Organic Process Research & Development **2000**, *4,* 403–406

Examples of the Selective Preparation of a Desired Crystal Modification by an Appropriate Choice of Operating Parameters

Robert Spruijtenburg

Roche AG, Vitamins and Fine Chemicals, CH-4334 Sisseln, Switzerland

Abstract:

If a compound can crystallize in more than one structural modification, this will generally also be manifested as different morphologies. In a manufacturing process crystal morphology can have a decisive impact on product characteristics such as filterability, drying time, flowability, etc. In addition, it is usually one particular modification that undergoes registration. In this lecture transcript, two examples of the influence of operating parameters on the obtained crystal modification are presented. The *first example* comprises a food colorant for which four crystal modifications are known. The conventional operating procedure always yielded modification D, which is characterized by extremely poor filterability. Systematic investigations have shown that in suspension each crystal modification is stable within a narrow temperature range. After solid−liquid separation no interconversion of the crystal modifications occurs. Through an appropriate change to the manufacturing process it was possible to reliably obtain modification C, the filterability of which is 30% higher than that of modification D. The drying time was also reduced by a half. The *second example* comprises a pharmaceutical active substance that can crystallize in one of two modifications, A and B, with B being the modification that has been registered. In the manufacturing process the product was obtained from a reaction in ethanol, and crystallized as modification A, with the desired modification B subsequently obtained by recrystallization from *n*-butanol. To avoid the costly recrystallization and extremely lengthy drying of the butanol-moist crystals, the goal was to obtain modification B from ethanol directly. It was found that it is not only the solvent used that determines which modification is obtained but that modification B can also be obtained through a thermal interconversion at 70 °C. This transformation is most simply achieved during drying.

Practical Consequences of the Existence of More than One Crystal Modification. If a compound occurs in more than one crystal modification, this will have various practical consequences:

Problem of Registration. Normally only one modification is registered. If further modifications are subsequently discovered, either the compound must be reregistered, or the production of the desired modification must be guaranteed. Both these options can prove very costly.

Bioavailability in the Dosage Form. This is a function of the compound’s solubility. The different modifications will have different solubilities, and the desired modification will be the one with the *highest solubility*.

Table 1. **Properties of modifications A, B, C, and D of food colorant**

modification	melting point (°C)	appearance	color
A	137−139	lustrous slate-like plates	reddish violet
B	approximately 133	?	?
C	134−136	needles	blue-black
D	121−123	plates	reddish violet

Stability. The different crystal modifications may undergo interconversion as a result of external influences: in suspension during crystallization, during processing (elevated temperatures, e.g. during drying), or under the storage conditions employed (pressure, temperature fluctuations). The most stable modification is therefore desired. Unfortunately, this is usually the one with the *lowest solubility* (see under bioavailability).

Different crystal modifications can also have *different morphologies*. Clearly, the properties of a solid product and its handling during the manufacturing process will depend on whether the crystals are obtained in the form of needles, plates, cubes, beads, etc. Therefore, different morphologies usually influence:

(a) speed of solid−liquid separation (centrifuge, filter)

(b) efficiency of the washing away of impurities and mother liquor

(c) speed of drying

(d) flow properties: as expected, these are more favourable for “three-dimensional” crystal types such as cubes and beads than for “two-dimensional” (plates) and “one-dimensional” crystals (needles)

(e) bulk density

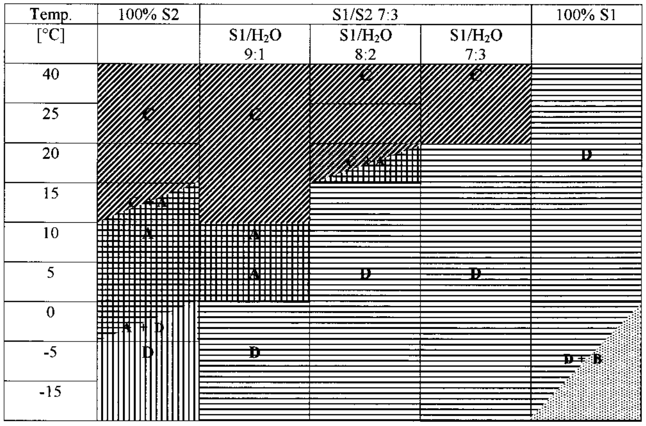
Unfortunately, there is not yet any generally applicable method which, for a given compound, can predict whether it will exist in more than one modification, and if so, how many; the number of modifications identified will depend on how much time has been invested in searching for them.

The first example is a substance whose crystal modifications can undergo thermal interconversion in suspension during crystallization, and the second, a substance which is converted into a different modification during drying at higher temperature.

First Example: Food Colorant. Four crystal modifications (A−D) are known for this food colorant. Table 1 lists a few of the properties of these modifications.

10.1021/op000015h CCC: $19.00

Table 2. Stability ranges of the various crystal modifications



Temp. [°C]	100% S2	S1/S2 7:3			100% S1
		S1/H₂O 9:1	S1/H₂O 8:2	S1/H₂O 7:3	
40			C	C	
25	C	C			
20			C + A		D
15	C + A				
10	A	A			
5		A	D	D	
0	A + D				
-5	D	D			D + B
-15					

It is not possible to give the appearance of modification B, as it could not be isolated in pure form during the investigation.

The conventional operating procedure always yielded modification D, which is characterized by extremely poor filterability. The crystallization process was not reliably reproducible with respect to the modification obtained, with the identity of the modification that crystallized seemingly a matter of chance. A systematic investigation was done concerning which factors determine this polymorphism, and studying cooling crystallizations, isothermal drowning-out crystallizations, and isothermal solvent-exchange crystallizations.

The results are summarized in Table 2 and show that the nature of the crystal modification obtained is largely determined by the temperature at the onset of crystallization, the solvent, and the water content.

- Modification C is mainly obtained at temperatures above about 20 °C, and modification A, in the 5−15 °C range. Modification D is formed below 5 °C in water-free mixtures of solvents S1 and S2, and the more water the solvent contains, the higher the temperature at which it occurs, with the gradual displacement of modification A until, at water contents of ≥30%, the latter is no longer present.
- In pure solvent S1 (cooling crystallization), in the 5−30 °C temperature range only modification D is observed. At lower temperatures mixtures of B and D occur.

Initial experiments seemed to suggest that the crystallization procedure determined which crystal modification was obtained. Thus, modification C (needles) was obtained only from isothermal drowning-out crystallizations (at 25 °C), whereas cooling crystallizations always yielded modification D (cooling end temperature <5 °C). Systematic investigations subsequently showed that the modifications can undergo interconversion in suspension, provided the crystallization is still largely incomplete when the temperature threshold between the two modifications is crossed.

- This was the case with the former operating procedure, in which the solvent ratio was S1:S2 7:3, and where the onset of crystallization was generally between 17 and 22 °C. Since the temperature threshold between modifications C and A is about 15 °C and the threshold between A and D is 5−10 °C, cooling invariably yielded modification D (Figure 1).

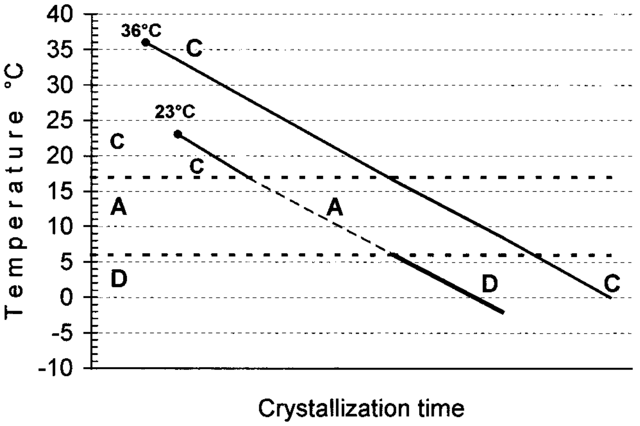


Figure 1. Conditions for the interconversion of the crystal modifications during cooling crystallization.

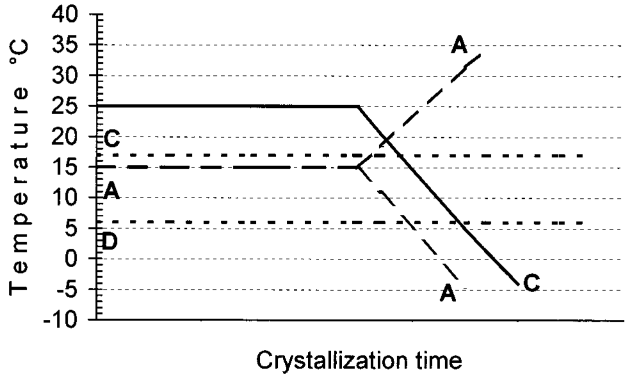


Figure 2. Stability of the modifications with *complete* drowning-out crystallization.

- If, on the other hand, the cooling crystallization is carried out with the same solvent ratio, but with a more concentrated solution, crystallization already begins at 37 °C, with the formation of modification C. In the course of further cooling, crystallization of C will be complete by the time the temperature thresholds to modifications A and D are reached, such that subsequent stirring for 2 h at 0 °C causes no interconversion of the initially formed modification C (Figure 1).
- Likewise, with isothermal *complete* drowning-out crystallization, after subsequent cooling (in the case of modifications C and A) or warming (modification A) the initially obtained modification remains stable far beyond the temperature threshold to the next modification (Figure 2).
- If, on the other hand, the drowning-out crystallization is *incomplete*, the initially obtained modification undergoes interconversion on cooling or warming (Figure 3):

(a) After incomplete drowning-out at 25 °C, the initially obtained modification C gives rise to modification D on cooling (interconversion at 7 °C), which is in turn converted back to modification C on rewarming (interconversion at 37 °C).

(b) After incomplete drowning-out at 10 °C, the initially obtained modification A gives rise to modification D on cooling to −5 °C, whereas on heating to 39 °C modification A is converted into C (interconversion at approximately 35 °C).

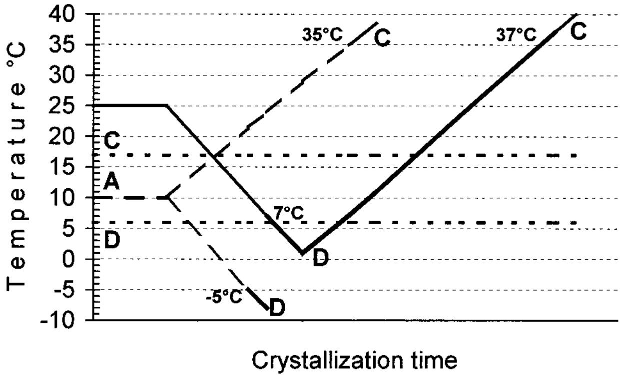


Figure 3. **Interconversion of the crystal modifications with *incomplete* drowning-out crystallization.**

Table 3. **Advantages for the process with modification C instead of D**

modification	D (plates)	C (needles)
residual solvent after centrifugation (%)	30−40	10−20
centrifuge throughput	-	+30%
drying time (days)	5	2

Apparently the interconversion of the modifications requires quite a high energy input, as the temperature necessary for the interconversion of the examples cited is in each case rather remote from the temperature threshold between the two modifications.

A appears to be an unstable modification since, although it can give rise to both C and D, the latter two modifications interconvert directly without the appearance of A.

The operating process was thus changed so that the initial drowning-out of the product with solvent 2 at minimum temperature of 25 °C is sufficiently complete in order that the initially obtained modification C remains stable during the subsequent cooling crystallization. The advantages of the improved process with modification C are listed in Table 3.

The lesson from this example is that if the product is obtained by a cooling crystallization and the nature of the crystal modification is determined by the temperature at the onset of crystallization, account must be taken of the possibility of interconversion of different modifications.

Second Example: Pharmaceutical Active Substance. The second example is a pharmaceutical active substance that can crystallize in one of two modifications, A and B, registration having been obtained for modification B. In the manufacturing process the product is obtained from a reaction in ethanol and crystallizes as modification A. The desired modification B is obtained by recrystallization from *n*-butanol. To avoid the costly recrystallization and extremely lengthy drying of the crystals from butanol, the goal here was to obtain modification A directly from ethanol. Table 4 lists a few of the properties of these modifications.

Known factors that can determine which crystal modification is obtained in a given solvent are the temperature at the onset of crystallization, the rate of crystallization, and the degree of supersaturation. These parameters were therefore selectively varied in an initial series of experiments in which the active substance was crystallized from ethanol by cooling rather than by direct precipitation (as in the manufacturing process), as the latter makes the above parameters difficult to control.

Table 4. **Properties of the two modifications**

modification	A	B
appearance	prisms	isotropic
melting point (°C)	113	145
heat of fusion (cal/mol)	6000	9000

The temperature at the onset of crystallization and the degree of supersaturation were varied via the concentration of the solution, and the rate of crystallization was varied via the rate of cooling and the concentration. Seeding with crystals of modification B was also carried out.

All of These Experiments Gave Only Modification A. In light of these findings, a wholesale revision of the precipitation procedure was undertaken, looking into the influence of all conceivable parameters:

- reagent quality
- reaction temperature
- degree of supersaturation at the onset of crystallization
- addition times of the reagent solutions
- seeding with modification B during the reaction
- stirring time after addition of the reagents
- rate of cooling after the reaction

These Experiments Also Gave Only Modification A. To shed further light on this process, active substance crystals of modification B were suspended in ethanol at various concentrations and stirred for 2 h at two different temperatures and stirring speeds. Under all such conditions pure modification A was observed, whereas if the active substance was precipitated from butanol instead of ethanol, pure modification B was obtained.

The conclusion from these investigations was that up to the point of isolation of the crystals the modification is determined solely by the nature of the solvent and not by other reaction and crystallization parameters.

One reason for these extensive investigations was that the plant laboratory appeared to obtain modification B from ethanol from time to time, but not reproducibly. An initial breakthrough subsequently emerged as a result of carrying out DSC investigations in parallel with the X-ray diffraction patterns used to characterize the modification, the following discrepancies being evident in the results obtained with the two methods:

Samples of crystals from ethanol that had been dried *for 3 h at 70* °C were characterized as modification A on the basis of their X-ray diffraction pattern, whereas according to DSC a mixture of the two modifications A and B was present, with two peaks corresponding to melting points of 113 and 145 °C.

Samples of crystals from ethanol that had been dried *overnight at 70* °C were characterized as a mixture of the two modifications on the basis of their X-ray diffraction pattern, whereas according to DSC pure modification B was present.

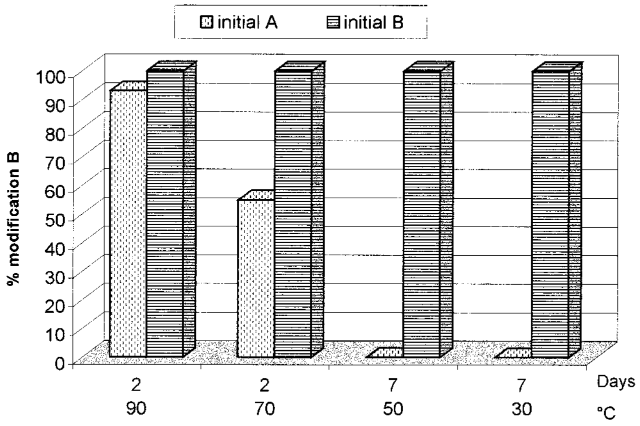


Figure 4. **Thermal stability of the two modifications during vacuum-drying.**

These discrepancies can be explained by a thermal conversion of modification A into modification B, which is possible with a dynamic measurement method such as DSC (temperature profile) but not during the isothermal X-ray diffraction technique.

The conditions and limits of the thermal interconversion of the two modifications were investigated in greater detail, with experiments carried out in a vacuum-drying cabinet fitted with a water-jet pump. The results obtained are shown in the bar chart, Figure 4, with the following results:

- At 90 °C modification A is completely converted into modification B within 2 days.
- At 70 °C modification A is partly converted into modification B within 2 days.
- At 50 and 30 °C modification A is stable even after 7 days.
- Modification B is unaffected by the temperature treatment.

In a further series of experiments the minimum temperature and treatment time necessary for thermal conversion of modification A into B were determined. These experiments were carried out in a rotary evaporator under a fine vacuum, and the results obtained are shown in the following diagram, Figure 5.

The results can be summarized as follows:

At 80 °C modification A is completely converted into modification B after about 40 h.

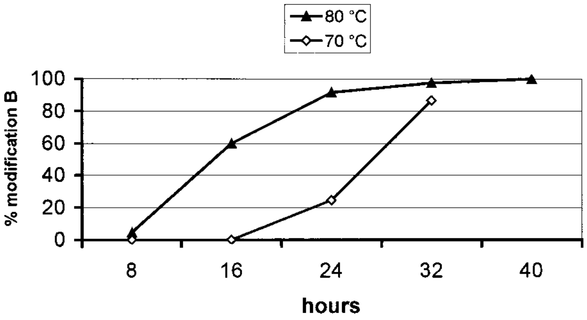


Figure 5. **Minimum conditions for thermal interconversion of A into B.**

At 70 °C this interconversion is considerably slower than at 80 °C, and is still not complete after 32 h.

For a selective conversion to take place within a feasible time scale, a temperature of at least 80 °C is necessary.

The lesson from this example is that a crystal modification obtained under controlled crystallization conditions can undergo further interconversion during subsequent operations. Process steps performed at different temperatures therefore have to be considered with special care.

Conclusions

The crystal modification can have a quite substantial impact on the processing of the crystals during the manufacturing process:

Thus, in the first example, introduction of modification C (needles) instead of the conventional modification D (plates) increases the centrifuge throughput by 30% and also reduces by about one/half both the amount of residual solvent after centrifugation and the drying time.

If it is the temperature that determines which modification is obtained, attention must be paid to the temperature difference between the onset of crystallization and the point of conversion: if the temperature difference is too small, a cooling crystallization can result in interconversion in suspension of the crystal modifications.

Interconversion of the modifications can also occur during further processing, particularly if subsequent steps take place at a temperature different from that of the crystallization step.

Received for review February 24, 2000.

OP000015H