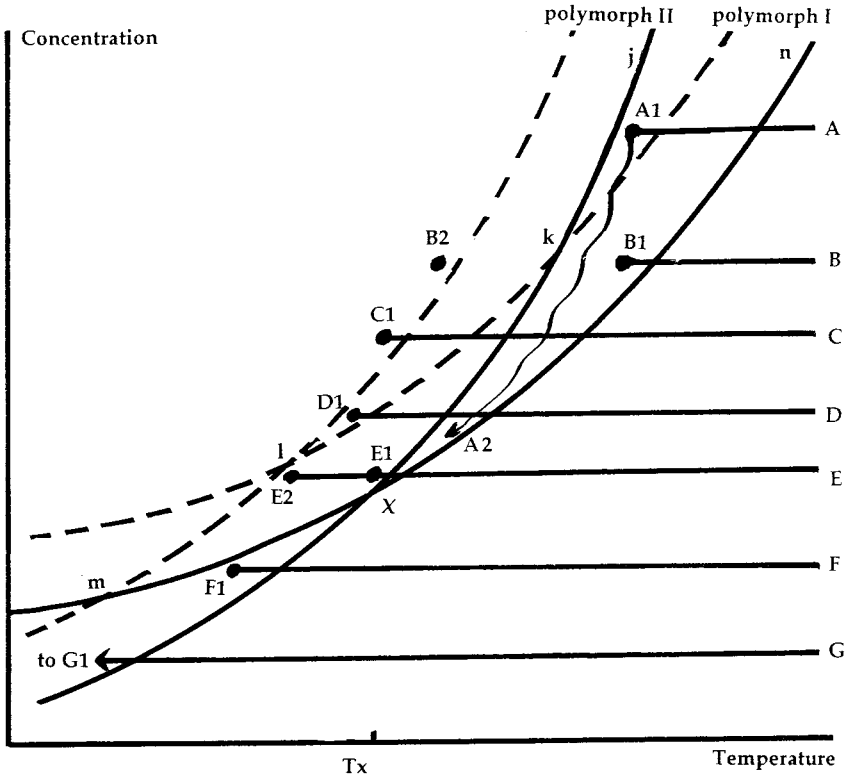

Figure 2. **Polymorphic system of two enantiomorphically related polymorphs I and II. Solubility curves, full lines; metastable zone limits, dashed lines. Transition point X at temperature T_x. A−G, initial state of hot, undersaturated solutions; A1−G1 and B2, E2 state of solution at point of initial crystallisation.**

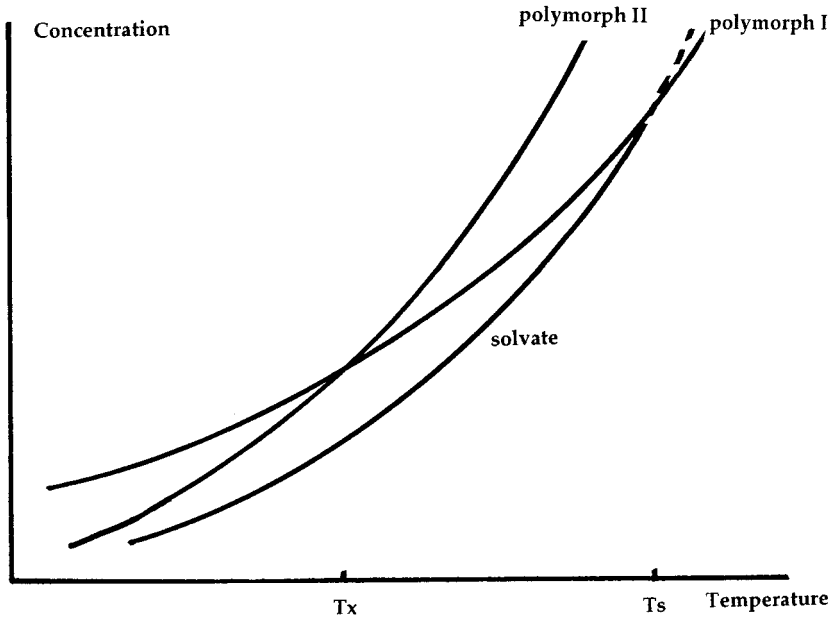

Figure 3. **Solubility curves for a polymorphic system with two enantiomorphically related polymorphs and a solvate. T_x, transition temperature between polymorphs. T_s, transition temperature between solvate and polymorph I.**

polymorph I and polymorph II, the solvent does not influence the outcome. And for any solution crystallising initially and substantially within this area, but then moving into another region of the diagram, the solvent is unlikely to influence the outcome.

(C) When a solution of concentration C is cooled, it crosses the solubility curve of polymorph II before leaving the metastable zone of polymorph I. If it fails to nucleate as polymorph I immediately, then on passing the metastable zone curve of polymorph II it reaches the spontaneous crystallisation region of polymorph II whilst still above the transition temperature. Which polymorph will be obtained will depend on the relative nucleation and crystallisation rates of the two polymorphs. Since polymorph I on the premise just set out does not nucleate readily, it is likely that polymorph II will preferentially crystallise despite the

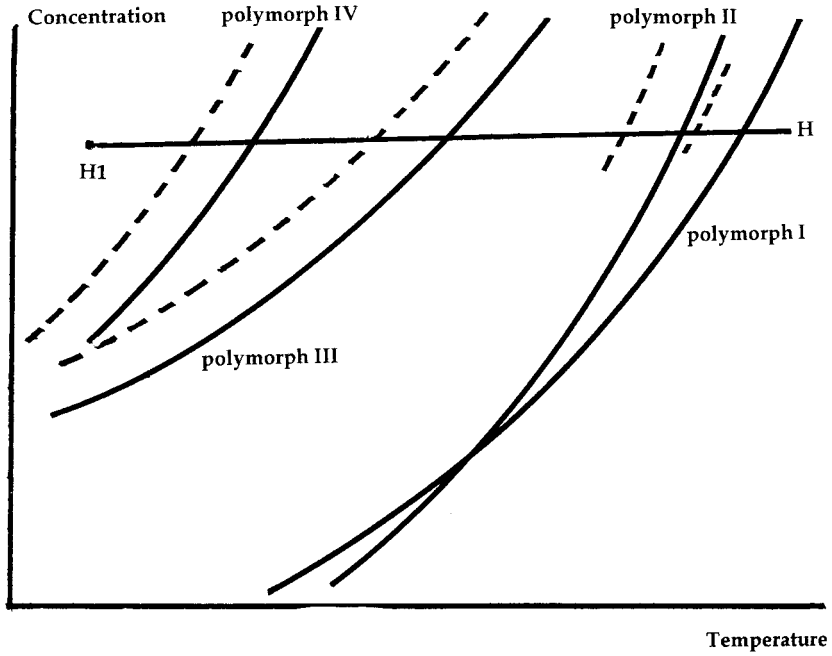

Figure 4. **Solubility curves for a polymorphic system with two accessible enantiomorphically related polymorphs I and II plus two possible but highly unstable polymorphs III and IV. Parts of the metastable zone limits have been drawn in as dashed lines. III and IV are monotropic in relation to I and II, but may be enantiotropically related to each other.**

circumstance that the temperature lies above the transition-point. Solvent is important in this case as it can accelerate the formation of one polymorph at the expense of the other.

(D) Cooling a solution of concentration D to the point D1 produces an even more surprising situation. Although the temperature corresponding to point D1 lies below the transition temperature, polymorph II is still in its metastable zone, whilst polymorph I has already reached its spontaneous crystallisation zone. Hence, the expectation is for polymorph I to be favoured, although the role of solvent could again be critical. The crystallisation behaviour implied by circumstances C1 and D1 needs to be contrasted with the result of equilibrating the products by heating an excess in solvent at those temperatures. Polymorph I will always be formed on equilibrating above the transition temperature, whilst polymorph II will always be formed below it, and this will be irrespective of the solvent used. The reason for this potential discrepancy between crystallisation and equilibration behaviour is that the latter is under thermodynamic control, whilst the former may be dominated by the kinetics, which in some cases, as just detailed, can even lead to the reversal of formation of the expected polymorph with temperature.

(E) Cooling a solution E to any point (E1, E2) within the area klmX, within which both polymorphs remain within their metastable zones, will again lead to a situation in which the polymorphic outcome is dependent on kinetics and especially on accidental seeding. The specific relation of the temperature of solution to the transition temperature is likely to be of little import. The polymorphic result need not be erratic, although it could be, but it is almost certainly unpredictable. The solutions considered under C and D will move into this region soon after the onset of crystallisation, which may lead to changed driving forces for the formation of each of the polymorphs. Hence, it is just in this region that a mixture of polymorphs ("concomitant polymorphs")[14] is likely to be formed. Apart from the solvent, the temperature is rightly regarded as the most significant parameter controlling polymorph formation, but it is clear from this analysis that the transition temperature cannot be regarded as a sharp watershed for the determination of polymorph formation. Rather, there is a broad temperature range either side of the transition point within which kinetic effects driven by solvent specifics and external conditions, such as stirring and material of vessel construction, are likely to dominate.

It can be seen that the analysis presented by Cardew and Davey refers to the behaviour of solutions at points B2 or C1.

(F) F mirrors the situation presented under B above, so that seeding will reliably produce polymorph II, irrespective of the solvent of crystallisation. It is worth noting that seeding of polymorphs is by no means always a reliable procedure.[10] Seeding may not produce the desired polymorphic result when carried out in the regions described under C, D, and E above.

(G) Cooling a solution of concentration G is absolutely safe in terms of producing polymorph II, irrespective of any kinetic considerations. At no point does the horizontal line cut the solubility curve for polymorph I. The remarks about change of solvent in respect of concentration A apply here also, but with even more certainty. Since no transformation is possible, any solvent will produce polymorph II.

The impression may be gained that the differences in the behaviour of the solutions of different concentrations A−G and particularly of C−E are an artifact of the drawing of the diagram and that for example the solubility differences indicated by the curves for the two polymorphs are exag-

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gerated. Some of the concentrations discussed indeed have been drawn so as to minimise clutter on the diagram. But this does not alter the fundamental messages being presented. In fact the diagram can be scaled as required and if this results in a very small temperature range for any of the features then it is a warning of the keen control required and of the how easy it is to slip into near-chaotic conditions. Solution B, for example, if taken to point B2 will behave as does solution C1, indicating the considerable width of the zone of ambiguous behaviour. Of course, either polymorph is capable of crystallising anywhere above the line jkXm, the area which represents solutions supersaturated with respect to both polymorphs, but we are concerned here with inevitable and with probable rather than with possible behaviour, see further discussion under H. The metastable zone width is interpolated to zero cooling rate by definition. In practice it can be considerably changed in real circumstances, for example at practical cooling rates or when different-sized vessels are used. This can complicate further the control of polymorphs. What these considerations do reveal is why it is often so difficult to control polymorph crystallisations.

The only exception to the certainties provided by cases A, B, F, and G is the possibility that a solvate can be formed and that the solvate, because of structural resemblances or favourable transformation pathways, can transform to polymorph I after removal from the solvent. As shown in Figure 3, the solvate solubility curve lies to the right of the polymorphs. The solvate must be less soluble than the polymorphs, otherwise there would be no thermodynamic incentive for its crystallisation.[13] Above the temperature at which the curve crosses that of polymorph I the solvate becomes unstable. There is often such a temperature limit to solvate formation. This behaviour of the formation from a solvate of a polymorph which is otherwise inaccessible or difficultly accessible is shown by sulphathiazole. Many sulphathiazole solvates (e.g., from acetone, acetonitrile, *n*-propanol, pyridine) are formed in cooled solutions (20−50 °C) and decompose readily in the absence of solvent, mainly to polymorph IV (pharmaceutical nomenclature, equivalent to polymorph II of the Cambridge Crystallographic Data Base) at temperatures at which polymorph IV is not the thermodynamically stable form.[10,12] Wirth and Stephenson[15] have described a situation in which it is necessary to obtain a polymorph via a solvate. From the trajectories of the curves of the solvate and polymorph II it would appear that in some circumstances there could also be a lower limit to the stability of a solvate. Although not of direct consequence in the system discussed here, one can foresee circumstances in which it could confuse investigation of polymorph crystallisation. The formation of unstable solvates as intermediates in polymorph crystallisation may be more common than has been supposed,[10] and provide a source of unexpected solvent influence.

In Figure 4 have been drawn two further curves of forms which are thermodynamically very unstable in respect of the two polymorphs I and II with which we have been so far primarily concerned. The curve for form III has been drawn with the intention that the virtual transition points with polymorphs I and II lie at high temperatures, above the melting points of those forms. For form IV the implication is that the virtual transition points lie below absolute zero. The diagram as set up is now a universal representation of a polymorphic system (except that the main protagonists are still represented only as dimorphic). The addition of the two very unstable forms III and IV on the diagram is realistic, whether these can or cannot be observed in practice. Computational studies generate many very unstable forms, for which the question of the reality of their existence always arises.[16]

Let us consider the implications of the presence of such unstable forms as III and IV on the polymorphic outcome.

(H) Suppose it is possible to cool rapidly and prevent the crystallisation of polymorphs I and II and reach the saturation curve and the metastable curve of polymorph III or even of polymorph IV as shown in Figure 4. If the nucleation kinetics of these forms are favourable, for example because of structural similarities between the conformation in solution and in the crystal, it may be possible to crystallise out these forms. However, the improbability of being able to do so needs to be emphasised. Certainly it will ultimately become impossible to reach even less stable forms V or VI lying further to the left. The difficulties of preparing such forms has always been described in terms of the instability of the crystal structure and of its potential transformation to a more stable form. One sees from the diagram further reasons for the difficulty of preparing such forms: the less stable they are, the greater the distance on the diagram from the stable polymorphs I and II. Hence, the solution spends more time in cooling, there are more competing forms to crystallise, and there is a greater temperature range over which other forms can crystallise. The significance of this latter point is that molecular mobility at higher temperature can lead to more rapid transformation in competition with the lowered supersaturation: at some point there will be a maximum rate of crystallisation.[1] Particle-free solutions, viscosity, and rapid cooling will favour the formation of polymorphs such as III and IV by minimising the possibility of pre-crystallisation of polymorphs I and II. In the case of polymorph IV, working at low concentrations will be favourable. For polymorph III there are competing factors such that it is not ascertainable theoretically whether higher or lower concentrations will be desirable.

The diagrams have been presented as fixed patterns with a variable concentration scale, to emphasise the underlying thermodynamic invariance. In practice and conceptually it is normal to consider, and easier to think of, a numerical concentration scale and place the curves appropriately. However, this viewpoint can lead to illusions about the role of the solvent. When a crystallisation experiment is undertaken, a solution of a given concentration is cooled and crystals are observed to form at a certain temperature. The supposed control of polymorph formation by solvent may

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(16) Gavezotti, C. A. *Theoretical Aspects and Computer Modelling of the Molecular Solid State*; Wiley: Chichester, 1997; Vol. 2.

not be due to any specific feature of the solvent (although this is sometimes strikingly the case)[10] but to the attainment of saturation at a certain point in the diagrams at the particular concentration attainable in that solvent. For example, if in solvent 1 a solution of concentration corresponding to A is cooled to A1 and at which point it behaves in an exemplary fashion and crystallises rapidly, then polymorph I will be obtained. If the same numerical value of concentration is employed in solvent 2 in which the polymorphs are twice as soluble, then this will now correspond for example to concentration F because of the expanded or offset abscissa. Consequently, the polymorph produced will now be II. Although the observations might be interpreted as a specific solvent effect, it is clear that the same result as in solvent 2 could be achieved by working in solvent 1 at half the concentration. Without the benefit of the diagram this might be interpreted as a specific solvent effect related to the solvent−solute interactions and to bulk effects (e.g., interfacial tension) of the concentrated solution. Of course the latter might be the case, but in the absence of the solubility diagram it will not be possible to begin to judge. Specific solvent effects are important in polymorph formation, but by definition this is not open to the generalised considerations presented here. Two nonspecific but solvent related effects needs to be emphasised, namely that there is a minimum solubility required in a given solvent to be able to reach all the points on the diagram and that the greater the concentration above A, the easier it is to control the crystallising conditions with respect to the coordinates on the diagram.

The structure of solutions has been little investigated. However, conformational effects in solution, alluded to above, could obviously favour kinetically the formation of specific solid forms, as could dimer or chain formation through hydrogen bonds and specific solvation patterns. It is well-known, but not in the scientific literature, that polymorphism is a persistent feature of final products but rarely of intermediates. One reason for this is undoubtedly McCrone's dictum[17] that the number of polymorphs is proportional to the time spent searching for them. Another reason is surely the elaboration from simple intermediates, often by concatenation, of multiply conformationally flexible molecules with myriad opportunities for packing. The increasing compexity of modern pharmaceutical products could also account for the increasing frequency of the observation of polymorphic behaviour as well as for the great frequency of the occurrence of polymorphism amongst pharmaceutical products in contrast with other categories of chemicals and for the increasing frequency of more elaborate crystal structures with multiple non-equivalent molecules in the unit cell.

Practical Implications

This discussion is presented as an aid to understanding the thermodynamic and kinetic factors and the role of solvent in the crystallisation of polymorphs. It is of less value in predicting polymorphic outcomes of crystallisation of novel materials for several reasons. First, prediction cannot be carried out until the solubility and the metastable curves have been determined. By such time, the polymorphic behaviour of the system may have already become apparent. Second, there is no means of knowing at the preliminary stage whether the supposedly dimorphic system may be tri- or polymorphic, so that working at a higher or lower concentration may simply generate these other forms. This does not alter any of the principles set out above but may render some of the detail irrelevant. Then there is always a phenomenon which renders the forecasting of polymorph crystallisation difficult, namely that of a solution well within the spontaneous crystallisation zone which hangs for hours up to weeks before crystallising either in a controlled manner or by suddenly crashing out.

What the above analysis may emphasise is that, once the solubility diagram for one solvent has been constructed, very few measurements will be needed to construct the whole diagram for any other solvent. The current philosophy of screening for polymorphs would appear to be to crystallise from as many solvents as possible, without concern for concentration. Thermodynamic realities would indicate that concentration issues ought also to be considered at an early stage of investigation, even before the solubility diagram has been drawn. In particular the temperature of first crystallisation ought to be noted. Intervention by solvates and hydrates in the process of crystallisation of polymorphs may be more common than is generally admitted. Because water is such a small molecule even a low concentration in the solvent may be capable of producing a hydrate, especially one involving a fractional mole of water. Therefore control of the dryness of solvents must also be a consideration in the control of polymorph crystallisation. Another important issue, the question of practical seeding, is too large a topic to be considered in detail here. Attention is drawn to the article by Beckmann in this issue.[18] It is worth emphasising that seeding can only be effective if the required form lies within a thermodynamically allowed area of the concentration−temperature diagram and is undertaken before competing nucleation has begun.

Conclusions

When crystallisation of a dimorphic compound from its solution is conducted sufficiently above or sufficiently below the transition point, the solvent used for the crystallisation is immaterial, provided that the solubility is adequate to allow the prescribed concentrations to be reached. Irrespective of the kinetics, the outcome is under total thermodynamic control.

Full knowledge of the solubility and metastable curves is required to be sure that the required points in crystallisation space are reached.

When crystallisation takes place near a transition point, the choice of solvent may or may not be critical, but this

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(18) Beckmann, W. *Org. Process Res. Dev.* **2000**, *4*, 372−383.

will be determined by the relative kinetics of formation, growth, and transformation of the two polymorphs in the various solvents.

The temperature of nucleation and crystallisation in a given solvent, whether just above or just below the transition point, may not, in contrast to what has always been supposed, be significant. The outcome will often be under kinetic control and in that case will be determined solely by the relative rates of nucleation of the dimorphs in a given solvent and by the rate of transformation of the polymorphs.

Acknowledgment

I thank Dr. Bob Lancaster of Glaxo Wellcome R&D, Stevenage, for his support and continuing encouragement.

Received for review June 1, 2000.
OP000058Y