Organic Process Research & Development **1998**, *2*, 298–304

Development of a Seeding Technique for the Crystallization of the Metastable A Modification of Abecarnil

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Abstract:

Abecarnil, a partial agonist of the benzodiazepine receptor, crystallizes in three modifications, A, B, and C. Depending on the solvent, the form crystallized in an unseeded process is one of the two metastable forms A or B. Isopropyl acetate was chosen as solvent for the crystallization of the drug substance Abecarnil, yielding the B form for an unseeded crystallization. However, the crystals undergo a slow solution-mediated phase transformation into the stable C form. More readily observed is a partial phase transformation into the A modification. The rate of transformation depends sensitively on the purity of the material. To access this second metastable form quantitatively, reproducibly and irrespective of the purity of the material, a seeding strategy for a batch cooling crystallization from isopropyl acetate is developed. The technique is optimized under laboratory conditions and transferred to pilot plant scale. The physicochemical data necessary for the effective development are given and their relevance is discussed.

Introduction

Polymorphism is a widespread phenomenon observed for organic substances. The reproducible crystallization of a desired crystal form is important in the agrochemical and pharmaceutical industry. The choice of the polymorph to be produced is governed both by the properties of the solid state forms and their relevance for the anticipated applications as well as by the ease and reproducibility of the production. Some of the properties determined by the solid state form important for pharmaceutical applications are solubility and dissolution rate as well as stability.[1]

Crystallizations in the pharmaceutical industry are often carried out as unseeded batch operations. In this case, the modification formed during nucleation is determined by Ostwald's law of stages,[2] i.e., the least stable polymorph is preferentially formed.

Seeding techniques are widely used in crystallization processes, both in the laboratory and at production scale. To name a few examples, seeding is used to inoculate otherwise difficult to crystallize products, such as proteins, or in order to grow large single crystals, e.g., for X-ray analysis. Seeds do not necessarily have to be crystals of the material to be inoculated; heterogeneous particles can also act as nuclei. In the electronics industry, seeding is commonly used to grow large and defect-free crystals with a predetermined orientation.

Seeded batch crystallizations are often performed with the aim of generating a product with a specific particle size or particle size distribution. A prominent example is the seeded crystallization of sugar to grow large crystals with a narrow size distribution.[3] Seeding is also used for the resolution of isomers forming eutectic phases via entrainment.[4]

Few accounts have been published on the use of seeding for the formation of specific polymorphs. Robertson[5] has shown that the stable form I of Piroxican-Ethanolaine can be obtained via seeding. Sudo et al.[6] have shown for Cimetidine, that the form obtained from a seeded crystallization is governed by the supersaturation attained during crystallization.

The polymorphic transitions from an unstable to a more stable form can be induced or facilitated by seeds, whether intentionally or unintentionally added. The process of seeding with one polymorph can be linked to the phenomenon of disappearing polymorphs.[7]

All seeding phenomena are directly linked to the amount and activity of the seed, the saturation conditions at which the seed is added and the cooling or evaporation program used to perform the batch process.

The amount of seed used is usually on the order of a few percent. An activation of the seed can be necessary, as crystals subjected to environmental conditions may not grow at low supersaturations, probably due to a contamination of the surface. The activation can be achieved, e.g., via washing or wet grinding with solvent prior to addition.

During cooling or evaporation, crossing the metastable zone into the labile region must be avoided. An early discussion of the topic can be found in Griffiths.[8] Time-optimized cooling or evaporation schemes can be derived by requiring the supersaturation to be constant over the process which leads to cubic curves.[9]

In this paper, it is shown for the inoculation of the A modification of Abecarnil that seeding strategies can be devised to obtain even metastable modifications of an organic drug substance that is otherwise not formed spontaneously in the chosen solvent. The data necessary for such a development and their relevance are discussed. Finally, the

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 S1083-6160(98)00029-2 CCC: $15.00
Published on Web 08/05/1998

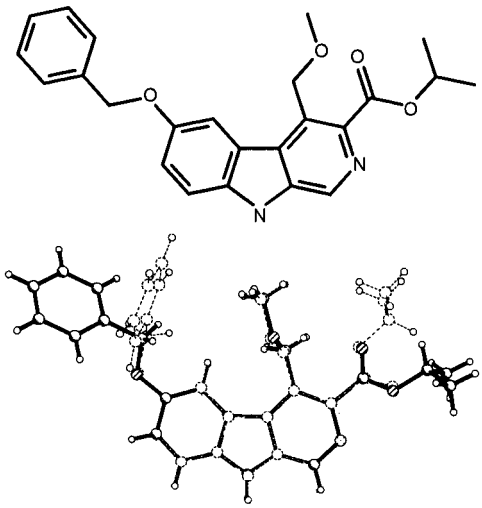

Figure 1. **Molecular structure (top) and rendering of the three-dimensional structure of Abecarnil (bottom). The intramolecular arrangement of the A and B modifications is identical (full lines), while the C modification (dotted lines) differs in the position of the isopropyl and in the tilting angle of the benzyl group.**

necessary steps during the transfer from laboratory to pilot plant scale are presented and discussed.

Characteristics of Abecarnil

Abecarnil is a β-carboline derivative acting as a partial agonist on the benzodiazepine receptor, Figure 1. It crystallizes in three modifications, A, B, and C. The structures of all polymorphs have been resolved.[10] The conformation of the Abecarnil molecule is identical in the A and B modifications. The molecules form two-dimensional layers in which they form chains connected via hydrogen bonds. These layers are nearly identical for the two modifications. The A and B form differ only in the stacking of these layers. However, a small lattice relaxation between the A and B form is also observed, entailing the A form to be more densely packed, having the lower enthalpy of formation. Contrarily, the C form is a conformational polymorph with respect to the aforementioned forms, Figure 1.

The thermodynamic stability of the three forms was assessed via careful measurements of the solubility in isopropyl acetate as a function of temperature,[11] Figure 2. The C form is the stable form at all temperatures and is thus the monotropic form. The A and B forms are close, and the A form is more stable at low temperatures, while the B form is more stable at higher temperatures. The cross-over temperature was estimated as ~80 °C. These data can be corroborated using enthalpy−temperature diagrams.[12]

The relatively steep solubility curve suggests a cooling crystallization for Abecarnil. The process is started with solutions slightly subsaturated at the normal boiling point of isopropyl acetate of 89 °C and carried to 25 or 20 °C where the increase in yield by further cooling is negligible.

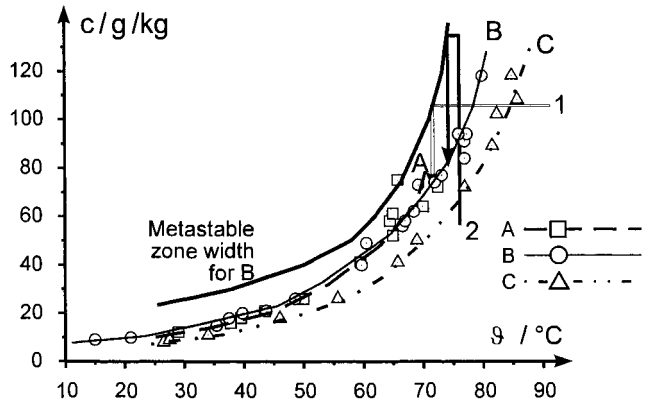

Figure 2. **Solubility of the A, B, and C modifications of Abecarnil in isopropyl acetate as a function of temperature. Also given is the border of the metastable zone width for a cooling rate of −1 K/min (thick solid line). The two other lines indicate experimental conditions for the unseeded processes of a cooling (1) and isothermal evaporative crystallization (2).**

The form obtained in an unseeded batch crystallization from isopropyl acetate is the B modification, irrespective of the crystallization technique used.[11,13] The metastable zone width for a cooling as well as an evaporative crystallization is broad, as expected for organic substances. The zone width is only a weak function of the cooling rate and has also been plotted in Figure 2 for a cooling rate of −1 K/min.

The A modification of Abecarnil is obtained via unseeded crystallizations by using alcohols as solvents, e.g., methanol or ethanol.[11]

For unseeded cooling crystallizations it was shown that the Abecarnil concentration reaches the saturation curve during unseeded as well as seeded cooling crystallization within a few minutes.[11,14] Thus, no stirring time after reaching the final temperature is required to increase the yield of the crystallization process.

It should be noted that neither modification of Abecarnil belongs to the species of disappearing polymorphs. Each one can be crystallized using its specific solvent no matter how infested the laboratory is with seeds of the other forms. This is a prerequisite for the successful development of this seeding technique.

The Problem

During early development the B modification was chosen as solid state form due to its ease of crystallization from isopropyl acetate. It was shown that this form was stable in suspension over more than 1 day and transformed only slowly into the more stable A form. A transformation into the stable C form was only observed for periods exceeding days. Such conditions can easily be avoided. With respect to the dry solid state, no transition of the B modification was observed, both for large crystals and comminuted material. Thus, the production of the B form was considered to be a safe choice.

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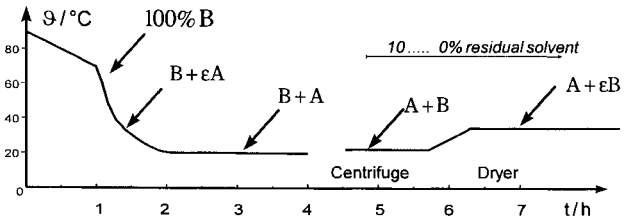

Figure 3. **Fraction of A and B form at different stages of the process. ϵ denotes trace amounts of the respective modification and A + B and B + A larger amounts of the A or B modification in mixtures of both forms. It is important to note that the nucleation and first stages of growth yield pure B form with no detectable amounts of A and that the transformation into A proceeds even at low solvent contents.**

During the technical transfer of the synthesis from development to production, some minor process adjustments had to be made, leading to a somewhat purer product. Unfortunately, this per se positive effect also caused the B modification to be less stable and to transform more readily into the A form. Figure 3 details the modifications obtained at different stages of the crystallization of material stemming from the modified route. During the nucleation phase, only crystals of the B modification are formed. These crystals transformed via a solution mediated phase transformation into form A. The first detectable quantities of A are found ~1 h after nucleation. At the time of drying, the transformation is nearly complete. The amount of solvent necessary for the phase transformation is small, a transformation is even observed after centrifuging resulting in an residual solvent content for ≤10%.

A detailed analysis showed the B-to-A transformation to be solution mediated and probably of the contact model type.[15] The kinetics of the transformation depends on the material. Material from the new synthetic route has a rate of phase transformation approximately 15-times higher than material from the old route decreasing the stability from 1−2 days to hours. A laboratory study proved the transition to be impurity controlled. The reduction in the level of one impurity, the hydrochloride of triethylamine, caused a destabilization of the B form[11] and is one possible explanation for the increase in the rate of B-to-A transition. Thus, batches exhibiting an increased rate of B-to-A transition cannot be reworked to a material with a slower rate, as a missing impurity causes the increase in rates.

This assertion was corroborated on the production plant scale by both repeated recrystallizations that did not change the behavior of the new lots and by adding the impurity whereby the B modification was again the modification reproducibly found after workup.

The transformation from the B form initially formed to A is not entirely complete. The fraction of A formed ranges from 50 to 100%. Thus, the B modification could no longer be produced in a pure form from isopropyl acetate. A change to the production of the C form would be most reliable, as it is the thermodynamically stable form. However, the physicochemical properties of B and C are quite different, while those properties of the B and A form are very close. The ICH guideline[16] allows for polymorphs having identical or near identical properties the substitution of the two. It was decided to produce the A modification instead of the B form via a seeded batch cooling crystallization.

Development of Seeding Strategies in the Laboratory

The goal of the seeding technique to be developed was a reliable and reproducible crystallization of the A modification of Abecarnil, with no detectable amounts of B or C modification. Control of crystal size or size distribution was not required, as the drug substance had to be comminuted.

The development of this seeding strategy required several parameters to be optimized, e.g., the type and pretreatment of the seed, temperature and saturation conditions at the point of seed addition, the amount of seed added and the cooling profile, and the final downstream processing.

Clearly, for the seeding process to be viable, the starting material has to be dissolved completely before crystallization to ensure that the modification of the starting material has no influence on the modification obtained.

Type of Seed. The seed crystals were obtained in two ways. For the laboratory work, Abecarnil crystallized from methanol in an unseeded cooling crystallization was used. This solvent is known to yield preferentially the A modification.[11] For the pilot plant work, a batch was used that had accidentally undergone a complete conversion to A. To maximize the surface-to-volume ratio, ground or micronized material of the A modification with a specific surface area of up to 2.5 m^2/g was used. In all cases, it was shown by using both DSC and powder X-ray techniques that the seed crystals were free of any detectable amounts of both the B and C modification; for the limit of detection see the text below.

Activation and Temperature of Addition of Seed. By activating seed crystals, their effectiveness can be drastically increased. As it facilitates handling, it was decided to activate the seed by preparing a slurry in isopropyl acetate. The volume of solvent used was ten times the weight of the seed, entailing a dissolution of ~10% of the seed. It is assumed that the pretreatment of the seed preferentilly dissolves impure regions on the crystal surface and cleans the growing faces.

The effect of an improperly activated seed is shown in two experiments, using 1% of A seed and a cooling rate of 0.5K/min. Two different materials were used, Abecarnil of lot no. 4 for which the B-to-A transition is relatively slow and lot no. 8, which is relatively labile for a B-to-A transition. The results are summarized in Table 1, where experiments with an nonactivated and an activated seed are compared. It can be seen that for Abecarnil that does not readily transform into the A modification, only the addition of activated seed yields crystals of pure A modification.

It should be noted that a slurry of the A modification is unstable and prone to a A-to-C transformation. As the slurry is added to a solution supersaturated with respect to the A and C modification with the supersaturation of C being

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Table 1. **Influence of the activation of the seed via partial dissolution on the modification obtained[a]**

lot no.	seed	modification: immediately after seeding	modification: after 1 h of stirring
4	1% A dry	A + 94%B	A + 93%B
	1% A as slurry	A	A
8	1% A dry		A + 7%B
	1% A as slurry	A	A

[a] Two lots of Abecarnil are compared, lot no. 4 having a slow B-to-A transition and lot no. 8 exhibiting a fast B-to-A transition.

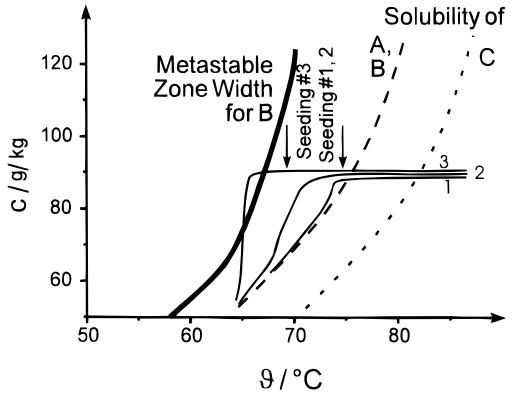

Figure 4. **Seeding strategies for the crystallization of the A modification. The amount of seed added and the cooling rates must ensure a supersaturation that is always well within the metastable zone. The lines indicate an early seeding with large (no. 1) and small (no. 2) amounts of seed. A passing of the metastable zone width will result in the nucleation of larger amounts of B modification (no. 3), e.g., by a late seeding.**

substantially higher small amounts of C in the seed will proliferate during cooling.

The activated seed can be introduced at temperatures corresponding to supersaturation of the A modification. Figure 4 summarizes the conditions. The addition should be made as closely as possible after the crossing of the line of solubility of the A modification, lines nos. 1 and 2 in Figure 4. Due to uncertainties introduced by upstream processes, the concentration of Abecarnil in solution is known only with an error of ±5−10%, entailing an error in the saturation temperature of ±1−3 K.

One condition to be avoided is a crossing of the metastable zone for the spontaneous nucleation of the B modification, which will result in the immediate nucleation of ≥30% of the B modification, line no. 3 in Figure 4. This metastable zone has a width of ∼10 K, so that the addition is made 2−3 K below the calculated saturation temperature of the A form.

Amount of Seed and Cooling Rate. The amount of seed and the permissible cooling rate are directly correlated. The seed added decreases the supersaturation via its growth, which is directly proportional to the amount or surface of seed added. The cooling in turn builds up the supersaturation. The exact amount of the seed to be used is a function of the cooling rate and was established in laboratory experiments.

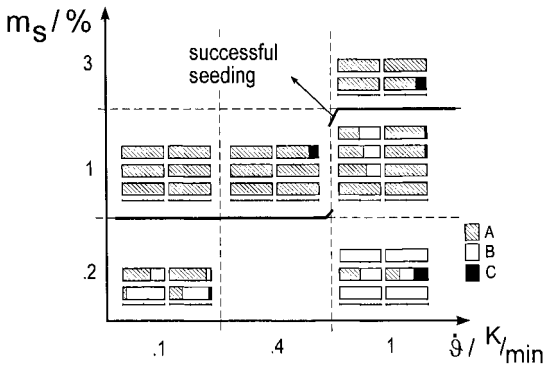

Figure 5. **Results of the optimization experiments for the amount of seed added for different cooling rates - $\dot{\vartheta}$. The modification at the end of the cooling is shown in the left block and at times of ≥14 h in the right block. The amount of seed is referred to as mass of seed per mass of Abecarnil dissolved.**

The experiments were carried out with two different batches of Abecarnil, having a different profile of impurities and that differ in stability against a B-to-A transition. Lot no. 4 has a slow B-to-A transition, while lot no. 8 has a rate of transition approximately 10−15 times faster.[11] Thus, improperly activated seed of the A modification can entail a nearly quantitative formation of the A form due to a B-to-A transition for lot no. 8, while the more stable lot no. 4 yields only minor amounts of A. On the other hand, a properly activated seed yields for both lots quantitatively modification A (cf. Table 1).

Consequently, the optimization experiments were carried out with activated seed only. The amount of seed used, referred to as mass of seed per mass of Abecarnil dissolved, ranged from 0.2 to 3%, and the cooling rates were between 0.1 and 1 K/min.

Samples of the crystals were taken after the cooling has reached 20 °C and after stirring for 10−40 h. The samples were dried quickly on a clay disk and analyzed for polymorphic modification as described below. The results of the experiments are summarized in Figure 5. For the different combinations of amounts of seed and cooling rates, the modifications present at the end of the cooling and after prolonged stirring are presented for 2−4 characteristic runs.

The data compiled in Figure 5 and the qualitative results discussed before are in good agreement. The higher the cooling rate, the more seed is needed to avoid the formation of the B modification. As indicated by the thick line, 1% of seed seems necessary and sufficient for the cooling rates of 0.1−1 K/min. Lower cooling rates offering the use of lesser amount of seed are not attractive, as the time required for cooling with 0.1 K/min is 10 h. It can also be seen from Figure 5 that a prolonged stirring of the suspension results in the formation of the C modification. A cooling program might be able to optimize this point; however, a near linear rate at the cost of more seed seemed more attractive.

The seeding scheme produced pure A modification both for batches that exhibit a slow (lot no. 2) or a fast (lot no. 8) B-to-A transition. Thus the resulting modification is truly the result of the seeding, and more important, the technique is independent of the type of Abecarnil used.

Table 2. **Details of the three pilot plant batches and differences to the laboratory scale experiments**

	batch			
parameter	laboratory	P1	P2	P3
seeding at	75 °C	75 °C	77 °C	78 °C
cooled to	20 °C	20 °C	30 °C	30 °C
average cooling rate	−1 K/min	−0.3 K/min	−0.4 K/min	−0.55 K/min

Table 3. **Modification if the three pilot plant batches for different stages of the crystallization and workup processes**

	modification		
batch	end of cooling	after centrifuging	after drying and sieving
P1	A	1% C	A + 5%C
P2	A	A	A
P3	A	A	A

Seeding Strategy. The experiments described above show that a successful seeding strategy for the reproducible crystallization of the A modification of Abecarnil from isopropyl acetate can be devised. This goal can be achieved by a proper activation of the seed and exceeding a certain combination of cooling rates and amounts of seed (cf. Figure 5). To minimize the possibilities of a solution-mediated transition to the C form, the cooling should be as fast as possible and the workup rapid. In addition, the amount of seed should be increased over the necessary amount. In conclusion, the following strategy for the seeding is proposed:

(a) Addition of 3% of seed (mass of seed per mass of Abecarnil dissolved) in micronized form as a slurry in isopropyl acetate. The slurry is to be prepared ≤5 min before addition using ten times the volume of the solvent per mass of seed.

(b) Addition of the seed at 75−78 °C for solutions containing 100 g/L of Abecarnil.

(c) Cooling of the solution from 90 to 20 °C with a rate approaching 1 K/min, however, the corridor is broad and 0.3 K/min seem to suffice in view of the 3% of seed used.

(d) Immediate workup when 20 °C is reached.

Transfer to Pilot Plant Scale

Three runs were performed in the pilot plant on the 30−40 kg of Abecarnil scale. Despite a close collaboration between the laboratory and pilot plant, several differences were encountered during the transfer. Besides the larger scales, the differences to the laboratory scale were in the lower cooling rate, the addition of the slurry via a centrifugal pump, and in the slower work- up using a centrifuge and a tray dryer. The conditions of the three runs and their differences to the laboratory scale experiments are summarized in Table 2.

The modification of Abecarnil in the pilot plant runs was monitored at the end of the cooling phase, after centrifuging, and at the end of the drying and sieving process. The modification produced in the three runs was A + 5% C, A, and A, respectively, as summarized in Table 3.

Cooling Rates. The maximum cooling rates that could be achieved in the pilot plant was −0.5 K/min, a rate within the corridor proven by the laboratory work. However, to achieve this rate the jacket temperature had to be lowered to −10 °C, see Figure 6.

A temperature difference of ≥60 K can result in an encrustation or in a primary nucleation of the B form, although this was not observed in the three runs. It should be noted that, in the laboratory, the temperature difference never exceeded 3 K, even for the high cooling rates.

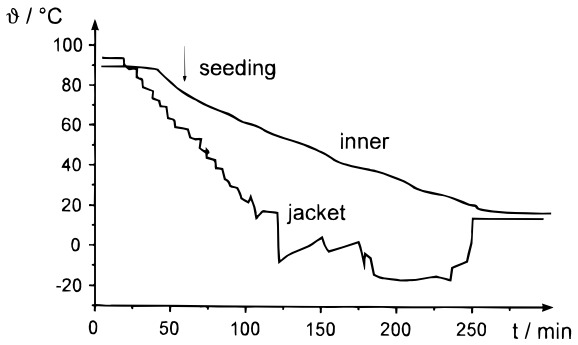

Figure 6. **Inner temperature and jacket temperature for the production runs. The maximum difference is 60 K to achieved a cooling rate of 0.3 K/min.**

Further Changes. The 1−5% of C modification obtained in the first pilot plant batch, P1, triggered modifications for the two following batches, P2 and P3, both for the seeding procedure and the workup.

For the seeding, the time between preparation of the seed and its introduction into the vessels was shortened to ≤5 min, and the seed was added 2−3 K earlier. As concerns the workup, the suspension was centrifuged immediately after 30 °C was reached, and the crystals were immediately transferred to the dryer after completion of the centrifugation process. Both measures shortened the time from crystallization to drying by ∼2 h, a time in which the crystals are moist and prone to a solution-mediated phase transformation. Finally, the thickness of Abecarnil on the trays of the truck dryer was decreased from 4 to 1 cm to speed up the drying process.

As can be seen from Table 3, the two pilot plant batches P2 and P3 produced crystals of pure A modification.

Characterization of the End Product

The crystal habit of the end product is different to the one usually observed for the A modification. Figure 7 shows a micrograph of A obtained via an unseeded crystallization from methanol and via seeding from isopropyl acetate. In the first case, the A modification crystallizes in very thin needles, a habit that might be in part due to the high supersaturations at which the nucleation and first stages of the growth occur. Contrarily, the seeding process yields anisotropic slabs, a habit expected for the A modification using algorithms for the prediction of the crystal habits.[11]

For seeding strategies to be successful, it is important that the crystals obtained can be used as seed. This point gains

Figure 7. **SEM micrographs of crystals of the A modification of Abecarnil obtained via an unseeded cooling crystallization form methanol (top) and photomicrograph of crystals of the A modification obtained via the seeded cooling crystallization (bottom). Note the differences in the scale bars.**

Table 4. **Modification of crystals obtained for different types of seed[a]**

	modification	
batch	seed	end product
P1	A + 5%C	A + 50%C
P2	A	A

[a] If a seed containing 5% C is used, the end product will contain more than 50% of C.

importance with the amount of seed used. The crystals produced in the three pilot plant batches were used as seeds in laboratory experiments. The results summarized in Table 4 show that the seeding process developed yields crystals that can be reused as seeds. However, the seeds have to be free of any detectable amounts of the C modification, as the 5% of C present in batch P1 proliferate to 50% during the crystallization.

Conclusions

A seeding method was developed to access the unstable A modification of Abecarnil from isopropyl acetate as solvent. In an unseeded crystallization, this solvent usually yields the second unstable modification of Abecarnil, the B modification.

A prerequisite for the method to be successful is a sufficient stability of the desired modification in suspension against a transformation into the thermodynamically stable C modification for periods long enough for the process to be completed.

The effective development of the seeding method was facilitated by the availability of the solubilities of all modifications as a function of temperature and of the width of the metastable zone. While information on the metastable zone width is easily generated, the determination of the solubilities is more time-consuming. Here, thermodynamic considerations might facilitate the task. Finally, the knowledge of the thermodynamics and kinetics of the phase transformations from the unstable to the more stable forms are valuable for the estimation of permissible times.

To speed up the crystallization process, knowledge on the completeness of the crystallization process as function of time were valuable. For the present case, the crystallization is complete within minutes after reaching the final temperature, so that the times for stirring post cooling can be kept to a minimum. This decreases the risk of a solution-mediated phase transformation.

It is worth mentioning that, from a production standpoint, the first choice for the modification is the stable one. If an unstable modification is chosen, the influence of impurities should be assessed, e.g., by investigating the behavior of a thoroughly purified laboratory batch. If an unstable form is to be produced, seeding might be an alternative, as presented for Abecarnil.

Experimental Section

The laboratory experiments were carried out in 100 mL and 1 L jacketed glass reactors equipped with a marine propeller. The temperature profile was realized by a computer-controlled thermostat.

The solutions to be crystallized were prepared in the laboratory as 10 g of Abecarnil dissolved in 100 mL of isopropyl acetate. To dissolve the Abecarnil completely, a jacket temperature of ∼90 °C, corresponding to ∼88 °C inner temperature, was used. These temperatures correspond to conditions close to the boiling point of the solvent. It is important to verify that all Abecarnil dissolves during this process and even more important that a crust of Abecarnil formed during the dissolution process is completely dissolved prior to cooling. Such a crust can consist of a mixture of all three polymorphs.

The totally clear solution was cooled to 80 °C with a rate of 1−2 K/min and further cooled to 20 °C with a linear rate of 0.1−1 K/min.

In the pilot plant, pairs of 1200 L steel vessels with an enamel coating on the inner surface were used. They were equipped either with an impeller or an anchor stirrer and had an immersion tube for the temperature probe that acted also as a flow breaker. The dissolution was performed in the first vessel with an ∼80−100% excess of solvent. The solution was filtered into the second vessel for crystallization. In this second vessel, the excess amount of solvent was removed by a boiling process until a concentration of 10 kg per 100 L of solution was reached. This boiling process can give rise to a crust that has to removed as discussed above.

The concentration of Abecarnil in both the laboratory and pilot plant was 10 g/100 mL corresponding to a saturation temperature for the A modification of 78 °C (cf. Figure 2). For the moderate cooling rates of 0.3−2 K/min, the temperature for the spontaneous nucleation of the B modification is ∼68−70 °C.

Samples of the suspension were withdrawn from both the laboratory and pilot plant vessel at different stages of the process and dried on a clay disk. An analysis for the modification using both DSC and powder X-ray techniques[14] were performed in our Department of Applied Physical Chemistry. Both techniques can determine qualitatively the presence of one polymorph in the other on the 5% level. However, only qualitative information can be given for the content of mixtures of the modifications.

Acknowledgment

The authors thank Dr. Otto and Mr. Mertins for their the laboratory work and Drs. Rehme and Lopez for their help in performing the pilot plant work. Thanks are also due to Dr. Winter for the characterization of the polymorphism of numerous samples.

Received for review March 23, 1998.

OP980029B