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Example of Finishing Technologies as Key Elements for Successful Active Pharmaceutical Ingredient Process Development

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Abstract:

Little has been published so far to emphasize the role of finishing technologies (crystallization, filtration, drying) as crucial elements for successful process development of active pharmaceutical ingredients (APIs). In the presented example high marketing forecasts stressed the objective for the process to be robust, simple, and tailor-made for high-volume production. The major hurdle was the purification of the reaction mixture of an intermediate containing inorganic salts, polymers, isomers, and colored byproducts that needed to be separated. Systematic application of finishing technologies paved the way to a commercial process. Removal of colored byproducts and isomers was found to be the most challenging task after separation of inorganic salts by quench and of polymers by charcoal treatment. The problem was resolved in three steps. First, solvent screening for the crystallization yielded toluene to be most efficient to separate colored byproducts. Second, solubility measurements of product and isomers provided an operating range of the process parameters for an economic crystallization at an unusually high concentration (60% w/w). Isomers could be separated since they remain soluble at endpoint temperature. To avoid the problem of wall crusts during scale-up, the metastable range was estimated experimentally. And third, near-infrared spectroscopy was implemented as an on-line measurement method for the product concentration in toluene to determine the endpoint of evaporation and thus to facilitate robustness and yield optimization. As further result of proper elaboration of crystallization conditions the crystals exhibited compact cubic morphology and large size. Consequently, filtration and washing of the wet product cake were efficient, and the drying process could be eliminated before continuing with the next synthesis step.

Introduction

Once introduced into production, robust processes that afford excellent and reproducible product quality and yield are the basis of acceptance by the health authorities and for solid profitability. While much has been published to illustrate the role of organic chemistry as a key innovator in process development of active pharmaceutical ingredients (APIs),[1,2] often major hurdles upon scale-up are represented by physics-related issues. They usually surface as technical problems such as long filtration and drying times or as unreproducible physical properties of the API such as polymorphism[3,4] or scattering particle-size distributions.[5] These deviations affecting manufacturing or stability of the dosage form are unacceptable.

Therefore, finishing technologies—such as crystallization, filtration, drying—are an important and growing field in the pharmaceutical industry to meet demanding shorter development times, fast process scale-up, smooth process transfer from pilot to production facilities and tailor-made physical product properties, which have become key success factors in the technical development of the pharmaceutical industry.

In the present example, high marketing forecasts stressed the objective for the process to be robust, simple, and tailor-made for high-volume production. The major hurdle was the purification of the reaction mixture of an intermediate (intermediate 7, abbreviation: I7) containing inorganic salts, polymers, I7-isomers, and colored byproducts that need to be separated. In this contribution we describe the systematic application of state-of-the-art finishing technologies to develop a commercial process.

The Early-Phase Workup Process

The process used to manufacture the early-phase clinical batches utilized a complex workup that was not suitable for high-volume production. The procedure involved the use of three different organic solvents, two charcoal treatments, and two crystallization and isolation steps. Thus, after completion of the reaction in toluene, the mixture was quenched with water followed by phase separation. The organic phase was treated with charcoal, and then toluene was exchanged with 2-propanol by azeotropic distillation. After a second charcoal treatment I7 was crystallized and isolated crude. The crude

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Table 1. **Results of absorbance of solution measurements of crude residue vs crystallized I7[a]**

solvent	absorbance of crude residue	absorbance of crystallized I7
ethanol	0.3	0.07
2-propanol	0.3	0.12
toluene	0.3	0.02
acetone	0.4	0.03
ethyl methyl ketone	0.4	0.02

[a] Results of solvent screening for crystallization of I7. Error of measurements: ±0.001.

product was then recrystallized from ethanol to ensure optimal color since colored byproducts could not be further separated in later synthesis steps.

Results and Discussion

1. Removal of Salts and Polymers. Salts were removed by quench and extraction of the reaction mixture in toluene−water followed by phase separation.

Charcoal treatment of the organic phase was necessary mainly to remove polymers that interfered with the crystallization process. Crystallization experiments conducted without charcoal treatment yielded nonhomogeneous and strongly colored product as lumps! Charcoal treatment was found to be useful also to improve the color of the product in case of very dark organic phase.

The amount of charcoal was reduced to 1% (w/w) compared to 5% in the original process. The treatment time was optimized to be 1 h. The results were the same at a temperature range from 60 to 90 °C. Prior to commissioning, the charcoal filter cake was determined to be incompressible.[6] Lower filter area to batch size ratio in production compared to that in the lab could thus be compensated by a higher filtration pressure, which was confirmed during commissioning.

2. Colored Byproducts: Removal by Proper Choice of Crystallization Solvent. Essential for the robust workup process is the removal of colored byproducts. A number of solvents were screened for the crystallization of I7 to find a suitable solvent that would most efficiently remove the color. From the tested solvents, toluene and ketones were found to be more efficient than alcohols on the basis of absorbance measurements (Table 1). The crystals from toluene exhibited compact cubic morphology and could be grown to large size (Figure 1: several 100 μm) which could be further exploited in many respects.

3. Isomers: Separation by Elaboration of Robust Crystallization Conditions. This process development was based mainly on solubility measurements as well as on crystallization experiments with variation of the operating parameters.

The solubility of I7 in toluene was very high (Figure 2): 5 to 10% at −10 °C, which represented a realistic final process temperature. Consequently, the desired economic process yield must be based on unusually high concentration.

(6) *Perry's Chemical Engineers' Handbook*, 6th ed.; McGraw-Hill Book Company; New York, 1985.

Figure 1. **Microscopic picture of I7 from toluene crystallization. Scale: distance between short bars corresponds to 13.2 μm. Rounded edges caused by attrition.**

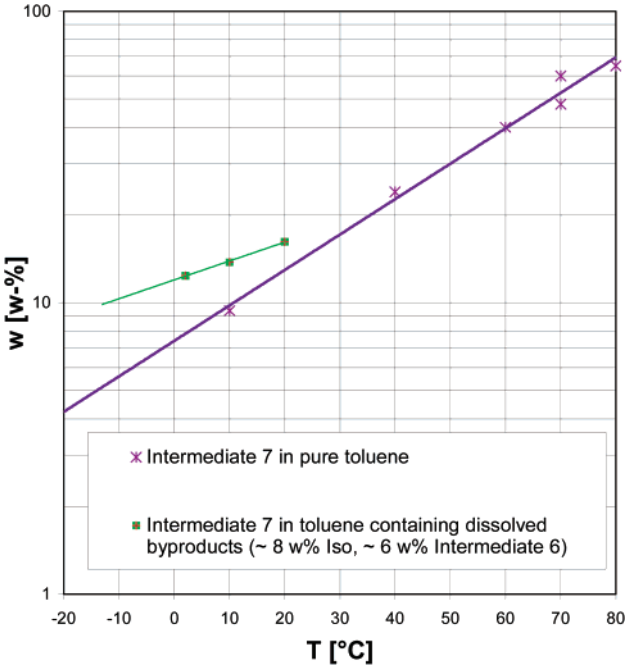

Figure 2. **Solubility of I7 in toluene.**

Numerous crystallization experiments were conducted to elaborate robust operating conditions. They are summarized as a function of the operating parameter "I7 concentration in toluene solution" ($w_{I7,solution}$) and "I7-isomer content in I7-solids" ($w_{iso,solids}$) in Figure 3. The results can be summarized as follows:

(i) Crystallization from an unusual 63% solution ($w_{I7,solution}$) was possible due to the compact cubic morphology of the crystals (Figure 1). Higher concentration led to blockage of the stirrer ($w_{I7,solution\ K.34} = 70\%$).

(ii) The crystallization experiments were consistent with the solubility assessment of I7-isomer, that is, all crystal-

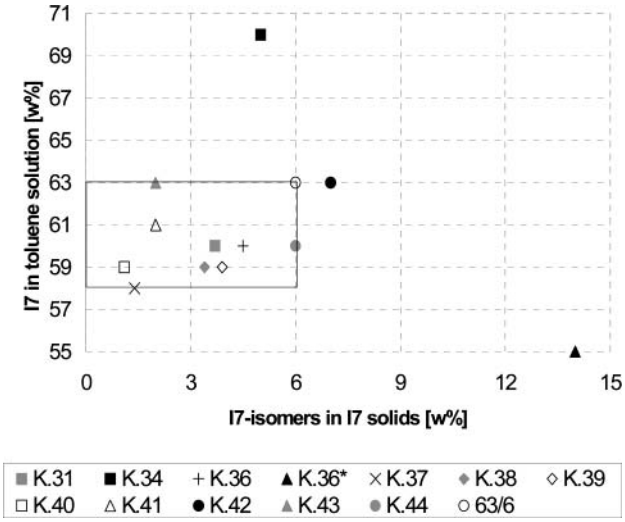

Figure 3. **Crystallization operation range. Overview of crystallization experiments. Information on "63/6": see text.**

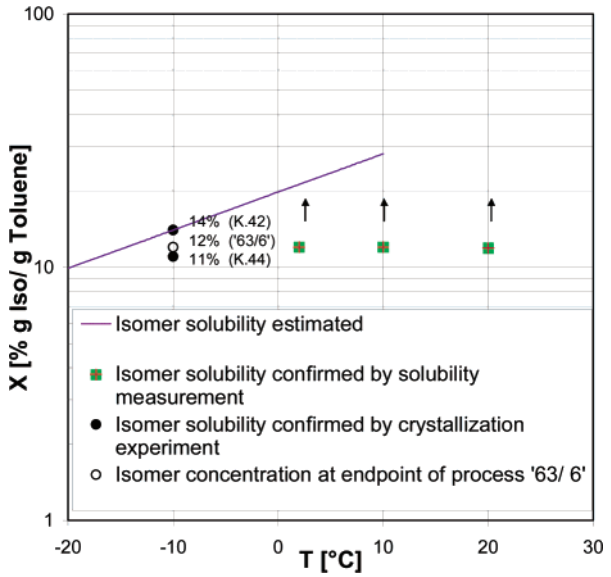

Figure 4. **Solubility of I7-isomer in toluene. Results of solubility measurements at 2, 10, and 20 °C are equal to the isomer concentration of the starting material. Therefore, it is concluded that the isomer solubility at 2, 10, and 20 °C exceeds the measured 12%. This also explains why all the solid residues at each temperature exhibit identical isomer concentration.**

lization conditions at concentrations lower than 63/6 resulted in isolated I7 that met specifications (i.e., I7-isomer ≤0.1% area) − and exhibited I7-isomer concentration in toluene (X_{iso}) lower than its solubility at −10 °C (Figure 4).

The solubility of I7-isomer at −10 °C ($X_{iso\ sat.\ -10°C}$) was 13−14% [g isomer/g toluene] based on crystallization experiments K.42/K.44: Crystallization K.42 ($w_{iso,solids\ K42}$ = 6.7%) yielded product containing 0.2% of isomer. Therefore, its isomer concentration $X_{iso,K42}$ = 14% was approximately equivalent to the saturation concentration in toluene. This conclusion was supported by crystallization K.44 ($w_{iso,solids\ K44}$ = 6.0%) which yielded I7 crystals free of isomer, thus $X_{iso,K44}$ = 11% is not saturated. Crystallization slurries have been stirred at final process temperature (−10 °C) for ≥10 h. Therefore, equilibrium of the solid solute was assumed.

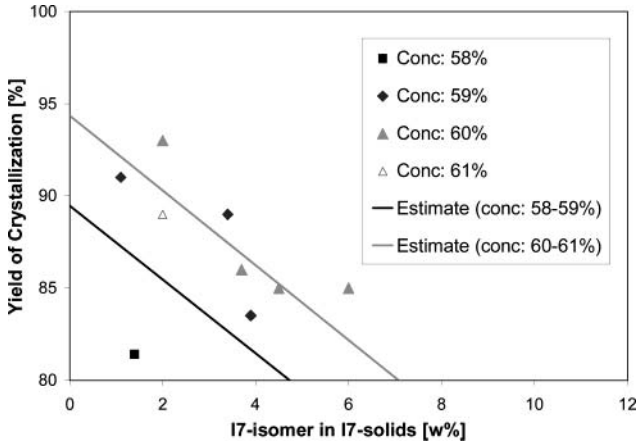

Figure 5. **Crystallization yield in function of $w_{iso,solids}$ and $w_{I7,solution}$.**

These data are also compatible with the results of solubility measurements of I7-isomer at 2, 10, and 20 °C where the solubility was confirmed to be higher than 12% [g isomer/g toluene].

"***63/6***" refers to a process conducted at 63% I7 in toluene solution ($w_{I7,solution}$ = 63%) containing 6% I7-isomers related to I7-solids ($w_{iso,solids}$ = 6%). The I7-isomer concentration that results at final temperature (−10 °C) of process '63/6' is soluble in toluene: At $w_{I7,solution}$ = 63% the I7-isomer content $w_{iso,solids}$ = 6% is equivalent to 12% related to toluene ($X_{iso,'63/6'}$) which is below the saturation concentration.

The solubility of unreacted intermediate 6 (I6) in toluene was 1 order of magnitude larger than its expected maximal concentration—according to the reaction conditions.

Figure 5 presents the crystallization yield as result of the operating parameters $w_{iso,\ solids}$ and $w_{I7,solution}$. Experiments conducted at similar I7 concentrations ($w_{I7,solution}$ = 58−59% and $w_{I7,solution}$ = 60−61%) are correlated in function of $w_{iso,solids}$. We speculated that the crystallization yield increases at higher I7 concentration as well as lower I7-isomer concentration. This conclusion is consistent with higher solubility of I7 in the presence of dissolved byproducts I7-isomer and I6 (Figure 2). In the literature it is also well-known that impurities effect the solubility of the solute.[9,10] However, the sum of the experimental errors did not allow for a clear conclusion based on these data. The highest lab yield (K.45) was 91% ($w_{I7,solution\ K45}$ = 60% and $w_{iso,solids\ K45}$ = 2%) which corresponds to a crystallization yield of 93%.

4. Filtration, Washing. Due to the compact cubic morphology and the large crystal size (several 100 μm, Figure 1) it was possible to filter and wash the product effectively. The residual mother liquor could be removed with ethanol based on plug flow displacement on a Nutsche filter.

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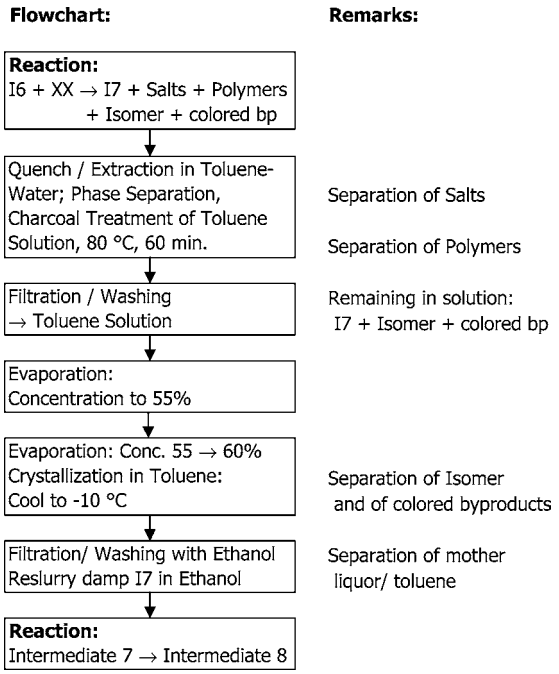

Figure 6. **Flowchart of new workup process of step I7. I6 is reacting with XX.**

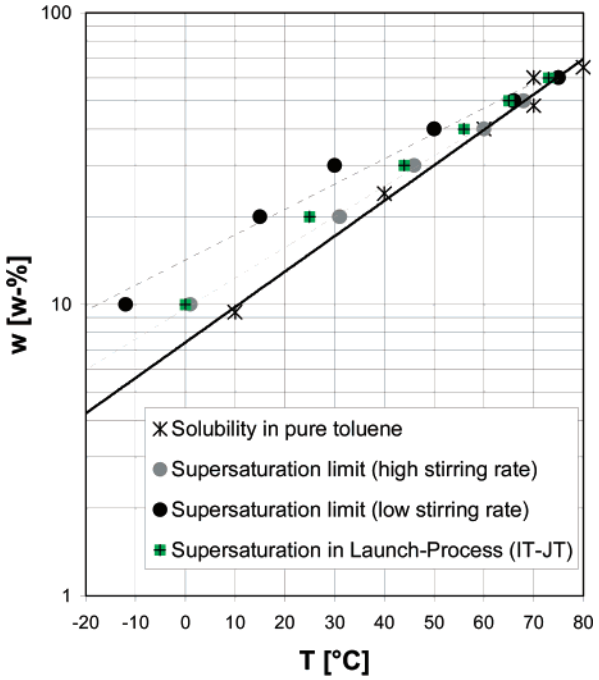

Figure 7. **Solubility and supersaturation limit of I7 in toluene. Metastable range of I7 in toluene estimated at high and low stirring rate.**

Since residual toluene content of damp I7 after ethanol wash was very low (0.04% [w/w]), it allowed the damp I7 to be transferred directly to the next synthesis step as slurry in ethanol, which was the solvent of the next step. Thus, the drying procedure could be eliminated.

5. Process Overview and Scale-up. The described improvements are summarized in the process flowchart (Figure 6).

Scale-up of the crystallization of a 60% solution provided a quite challenging task. The risk of wall-crust formation needed to be adressed since a small difference (ΔT) between internal (IT) and jacket (JT) temperature corresponds to a large increase in supersaturation that can cause precipitation at the wall. Since the surface-to-volume ratio is much smaller in production equipment compared to that in the lab, the problem appears pronounced during scale-up. Therefore, the principle of cooling with controlled supersaturation has been applied. As supportive data the metastable range of I7 in toluene has been estimated in the lab (Figure 7). The width of the metastable range depended on the stirring rate—as expected in good agreement with the literature.[7] Even though the nucleation mechanism in the lab experiments (spontaneous) compared to wall-crust formation (secondary) is not the same, the experiments give a reasonable and helpful indication for the applicable ΔT in the production process. In the production process the difference between IT and JT was increased gradually with decreasing concentration of the batch, resulting in a quadratic cooling profile. This ΔT did not exceed the experimentally estimated metastable range. The batch was commissioned in a 4000-L vessel with an overall cooling time of 30 h that has been optimized to 18 h, yielding approximately 850 kg of I7 at maximum batch size.

6. Near-Infrared Spectroscopy (NIR). During commissioning, vessel load cells were used together with manual laboratory determination of batch concentration prior to evaporation. It was found that a large amount of load-cell calibration effort was required to achieve the necessary accuracy together with skill and judgment of the plant chemist to determine the endpoint of the evaporation phase. The average yield achieved was 80% with little chance of improvement. The manual testing required would also extend the time cycle possibly to as long as 48 h.

From a feasibility study that covered several alternatives it was concluded that NIR in a recirculation loop would be the best option to meet the following production requirements: improved process robustness required for daily production, increase in yield by >5%, decrease of time cycle to 24 h, and elimination of a process steering control.

NIR has been implemented for the launch campaign (i.e., preapproval campaign) that met the set goals. The instrument proved reliable and robust in the production environment. The targeted improvements were met.

Experimental Section

Materials and General Methods. I7 refers to a poorly water-soluble aromatic hydrocarbon with functional groups. Its molecular mass is between 200 and 600 g/mol, and its melting point is approximately 130 °C.

The solubility of I7 was measured in the solvents, ethanol, 2-propanol, toluene, acetone, ethylmethyl ketone—each of technical quality—applying state-of-the-art methods.[7] To identify the solubilities of solute mixtures (I7, I7-isomer, I6) GC-analysis has been used. Filtration experiments were conducted at constant pressure (1, 3 bar) and controlled temperature in modified, jacketed 300-mL Milipore equipment. Production filter media were tested. Compressibility of the filter cake was assessed according to filtration theory by Darcy and Carman.[6] Crystallization experiments were

conducted in state-of-the-art jacketed, temperature-controlled glass vessels at 80-, 500-, and 1000-mL scale. Programmable Midilab units controlled the temperature between 90 and −20 °C. The turbidity of the suspension was monitored by a Minifipps probe.

The reacted product was obtained as a melt and quenched in toluene−water followed by phase separation. GC analysis delivered the composition I7 vs I7-isomer vs unreacted I6. The organic phase was then treated with charcoal followed by clear filtration and evaporation to dryness. This crude residue was then used for the preliminary crystallization experiments in different solvents at various concentrations.

Purity of the crystallized I7 was determined by HPLC. Color of the solids (crude residue, crystallized I7) was assessed by UV-absorbance measurement of the DMF solution. Residual solvent content (I7) was based on GC−headspace analysis.

After elaboration of the main operating conditions the entire process was demonstrated, including distillation to the desired concentration prior to crystallization.

The metastable range (Figure 7) was estimated according to the following method: I7 and toluene were weighed and added together, according to saturation concentration at 60, 50, 40, 30, 20, and 10 °C. After dissolving all solids the solutions were cooled to saturation temperature. At time intervals of 10 min the clarity of solution was checked visually, followed by lowering the temperature by 2−5 °C. The difference between saturation temperature and the last temperature where a clear solution was observed is called supersaturation limit. These experiments were conducted at 10-mL scale using vials with gastight caps to prevent solvent loss. To ensure uniform temperature the vials were kept inside temperature-controlled metal jackets. The vials were stirred at two different rates (high, ∼600 rpm; low, ∼100 rpm) by magnetic rods.

Conclusions

In conjunction with innovative organic chemistry the systematic application of finishing technologies played a key role in developing a robust, simple process that is suitable for high-volume API production. Application of finishing technologies should be considered at all stages of development—however, the needs must be balanced against time−cost-benefit.

In the present example the major hurdle was the purification of the reaction mixture of an intermediate (I7) containing inorganic salts, polymers, I7-isomers, and colored byproducts. Compared to the process that was utilized for manufacture of early-phase clinical batches, the new process eliminated one crystallization, one solvent exchange, one charcoal treatment, and two drying steps. Most importantly, the proper choice of the crystallization solvent led to significantly improved product quality (color). Process yield and robustness were further optimized by implementation of NIR on-line spectroscopy.

Definitions

General.

Mass fraction of component *i*:[8]

$$w_i = \frac{m_i}{\sum_j m_j}$$

Loading of component *i* relative to 1:[8]

$$X_i = \frac{m_i}{m_1}$$

I7-isomer in I7-solids:

$$w_{\text{iso,solids}} = \frac{m_{\text{iso}}}{m_{\text{total,solids}}}$$

using simplification:

$$m_{\text{total,solids}} = m_{\text{I7}} + m_{\text{iso}}$$

I7 in toluene solution:

$$w_{\text{I7,solution}} = \frac{m_{\text{I7}}}{m_{\text{total,solids}} + m_{\text{toluene}}}$$

I7-isomer in toluene solution:

For experimental reasons it is more appropriate to discuss the I7-isomer solubility as loading related to the single component toluene: g of isomer/g of toluene in %:

$$X_{\text{iso,toluene}} = \frac{m_{\text{iso}}}{m_{\text{toluene}}}$$

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