Organic Process Research & Development **2001**, *5*, 387−392

Crystallisation of the Stable Polymorph of Hydroxytriendione: Seeding Process and Effects of Purity

Wolfgang Beckmann,* Wolfgang Otto, and Uwe Budde
Chemical Engineering Department, Schering AG, Berlin, Germany

Abstract:
The drug substance hydroxytriendione has been found to exist in three modifications, which are equal in their pharmaceutical profile and are equally stable. Thus, Form II, the polymorph thermodynamically stable at room temperature, was chosen as the solid-state form for the active pharmaceutical ingredient. Spontaneous nucleation will lead to either of the two other forms. Thus, a seeding process was developed to ensure the reproducible crystallisation of the desired Form II. The solvent used for crystallisation was chosen according to the preparative HPLC method used to prepare the crude material, and the solubility was modified by using an appropriate cosolvent. The measurements and data necessary to develop this process are described. The process has been successfully transferred to production with extremely limited data on the system. Careful consideration shows that the conditions chosen are valid only for an impure system. A pronounced influence of the purity of the starting material on the window of seeding has been found. The point of addition of the seed should be determined according to solubility and experimentally via the addition of small amounts of seed to a continuously cooled solution.

1. Introduction

Polymorphism is a widespread phenomena observed for more than half of all drug substances.[1] The choice of the most appropriate solid-state form is of considerable importance. One aspect to be considered is stability, which means the thermodynamic stability of the solid state forms, as well as the chemical stability and the stability against excipients. In most cases, the modification thermodynamically stable at room temperature is the most appropriate one. This is the solid-state form into which all other forms will eventually transform. However, high energy processes such as milling can induce transformation to a form not stable at room temperature. This transformation can lead both to another crystalline or an amorphous state and is not necessarily complete.

Several techniques have been proposed to determine the thermodynamically stable form, for example, measurements of solubility,[2] observing the development of a mixture of forms in suspension,[3] thermoanalytical data such as the melting points of the pure polymorphs or the behaviour of eutectic mixtures at reduced temperatures,[4] and enthalpy-temperature diagrams.[5,6]

According to Ostwald's rule of stages,[7] an unseeded crystallisation that relies on spontaneous nucleation will in most cases yield a metastable form. Although this unstable form will eventually transform into the stable one, the transformation may be slow as well as incomplete. This latter process is often called solution-mediated phase transformation.[8,9] However, as it may be slow and incomplete, it is attractive to use seeding techniques to grow the stable form in the first place. Few accounts of seeding techniques to control polymorphism during growth have been published.[10−13]

The development of a seeded crystallisation process for the thermodynamically stable form is more or less straightforward, as in no instance does a danger exist of losing this form, for example via a solvent-mediated phase transformation. In addition, any small amounts of an unstable modification present will undergo a solution-mediated phase transformation to the stable modification, so that the process is self-regulating. Only the border of the metastable zone should be avoided so that no spontaneous nucleation of an unstable form occurs. Thus, only a minimum of data, effort, and amount of substance should suffice. The data necessary to select the crystallisation technique and to determine the point of seeding includes solubility and metastability.

If the crystallisation process is to be developed early during the development, the amount of material available may be small, and the purity may be low. It is well-known that impurities can have a pronounced and often unpredictable effect on any crystallisation process. In most cases, impurities will hamper nucleation, leading to an increased metastable zone width and a decreased rate of crystal growth. A large number of examples can be found in the literature,

* Author for correspondence. Chemical Engineering Department, Chemical Development, Schering AG, D 13342 Berlin, Germany. Telephone: ++49-30-468-15076/ Fax: ++49-30-468-18196. E-mail: wolfgang.beckmann@schering.de.

(1) Henck, J.-O.; Griesser, U. J.; Burger, A. *Pharm. Ind.* **1997**, *59*, 165.
(2) Beckmann, W.; Sato, K.; Boistelle, R. *J. Chem. Eng. Data* **1984**, *29*, 211.
(3) Sato, K.; Suzuki, K.; Okada, M.; Garti, N. *J. Cryst. Growth* **1985**, *72*, 699.
(4) Yu, L.; Stephenson, G. A.; Christine, A. M.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J. J.; Borchardt, T. B.; Stowell, J. G.; Byrn, S. R. *J. Am. Chem. Soc.* **2000**, *122*, 585.
(5) Burger, A.; Ramberger, R. *Microchim. Acta* **1979**, *2*, 259 and 273.
(6) Yu, L. *J. Pharm. Sci.* **1995**, *84*, 966.
(7) Mullin, J. W. *Crystallisation*, 3rd ed.; Butterworth-Heinemann: Oxford, 1993.
(8) Cardew, P. T.; Davey, R. J. *Proc. R. Soc. London* **1985**, *A398*, 415.
(9) Davey, R. J.; Cardew, P. T.; McEwan, D.; Sadler, D. E. *J. Cryst. Growth* **1985**, *79*, 648.
(10) Beckmann, W.; Budde, U.; Nickisch, K. *Org. Process Res. Dev.* **1998**, *2*, 298.
(11) Beckmann, W. *Org. Process Res. Dev.* **2000**, *4*, 372.
(12) Marti, E.; Oechslein, W.; Geoffroy, A. J. Patent WO 99/10333.
(13) Chemburkar, S. R.; Bauer, J.; Deming, K.; Spiwek, H.; Patel, K.; Morris, J.; Henry, R.; Spanton, S.; Dziki, W.; Porter, W.; Quick, J.; Bauer, P.; Donaubauer, J.; Narayanan, B. A.; Soldani, M.; Riley, D.; McFarland, K. *Org. Process Res. Dev.* **2000**, *4*, 413.

10.1021/op010013c CCC: $20.00
Published on Web 05/25/2001

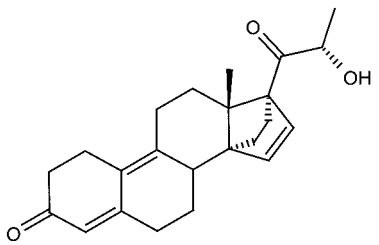
showing effects both on the ppm scale for some impurities, as well as on the 1−10% level.[14,15]

Two types of analytical data have to be discerned, the assay and the purity. The assay quantifies the actual amount of compound in the sample, correcting both for structurally related substances as well as for unknown ones, such as solvent. The purity is usually established via a 100% HPLC analysis and provides information on the amount of structurally related substances present in the sample. The assay is less than or equal to the purity data. In the case of crude material, the inequality between purity and assay might be considerable. The assay of the material should be taken into account when calculating the concentration and, thus, the saturation temperature of the starting solution. The purity, which gives information on the concentration of related substances, is the most important information indicating the influence of impurities on the kinetics of nucleation and on crystal growth.

In this contribution, the development of a seeding process for the stable modification of a steroid, hydroxytriendione, will be discussed. Only small amounts of material were available for the development so that micro-methods for the determination of important parameters had to be used. The purity of the crude material was low. However, it will be shown that the purity of the various crude materials does not influence the equilibrium solubility. However, the purity does have an overwhelming influence on the width of the metastable region and, thus, on the window of seeding.

2. Polymorphism of Hydroxytriendione and Choice of Solid-State Form

Hydroxytriendione,[16] (21*S*)-21-Hydroxy-21-methyl-14,-17-ethano-19-norpregna-4,9,15-triene-3,20-dione, **I**, is a gestagene having no androgen potential. The polymorph



I

screening for hydroxytriendione revealed three modifications, named I, II, and III. All three forms are an-solvates and no hints of a formation of a pseudopolymorph were found. All three forms can be discriminated unambiguously via X-ray powder diffractometry.

A cursory measurement of the solubility of all three modifications of **I** in water at a temperature between 5 and 40 °C shows Form I to be the least stable one. However, the solubilities of both II and III are equal within the experimental margin of error. Thus, a mixture of Forms II and III was stored at temperatures between 20 and 50 °C in water−ethanol mixtures. At temperatures of 40 and 50 °C, a transformation to Form III occurred, while at 20 and 30 °C a transformation to Form II showed the latter to be the stable one at room temperature.

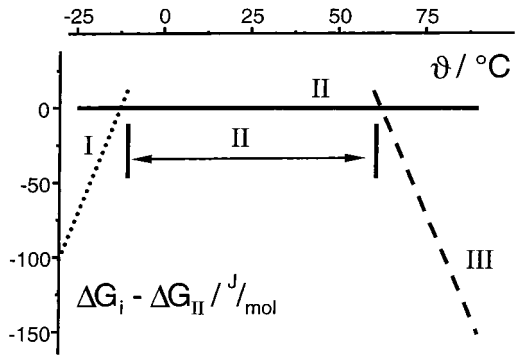


Figure 1. **Enthalpy-temperature diagram for the three modifications of hydroxytriendione using enthalpies and temperatures of fusion. The data are referenced to Form II to discern the minute differences between the forms. The lines show Form II to be the most stable one at and around room temperature.**

These findings have been corroborated using temperature and heat of fusion data for all three forms. For the determination of these values, DSC experiments were used, as no solid-state transformation occurs up to the melting point of the respective forms. The values obtained and used here are 70.0, 65.7, and 60.5 J/g and 105, 116.5, and 122 °C for Forms I, II, and III, respectively.

The free enthalpy of any modification can be written as $\Delta G = \Delta H - T\Delta S$. By plotting ΔG as a function of temperature, the intersection of the ΔG curves indicates the transition temperature and, most importantly, the modification with the lowest ΔG value for a given temperature is the stable one. For modifications thermodynamically close, it is more convenient to reference ΔG to a certain form, Form II in the present case, and to plot the difference $\Delta G_i - \Delta G_{II}$, with i being either Form I, II, or III. Negative values of ΔG for a certain form indicate that this form is more stable than the reference (Form II). In the present discussion, the Δc_p terms have been precluded due to the small range of temperature covered. The enthalpy-temperature diagram in Figure 1 corroborated the experimental results that Form II is stable at room temperature.

All three forms undergo a partial phase transformation upon comminution, for example up to 5% of Form III is generated when milling Form II. This point is of importance both to the use of the compound in pharmaceutical applications as well as to the development of seeding processes. For seeding, a large surface area, which can be generated by milling, is desired. But, if polymorph purity plays a role, such as in the seeding of a metastable form, this transition might cause problems.

An assessment of the chemical stability and stability against excipients showed no preference for any of the forms, so that the form thermodynamically stable at room temperature was chosen as the solid-state form for the drug substance.

(14) Beckmann, W.; Behrens, M.; Lacmann, R.; Rolfs, J.; Tanneberger, U. *J. Cryst. Growth* **1990**, *99*, 1061.
(15) Hendriksen, B. A.; Grant, D. J. W. *J. Cryst. Growth* **1995**, *156*, 252.
(16) Schöllkopf, K.; Halfbrodt, W.; Kuhnke, J.; Schwede, W.; Fritzemeier, K.-H.; Krattenmacher, R.; Muhn, H.-P. Patent WO 96/20209.

Table 1. **Solubility of hydroxytriendione in MIBK and MIBK−DIPE mixtures[a]**

	c_{sat}/g/mL$_{solvent}$		
ϑ/°C	MIBK	MIBK:DIPE 1:3	DIPE
75	.8	-	-
65	.7	-	-
25	.12	.03	.001
−10	.1	-	-

[a] The purity of the material was ≤95%. Throughout this paper, the dimensions used are mass of solute per volume of solvent on a solute-free basis.

Crystallisation experiments using a variety of solvents, as well as cooling and evaporative crystallisation techniques, revealed the formation of either the unstable Form I or the unstable Form III. Thus, a seeding process which arrives reproducibly at the desired Form II was developed.

3. Fast-Tracking Development of a Crystallisation Process

Because of the very short project timelines, the development of the crystallisation process had occurred quickly. This necessitated prompt decisions on the solvent of crystallisation as well as on the crystallisation and seeding process, all done with only the minimal data and the low-purity material available in the early stages. The development and successful transfer to the pilot plant will be described first. To ensure a stable process, the database was later broadened. The information gathered shows that at least some of the process parameters chosen were valid only for the impure crude material, emphasising the important influence of impurities on crystallisation processes.

3.1. Choice of Solvent of Crystallisation and Preliminary Solubility. The crude material for the crystallisation process of hydroxytriendione comes from production scale HPLC chromatography that uses a mixture of hexane and methyl isobutyl ketone, MIBK, as eluent. While hexane is readily removed by distillation, MIBK has a high boiling point. Its removal or re-distillation to other solvents would result in a thermal stress on the substance. According to the ICH guideline,[17] MIBK is a class 3 solvent with an upper limit of 0.5% in the drug substance (case 1 of the ICH guideline). Thus, MIBK was chosen as the solvent for crystallisation.

The solubility of hydroxytriendione in MIBK, Table 1, has a sufficient temperature dependence so that a cooling crystallisation was used. However, absolute solubility in MIBK is high. For a crystallisation with sufficiently high yields, this would result in a high-suspension density.

Preliminary experiments had shown that the use of isopropyl ether, DIPE, as a solvent has a favourable influence on the purification of hydroxytriendione. Limited measurements of the solubility of hydroxytriendione in MIBK−DIPE mixtures showed that the solubility varies nearly linearly with the composition of the MIBK−DIPE mixture, Table 1. Thus, DIPE can be used as a cosolvent to modify solubility. DIPE has not yet been classified by the ICH guideline as to its toxicological potential. Nevertheless, it was decided to crystallise hydroxytriendione from a mixture of MIBK and DIPE.

3.2. Crystallisation and Seeding Process. According to the limited data gathered, Table 1, cooling crystallisation was chosen as a convenient crystallisation technique for the seeding process. The temperature level was set at 70 °C for the saturation of the solution, and cooling was set to end at 20 °C. This should lead to a theoretical yield of ∼85%. The initial concentration was set at 1 g/mL$_{MIBK}$, that is, referenced to the amount of MIBK.

A limited number of experiments showed that a suspension density of 1 g/mL could not be stirred, while a suspension having a density of 0.7 g/mL could be stirred. Thus, a ratio of MIBK:DIPE of 5:3 was selected to ensure a suspension easily stirred. This ratio results in a decrease of the density of the suspension of ∼30%.

Because the stable Form II was to be seeded, only a few precautions had to be taken for the generation and preparation of the seed. The seed initially used originated from the polymorph screening. The small amount available was used in a first seeding experiment to yield larger and sufficient amounts of Form II for the experiments to follow. The latter batch was characterised in depth and shown to consist of pure Form II. X-ray powder diffractometry gave no indication of the presence of the other two forms. The limit of detection is estimated to be <5−10%.

Prior to addition, the seed was suspended in DIPE at room temperature to activate the surface by dissolution. However, it was not ground to increase the surface area due to the partial transformation into Form III which would occur, see above. On the basis of the results of other seeding processes,[10] the amount of seed was set at 0.1−1%, while the rate of cooling was kept at −0.25 K/min, which is relatively slow. Finally, the addition was set to occur at low supersaturations.

The width of the metastable zone defines the upper limit at which the seed may be added. Due to the fast tracking and the fact that the thermodynamically stable form was desired, the width was only roughly determined by recording the temperature of spontaneous nucleation in an uncontrolled cooling crystallisation. During the early stages of the development, this nucleation occurred at high subcoolings of 10−20 K.

Thus, the selection of the point of seeding was straightforward, seeds were added at a point somewhere around 10K into the metastable region using the solubility given in Table 1, that is, at 52 °C for a concentration of 1 g/mL$_{MIBK}$. The point of addition of the seed was varied slightly for several crystallisations always yielding the desired Form II.

Crops of one seeding process have been used as seeds for further seeded crystallisations; yielding again Form II unambiguously shows that the crops of the crystallisation process can be reused for further seeding. Again, as a stable modification was sought, only a few experiments were sufficient to confirm the further use of crops as seed.

(17) ICH guideline Q3C, European Agency for the Evaluation of Medical Products, 1997, http://www.eudra.org.

Table 2. **Assay and purity of the two crude materials used for the seeded cooling crystallisation of hydroxytriendione as well as the yield and purity of the crop**

	crude material		crop			
batch	assay, %	purity, %	yield, %	assay, %	purity, %	form
A	75	92	72	98	97.0	II
B	95	98	89	98	99.7	II

Table 3. **Residual solvent content of batch B both for the dried crop of the crystallisation and for the micronised material**

	$c_{solvent}$/ppm	
state of batch B	MIBK	DIPE
macro	500	300
micronized	220	60

3.3. Transfer to Pilot Plant. On the basis of these few experiments, the seeding technique was transferred to the pilot plant, where it worked successfully in two batches. The seed used was prepared in the laboratory.

The assay and purity data for the crude material, as well as for the first crop of the crystallisation process and its yields and polymorphic forms, are summarised in Table 2. In essence, the fast-tracking development and the process were successful.

The residual solvent content of batch B was determined both for the dried crop and for the milled material. The solvent content is sufficiently low and undergoes a further decrease by a factor of 3−5 upon milling, Table 3.

4. Development Revisited: Stability of the Crystallisation Process

The conditions used for the crystallisation and especially for the seeding process were reworked to ensure a stable process. A discussion of the results supports the assumptions made during development and may clarify some arguments. In addition, the results reveal some drastic effects of purity that should be considered both during the early stages of development and during scale-up.

4.1. Measurements of Solubility. The solubility of hydroxytriendione in MIBK and MIKB−DIPE mixtures was assessed for the hydroxytriendione from the crystallisations in the pilot plant, which have a purity of ≥99%. These data can be compared with the data determined from impure material, summarised in Table 1. As the effects of various assays of the material are to be compared, the concentrations were corrected for the assay, that is, $c_{corr} \equiv c{\cdot}assay$, Figure 2. It can be seen that the purity of the material has no significant influence on the equilibrium solubility. Although the activity of the solute does decrease with the amount of impurities present in the solute, the effect is negligible. The heat of dissolution estimated from the data is ∼30 kJ/mol, which corresponds with the enthalpy of fusion determined via DSC.

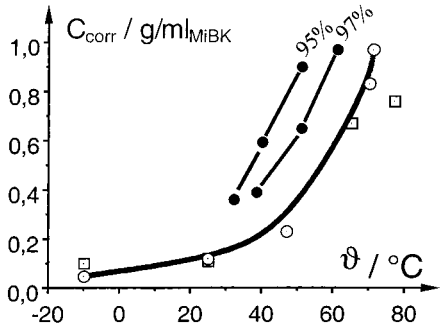


Figure 2. **Solubility and width of the metastable region of hydroxytriendione in MIBK as a function of temperature. The solubility data is for materials with a low purity of ≤95% −⊡− and a high purity of ≥99% −⊙−, and the width of the metastable region was determined with material with a purity of 95 and 97%.**

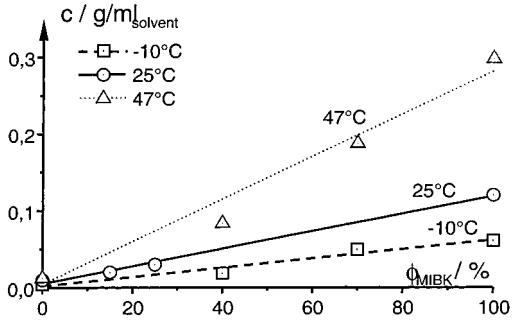


Figure 3. **Solubility of hydroxytriendione in mixtures of MIBK and DIPE at −10 to 47 °C. Considering the experimental margin of error, the solubility varies linearly with the composition of the solvent.**

The solubility of hydroxytriendione in mixtures of MIBK and DIPE has been determined at −10, 25, and 47 °C, Figure 3. As stated, the solubility of hydroxytriendione varies linearly with the amount of cosolvent added to the primary solvent. Using c_{MIBK} and c_{DIPE} to represent solubility in the pure solvents and ϕ_{MIBK} and ϕ_{DIPE} to represent the volume fractions of the two solvents, the solubility can be approximated via $c = c_{MIBK}{*}\phi_{MIBK} + c_{DIPE}{*}\phi_{DIPE}$. Because $c_{DIPE} \ll c_{MIBK}$, one can write $c \approx c_{MIBK}{*}\phi_{MIBK}$. Thus, the solubility is given by the one referenced to the volume of MIBK. This is convenient for the development of the crystallisation process, as the solubility measurements for pure MIBK as a function of temperature can be used directly for all MIBK−DIPE mixtures. In addition and more importantly, the suspension density can be varied easily by adding DIPE.

It is noted that this behaviour is only one of several possibilities, more often concavely shaped solubility curves are found, enabling a drowning-out crystallisation.[7]

4.2. Measurements of Metastability. The width of the metastable region was determined with ∼0.5−1 mL of solution, using the laboratory set-up already described.[11] The results of experiments to determine the influence of (i) the purity of the material, (ii) the ratio of the primary solvent MIBK and the diluting solvent DIPE, and (iii) different cooling rates are listed in Table 4. Also given is the equilibrium solubility. For a given concentration referenced to the primary solvent and a given purity of the material, the width of the metastable region does not significantly

Table 4. **Influence of the cooling rate and mixing ratio of the two solvents MIBK and DIPE on the temperature for spontaneous nucleation[a]**

				$\vartheta_{spontaneous\ nucleation}$/°C		
c_o g/mL	MIBK:DIPE vol:vol	c_o g/mL$_{MIBK}$	$-d\vartheta/dt$ K/min	95% purity	97% purity	ϑ_{sat}/°C
0.625	1:0.6	1.0	4	51	61	71
			1.5	51.5	60.5	
0.66	1:0	.66	4	39	52	62
			1.5	41	50.5	
0.4	1:0	.4	4	27	38	51
			1.5	34.5	40	

[a] Data are given for two different qualities of materials with a purity of 95 and 97%. Also tabulated are the saturation temperatures, which can be used to calculate the width of the metastable zone

depend on the amounts of DIPE added to MIBK. Within the limits, the rate of cooling also has only a negligible influence on the width of the metastable zone. As is to be expected, the width increases slightly with an increasing cooling rate; however, due to experimental errors, some points do not reflect this.

However, the assay (and thus purity) of the crude material has a pronounced influence on the width of the metastable region. The width or the degree of subcooling necessary for spontaneous nucleation nearly doubles when going from pure, 97%, to less pure, 95%, assay material. Although tempting, no correlation of the width of the metastable zone to the assay is made. The assay is entirely unspecific as to what impurity has been reduced. More importantly, only an extensive investigation could possibly show which impurities inhibit the nucleation process.

Figure 2 shows the lines of the metastable zone width for 95 and 97% purity together with the solubility line. In essence, the window of successful seeding is narrowed down considerably by increasing the purity of the material. This is an important point to be considered when transferring and especially when improving synthesis.

4.3. Determination of the Point of Seeding. During the initial development of the seeding process, the point of seeding was set quite arbitrarily using the inaccurate solubility data given in Table 1, and using the fact that spontaneous nucleation occurred at high subcoolings of $\Delta T \geq 10-20$ K, for the highly impure material. With this setting, crystallisations yielded the desired Form II. The point of addition of the seed in the pilot plant batches was 1 g/mL$_{MIBK}$ at 50 °C uncorrected for the assay. Using the assays given in Table 2, this transforms into $c_{corr} \approx 0.8$ g/mL$_{MIBK}$ for batch A and $c_{corr} \approx 0.95$ g/mL$_{MIBK}$ for batch B. This lies within the region of metastability for lower and outside for higher purity material, cf. Figure 4.

The interval for seeding has been shown[11] to start shortly above saturation and to end well before the border of the metastable zone. The width of this interval depends on the operation conditions, such as the rate of cooling. The crossing of the saturation line is the earliest point of seeding independent of the operation conditions, so that it is defined as the point of seeding.

Table 5. **Comparison of the points of seeding for solutions with and without the addition of cosolvent DIPE and for solutes with a purity of 95 and 97%[a]**

MIBK:DIPE vol:vol	c_o g/mL$_{MIBK}$	$\vartheta_{seeding}$/°C		ϑ_{sat} °C
		95% purity	97% purity	
1:none	.66	60	64	62
3:2	1.0	71	71	71

[a] Also given are the saturation temperatures, ϑ_{sat}, according to Figure 2, indicating the confidence in the determination of ±2 K.

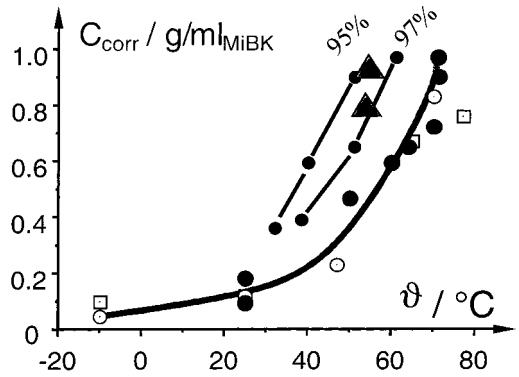


Figure 4. **Points of seeding, ●, as developed by the trial-and-error method for materials with an assay of 95 and 97%. Also given are the points of seeding in the plant, upper ▲ for batch B and lower ▲ for batch A. The data can be compared with the width of the metastable zone for the different materials and with the equilibrium solubility. Note that the concentrations are corrected with the assay.**

The point of seeding can be directly taken from solubility data; however, to show equivalence, the solubility data was supplemented with data arrived at by using the trial-and-error method.[11] Solutions with known concentrations were continuously cooled at 1−5 K/min, and seeds were added every ∼2 K, that is, every 1−2 min. The temperature at which the seed added no longer dissolved but started to grow was recorded as the highest temperature for the addition of the seed. Typically, three to four trials were necessary before the seed ceased to dissolve.

Four experimental points are summarised in Table 5, showing that the amount of cosolvent DIPE added and that the purity level of the solute does not influence the point of seeding. This behaviour is to be expected, as the dissolution and growth of the seed depends on solubility that is not significantly affected by impurities. Only kinetic processes such as spontaneous nucleation or the kinetics of dissolution and growth are slowed by impurities. Table 5 suggests the seeding at or even above a temperature where Form II becomes unstable and Form III is the thermodynamically stable one. As stated above, the transition occurs at ∼67 °C. Seeding some few Kelvins into metastability does not pose any danger when a properly prepared seed is used and as the region of stability of Form II is quickly reached.

All points of seeding are given in Figure 4 and cluster around the solubility curve. From a comparison of the new points of addition of the seed, it can be seen that these points are within the experimental margin of error both of the measurements of solubility as well as the margin of error in

the preparation of the solutions and the measurement of temperature, Figure 4. This is the way the system should behave. These errors are on the order of ±2K. Figure 4 also shows the point of addition used in the first development of the process. A comparison with the width of the metastable zones for different purities shows the point to be outside the metastable region for a pure material. Thus, the conditions initially chosen and applied in the first batches only work if impure material with a large metastable zone width is used.

5. Seeding of the Metastable Form I

Finally, it should be noted, that seeding for metastable Form I was also tried, using the process parameters described above and developed for Form II. For the seeding of a metastable form, polymorphic purity plays a role. As hydroxytriendione undergoes a phase transformation upon comminution, the use of larger grains was selected. The modification obtained was Form I.

The success can be rationalised by the derivations made above. Although the solubility was assessed only for Form II, the difference in solubilities can be derived from the thermoanalytical data. Figure 2 suggests the maximum in the difference in the free enthalpy of any of the forms to be $\Delta G \leq 400$ J/mol over the entire range of temperatures, that is, −25 to +100 °C. This transforms into a maximum supersaturation of any of the unstable polymorphs of $\sigma_{max} \leq 15\%$ or into a maximum difference in saturation temperatures of $\Delta T_{max} \leq 5$ K. This is well within the zone of metastability of the system, even for the pure starting material. Thus, no danger of spontaneous nucleation exists.

It has been shown for Abecarnil that a properly prepared seed is possible to yield an unstable modification in high polymorphic purity.[10]

6. Conclusions

Hydroxytriendione is found to exist in three modifications. From an assessment of the pharmaceutically relevant properties of the forms, such as stability, a decision to use the thermodynamically stable Form II was made. The thermodynamic stable form is also the most readily accessible form. To make the crystallisation process stable, a seeding procedure was chosen.

The crystallisation process was developed with a minimum amount of material, data, and time. The choice of the solvent of crystallisation was determined by the solvent mixture used in the upstream preparative-HPLC process and by using a second solvent that modified the solubility in a linear manner. The point of addition of the seed was roughly estimated from solubility data and the width of the metastable zone. With this limited data, the thermodynamically stable form could be reliably accessed. Two factors contribute to this success, the stable modification was called for, and the amount of seed used was sufficiently high in relation to the rate of cooling.

The results from the fast tracking were tested to determine the boundaries for the process. It was found that the assay of the crude material has a pronounced influence on the metastability of the system, namely the width decreases with increased purity. As the width of the metastable zone determines the window of seeding, this effect has a pronounced effect on operating conditions. Thus, it is preferable, even during fast-tracking development, either to use purified material to determine kinetically controlled values such as metastabilities or, at least, to take the purity of the crude material into consideration. Fortunately, thermodynamic quantities such as solubility are nearly independent of the purity.

The point of seeding can be deduced experimentally by adding small amounts of seed to a continuously cooled solution. It was shown, that the point of seeding thus obtained is independent of the purity of the material. All data, solubility, metastability, and points of seeding, should be plotted, for example in a c-ϑ-diagram like Figure 4.

In essence, the development of a crystallisation process for the thermodynamically stable form is straightforward, especially if a seeded crystallisation process is used. Limited but carefully chosen data suffices to develop the process.

Experimental Section

The crude material was synthesised at Schering. The immediate step before crystallisation was a preparative HPLC using a MIBK−hexane mixture as eluent. The method was optimised to remove the educt of the prior synthetic step and not specifically to remove impurities.

The solubility of hydroxytriendione was assessed using a simplified flask method. To keep the measurements as simple and straightforward as possible, the modification of the residue was not assessed as the three modifications are quite close and as previous experiments have shown, the time required for equilibration suffices for the residue to undergo a complete solvent mediated phase transformation to the stable form.

The modification of the batches was determined using a STOE Powder diffractometer and by using a small linear position-sensitive proportional counter. The samples were prepared between two polyacetate films held together by double-sided adhesive tape.

Acknowledgment

We are in indebted to Dr. Gabriele Winter for providing the first seed of Form II and for determining the modifications of the batches produced during the development of the process and to Dr. Carlo Skötsch and Mr. Peter Knackmus for their help in transferring the seeding process to the pilot plant.

Received for review February 6, 2001.

OP010013C