



Industrial Crystallization Processes

Process optimization using an Automatic Laboratory Reactor

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Process Optimization using an Automatic Laboratory Reactor

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Reaction products with suitable crystal size distributions result in short filtration and washing times. This leads to shorter process cycles and an improvement in the product quality (e.g. purity). A knowledge of the solubility curves and cooling profiles forms the basis for optimum crystallization from the solution.

The use of automatic lab reactors with heat balancing and turbidity measurement allows rapid determination of the solubility curves and cooling profiles¹. The influences of stirring, evaporation, dosing, seeding, etc. are already recognized during the development stage in the lab. An example from the pharmaceutical industry, the crystallization of a pharmaceutical product from solution² is described below.

Description of problem

A critical factor in the manufacture of tablets with high proportions of active substance was found to be the bulk density of the latter. This had to be as high as possible to ensure complete filling of the dies of the tablet press. While an improvement in the particle size distribution could normally be achieved by milling and wet granulation of the product, the resulting development and production costs would amount to around 50% of the manufacturing costs.

The main reason therefore was that the normal «natural» cooling of the product mass following the last reaction step resulted in an unfavorable particle size distribution. Numerous small crystals formed spontaneously owing to uncontrolled nucleation.

Development aim

To lower development and manufacturing costs, an optimum product should be produced by separation in a single step. The crystallization following reaction must be so controlled that milling and granulation are no longer required.

Owing to the high temperature dependence of the solubility of the product, cooling crystallization was selected as a suitable method. Lab experiments in the RC1 automatic lab reactor were used to determine the temperature at which spontaneous primary nucleation sets in and crystallization starts. This could be established using the increase in the stirrer power (viscosity) and the heat generation rate (figure 1). The influences of undercooling and the amount of seed crystals were investigated so that with use of the controlled cooling procedure sufficiently large crystals could be produced directly. The product could be immediately tableted after filtration owing to the around 50% increase in the bulk density. These optimizations would have been virtually impossible without the highly precise temperature control and automatic operating mode of the RC1.

This improvement in the process led to an appreciable reduction in the manufacturing costs and hence to increased profits.

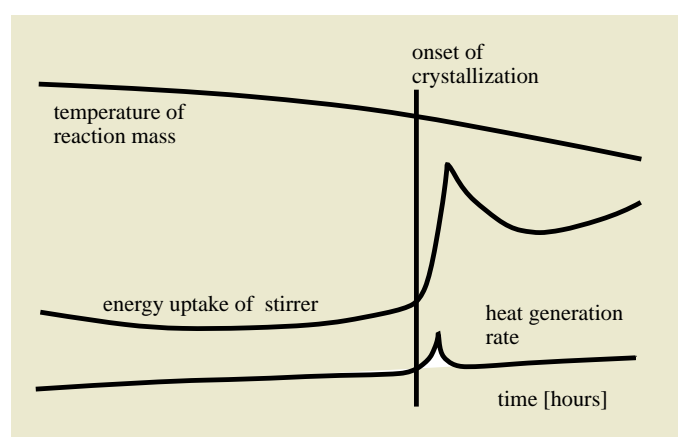


Figure 1: Example of a crystallization experiment of a pharmaceutical active substance in the automatic lab reactor. The temperature of the reaction mass drops from 65 to 56°C within 11 hours. Spontaneous crystallization starts at 62°C as shown by the increasing heat generation rate of the crystallization (maximum 10 W) and by the jump in the energy uptake of the stirrer.

Fundamentals

Solid products are usually produced by crystallization or precipitation from solution and then filtered, washed and dried³. The crystallization and hence the macroscopic product properties are essentially controlled by the relation between solubility and supersaturation. Supersaturation is achieved by cooling, evaporation or modification of the solvent and influences the nucleation and growth rate. Knowledge of the solubility and supersaturation of a reaction mass thus forms the basis for the optimization and proper control of crystallization.

The following comments and examples refer only to crystallization through cooling and demonstrate how the solubility curves are determined in automated experiments (figure 2). To determine the onset of a spontaneous crystallization, the turbidity of the solution is usually observed or measured. In addition, the change in the viscosity and hence the change in the stirrer power or the appearance of heat of crystallization can be employed to record crystallization as the example in figure 1 shows. The dissolution process is followed primarily by turbidity measurements or with the aid of the heat of solution.

Important factors in the process engineering associated with the production of optimum crystals in as short as possible time are a knowledge of the solubility curve of a product and proper selection of the required cooling profile. The kinetics of nucleation and crystal growth must also be taken into account [e.g. 4, 6, 7]. In practice, in many cases spontaneous crystallization is avoided and instead a specific quantity of crystal nuclei added to the reactor, e.g. by seeding with pure product or by addition of a small amount of crystal suspension from a previous batch.

Determination of the solubility curves

Experimentally, the solubilities are determined as a function of concentration and temperature by the following steps (figure 2):

- dissolution of the product to form a homogeneous solution (point S) (1),
- slow cooling until the onset of crystallization; the appearance of the first crystals defines point N on curve n (2),
- slow heating until a homogeneous solution is again attained; the disappearance of the last crystals defines point D and hence the solubility curve d (3),
- addition of solvent or product to change the concentration (4).

Steps (2) through (4) are repeated a number of times to obtain several experimental points to establish curves d and n (4). This experimental procedure is very time con-

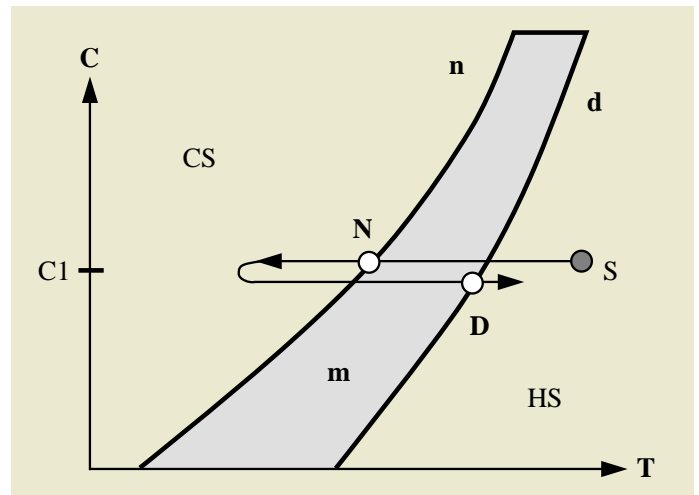


Figure 2: Schematic representation of the solubility curves. C: Concentration of product in the solution, T: Temperature, d: Solubility curve, D: Clear point, n: Supersolubility curve, N: Cloud point, m: Metastable region (no primary nucleation), S: Start point (homogeneous solution) for the measurement cycle at concentration C1, HS: Region of homogenous solution (below curve d), CS: Region of crystal suspension (above curve n).

suming and tiring when performed manually as the cooling and heating cycles last a relatively long time owing to the low rate (e.g. $0.5 \text{ K}\cdot\text{min}^{-1}$). In addition to this the results are also dependent on a subjective interpretation by the user since the cloud and clear points are determined by visual observation.

Use of an automatic lab reactor considerably facilitates the experimental procedure and increases the accuracy of the determination:

- preprogrammed, unsupervised automatic experiments which, depending on the reaction mass, can also be run overnight;
- accurately controlled temperature ramps;
- weight-controlled addition of solvent to change the concentrations automatically;
- continuous plotting of all important measured values (temperature, heat generation rate, turbidity, stirrer power, etc.);
- simple detection of the onset of crystallization by use of the FSC402 Optical Controller (turbidimeter).

The RC1 and LabMax[®] automatic reactors are computer-controlled lab reactors for the manual or automatic execution of industrial chemical processes in batch or semibatch operation (figure 3). These lab pilot experiments on a liter scale allow the measurement of important parameters such as temperature, dosing, pressure, pH, stirring and turbidity under realistic process conditions and also their control where appropriate. In the case of the RC1 reactor, the generated or consumed of the reaction mass is also determined (reaction calorimetry).

Determination of the cloud point N and clear point D

Detection of the cloud point and clear point is facilitated or indeed made possible in the first place by the use of appropriate sensors. Depending on the nature of the reaction mass (ranging from simple solutions to heterogeneous, opaque, pulpy masses), either a turbidimeter is used or the enthalpy of crystallization or solution measured.

The difference between a calorimetric determination and a turbidity measurement (figure 4) lies primarily in the scale of the observed effects and the size of the crystals. The turbidity measurement can cover a wide range by appropriate selection of the gain. Use of a high sensitivity allows the onset of crystal formation (small particles) to be detected. The calorimetric experiments primarily allow crystal growth to be followed when the heat of crystallization is sufficiently large; here, the heat generation rate is proportional to the growth rate.

Turbidity measurement

A fiber-optical sensor is used for continuous measurement of the light backscattering of particles (crystals) directly in the reaction mass and the solubilities are determined as follows (figure 4):

- Point N: Onset of crystallization = start of increasing turbidity = cloud point; thanks to the high sensitivity of the turbidimeter, the appearance of the first crystal nuclei is detected at an early stage.
- Point D: Dissolution of the last remaining crystals = end of turbidity decrease = clear point.

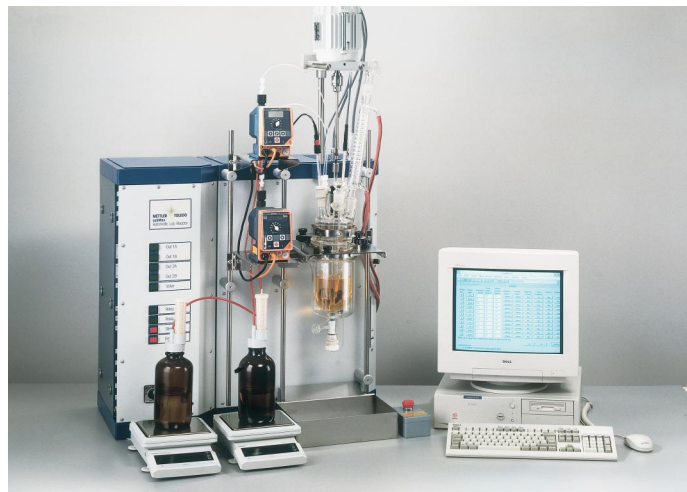


Figure 3: The automatic lab reactors LabMax[®] and RC1[®] (reaction calorimeter with heat balancing) are used for the optimization of chemical products and processes.

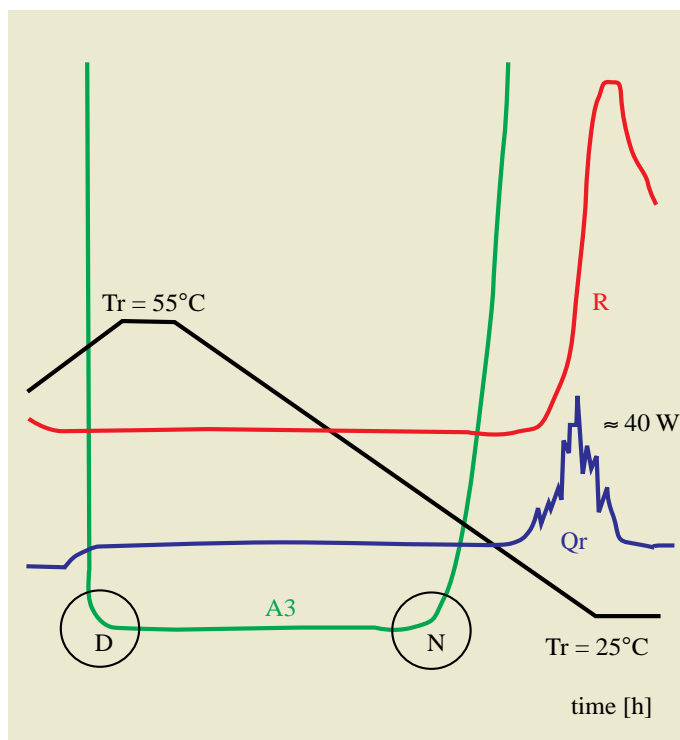


Figure 4: Typical profile of the turbidity measurement on heating and cooling at a rate of $15 \text{ K}\cdot\text{h}^{-1}$ using the example of 15.3% calcium lactate in water, measured with an RC1 and FSC402 Optical Controller (turbidimeter) in the glass reactor with anchor stirrer (100 rpm). T_r : temperature of the solution, A3: turbidity signal (relative value), Q_r : heat generation rate maximum = 40 W, D: clear point, N: cloud point, R: stirrer power.

The calorimetric measurement

Depending on the product, crystallization can be exothermic (see figure 5) or endothermic, i. e. the signal change is either positive or negative. However, this has no influence on the determination of the cloud point. The temperature points N and D are determined using the heat generation rate (Q_r) by extrapolation of the start or end of the observed effect:

- Point N: Start of the increase in the heat generation rate during cooling = cloud point. On completion of cooling, the heat production due to crystal growth also ends as at a constant temperature the solution and solids reach equilibrium.
- Point D: End of the heat uptake through dissolution of the crystals = clear point.

Rate dependence of temperature points N and D

The cloud point N and to a lesser extent also the clear point D depend on the cooling/heating rate as mass transfers, diffusion rates and nucleation rates have a large influence on the crystal growth.

To determine the equilibrium conditions D and N , the following two methods can be used:

Method 1 includes extrapolation over several experimental points to heating/cooling rate zero as shown in figure 6a using experimental data. With this method, extrapolation and interpolation can also be used to determine the cloud or clear at other heating/cooling rates.

With rapid crystallizations (method 2), often only slight undercooling occurs and spontaneous nucleation follows rapidly. The crystals then grow very quickly owing to the high supersaturation and this can clearly be seen from the large increase in the heat generation rate (signal peak of Q_r in figure 6b). Owing to the high crystal growth rate, a dynamic equilibrium established on further cooling, i.e. each additional supersaturation immediately leads to further growth of the crystals and is associated with a practically constant release of heat P_x .

For the same reasons, following the spontaneous crystallization the deficiency in the quantity of crystals at the start as a consequence of the rate-dependent undercooling is immediately made good. The overshooting of Q_r in comparison with the subsequent normal heat generation rate P_x can thus be used to determine the cloud point \tilde{N} under equilibrium conditions. For this, in the evaluation \tilde{N} is varied with the associated integration limit until the hatched area is equal in size to the dotted area regarding curve Q_r .

An example of an automated determination of the solubility curve (onset of spontaneous crystallization and of the dissolution point) is shown by the experiment with potassium nitrate (figure 7). An initial concentration of 600 g salt in 0.4 l water was used. After a cooling and heating cycle, the concentration was lowered by the addition of water. Figure 7 shows an overview of the temperature profile (Tr), the heat generation rate (Q_r) and

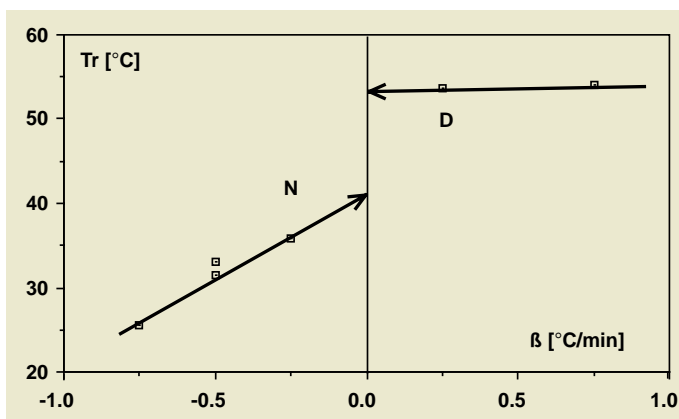


Figure 6a: Representation of the influence of the cooling/heating rate on cloud points N and clear points D using the example of a 15.3% calcium lactate solution. The plot shows the temperatures at various heating or cooling rates corresponding to the disappearance of the last traces of turbidity (D) or the appearance of the first signs of turbidity (N).

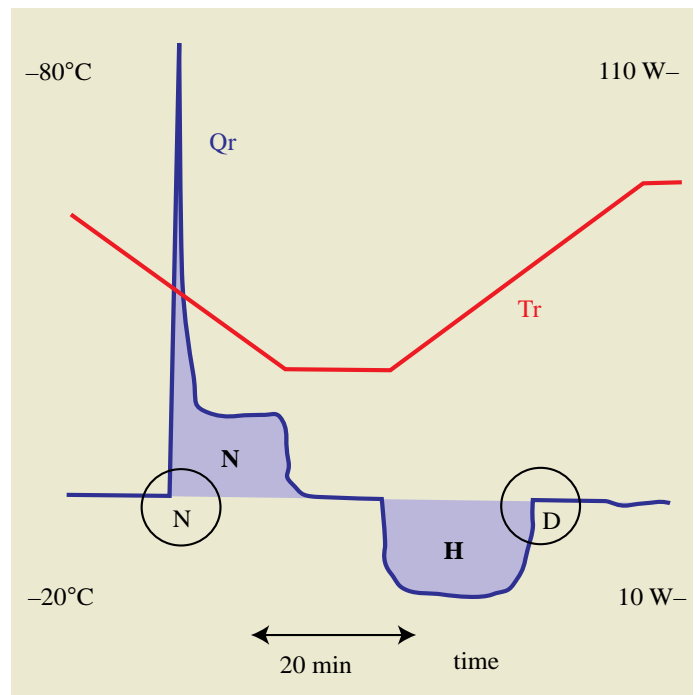


Figure 5: Typical profile of the heat generation rate (Q_r) in the cooling and heating of potassium nitrate solution (measured with RC1). Tr : temperature profile, G : crystal growth during cooling, H : dissolution during heating, N : onset of spontaneous crystallization, D : end of dissolution.

the reaction mass (m_r). A detail with the cloud and clear points for a temperature cycle read off from the Q_r curves is shown in figure 5. A summary of the results for the concentrations can be seen in table 1 (see next page). The table also shows the points \tilde{N} for equilibrium conditions determined by method 2 described above (area comparison). The dissolution point and the crystallization point differ by only 1°C.

Selection of the optimum cooling method

In many cases, a controlled crystallization is performed in the following manner:

- Cool until the metastable region is reached.
- Seed with a small amount of pure product to start crystal growth.
- Cool further but at a rate which ensures that the concentration remains between solubility and supersolubility curve in the metastable region and hence prevents primary nucleation (fig. 2).

The cooling rate must therefore be matched to the crystal growth. Here, optimum selection of the stirring speed is also important to ensure on the one hand a fast mass transfer through as high a turbulence as possible and on the other hand no appreciable further nucleation due to abrasion.

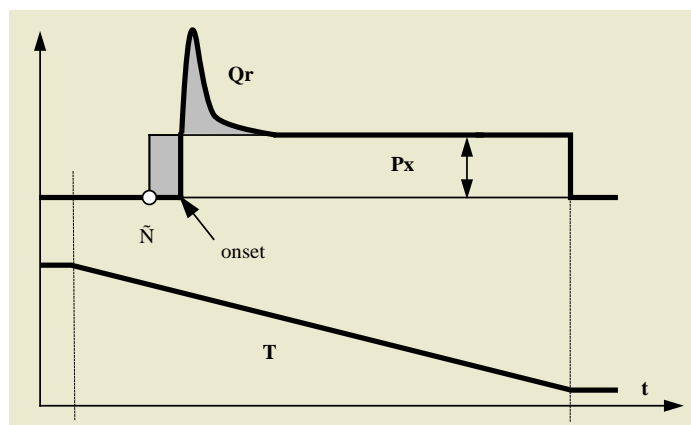


Figure 6b: Schematic profile of the heat generation rate (Q_r) during cooling and crystallization (see also figure 4). T : temperature; time axis; Onset: onset of spontaneous crystallization; \tilde{N} : cloud point under equilibrium conditions (the dotted area is equal in size to the hatched area); P_x : heat generation rate due to crystal growth.

The optimum cooling rate can be calculated from the crystal growth rate and the solubility curve. Here, it is assumed that, as mentioned above, in batch operation there is practically no primary or secondary nucleation. It is important to ensure that the cooling rate is very low at the onset of cooling. With decreasing product concentration, the danger of spontaneous nucleation usually diminishes and, owing to the increase in size of the crystals, cooling can be performed quicker. The natural cooling profile, on the other hand, shows a high cooling rate at the start and slow cooling at the end.

To simplify the situation, the temperature profile for an optimum crystallization is often shown as a quadratic function of the time, but here it must above all be ensured that the temperature at the start changes only slightly:

$$T = T_{\text{start}} - k \cdot t^2$$

The constant k is varied until the production time (cooling time) and the crystal forms produced are optimum.

An example from the speciality chemicals field

Optimization of the crystallization and separation of an optical brightener⁵. The following limiting conditions for the investigation were imposed by the process:

- initial concentration: 0.21 kg/kg solution.
- cooling from 116°C to 30°C within 45 min. To solve the problem, the method described above involving the automated experimental determination of the cloud and clear points by turbidity measurements was employed. The solubility and supersolubility curves were very similar (figure 8) so that accurate temperature control was necessary to allow the crystallization to be performed in the optimum metastable region.

To investigate the influence of the cooling profile on the product quality and the filtration time, three different cooling rates were selected (figure 9):

- Linear cooling at a constant rate, $B = 1.911 \text{ K/min}$.
- Natural cooling at a rate = factor $\cdot (T_{\text{reactor}} - T_{\text{cooling medium}})$. Here the jacket temperature of the lab reactor and not the temperature of the reactor content was controlled.
- Calculated optimum temperature profile with a very low cooling rate at the start.

The experimental results of the three different cooling methods are summarized in table 2. The «natural» cooling led to many structureless crystal clumps (figure 10) with correspondingly poor filterability and occluded by-products. With linear cooling, very fine crystalline needles of length max. 0.2 mm were obtained. Optimum cooling led to thicker and longer crystals (up to 0.5 mm), the processing time was shortened by a factor of two and the proportion of by-products fell to below 0.1%. The development aim «good product quality with a shorter cycle time», could thus be achieved rapidly and simply.

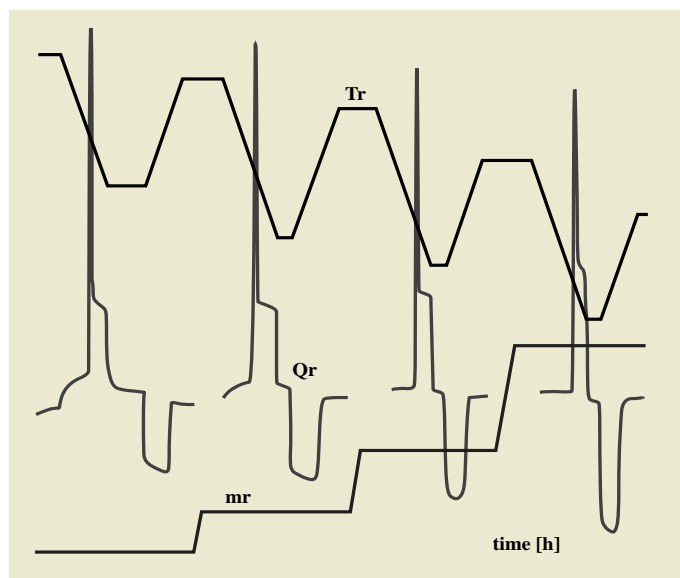


Figure 7: Heating and cooling cycles ($\pm 0.5 \text{ K/min}$) of potassium nitrate in water at concentrations of 600 g salt in 400, 480, 600 and total 800 g water. The experiment was preprogrammed and run automatically in the RC1 with a 2 l glass reactor.

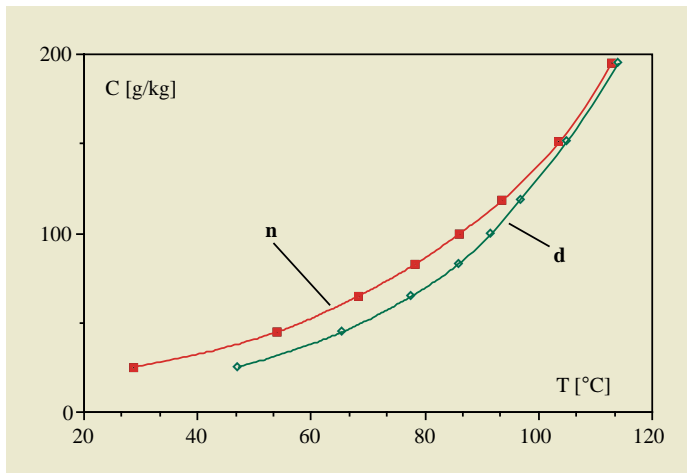


Figure 8: Solubility curves for the product determined automatically by turbidity measurement: Heating/cooling rates used: = ±0.5 K/min; C: Concentration in g of product per kg solution; n: supersolubility curve; d: solubility curve.

Concentration (g KNO ₃ / g solution)	0.6	0.556	0.5	0.429
Cloud point (-0.5 K/min, °C), point N	69.0	61.8	53.5	42.1
Cloud point (equilibrium, °C), point Ñ	73.9	65.4	55.8	45.0
Clear point (°C), point D	74.5	66.1	56.8	46.2
cp measured (J·kg ⁻¹ ·K ⁻¹)	2250	2394	2550	2793
cp calculated (J·kg ⁻¹ ·K ⁻¹)	2246	2388	2567	2798

Table 1: Clear and cloud points of potassium nitrate in water, determined from the experiment shown in figure 7. The equilibrium point Ñ was determined from the Qr curve using method 2. As additional information, the specific heat of the solution was calculated automatically by the RCI evaluation program. The calculated cp value is based on the total of the heat capacities of the individual components in the solution (water and potassium nitrate).

Conclusions

The present investigations have centered on cooling crystallization from product solutions, but the measurement methodology can also be used for other crystallization procedures such as evaporative cooling or polarity change of the solvent.

The particle size distribution and the crystal forms have an appreciable influence on the separation, processing and application of the product. To avoid undesired nucleation, uncontrolled supersaturation of product in the solution must therefore be prevented.

Optimum crystal form and size is usually attained in practice by seeding and control of the growth rate, i.e. a constant supersaturation is achieved by the use of special cooling profiles. The optimum crystallization from solution consequently requires a knowledge of the solubility curves and the metastable region. Detection of turbidity, plotting of the stirrer power or the enthalpy of crystallization are used for accurate determination of the onset of crystallization or the end of dissolution. Solubility curves and optimum cooling profiles are determined precisely using an automatic and programmable lab reactor.

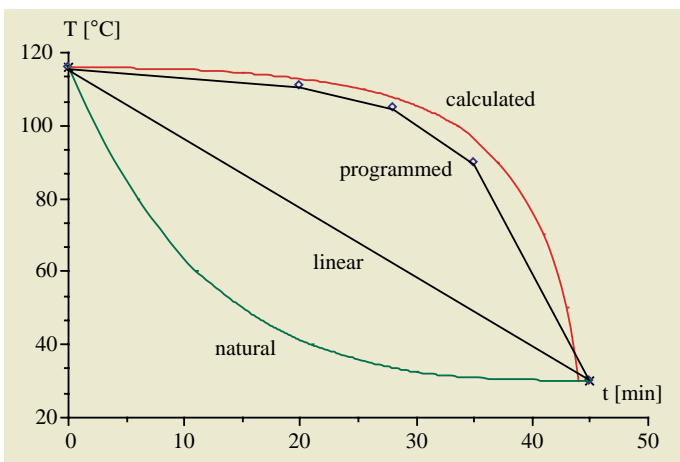


Figure 9: Cooling profile used for the investigation of the crystallization behavior, the filtration possibilities and the product quality (see Table 2). The optimum cooling profile (calculated) was made up of four linear cooling ramps to allow its preprogrammed reconstruction in the automatic lab reactor.

Cooling profile	natural	linear	optimum
Filtration time	27 min	19 min	13 min
Washing	60 min	35 min	29 min
By-products	0.6 %	0.1 %	< 0,1 %

Table 2: Filtration tests and washing times with different cooling rates. Pressure filtration: 0.2 bar, 8.5 cm filter cake, 9 cm diameter; washing with 2 · 200 ml solvent.

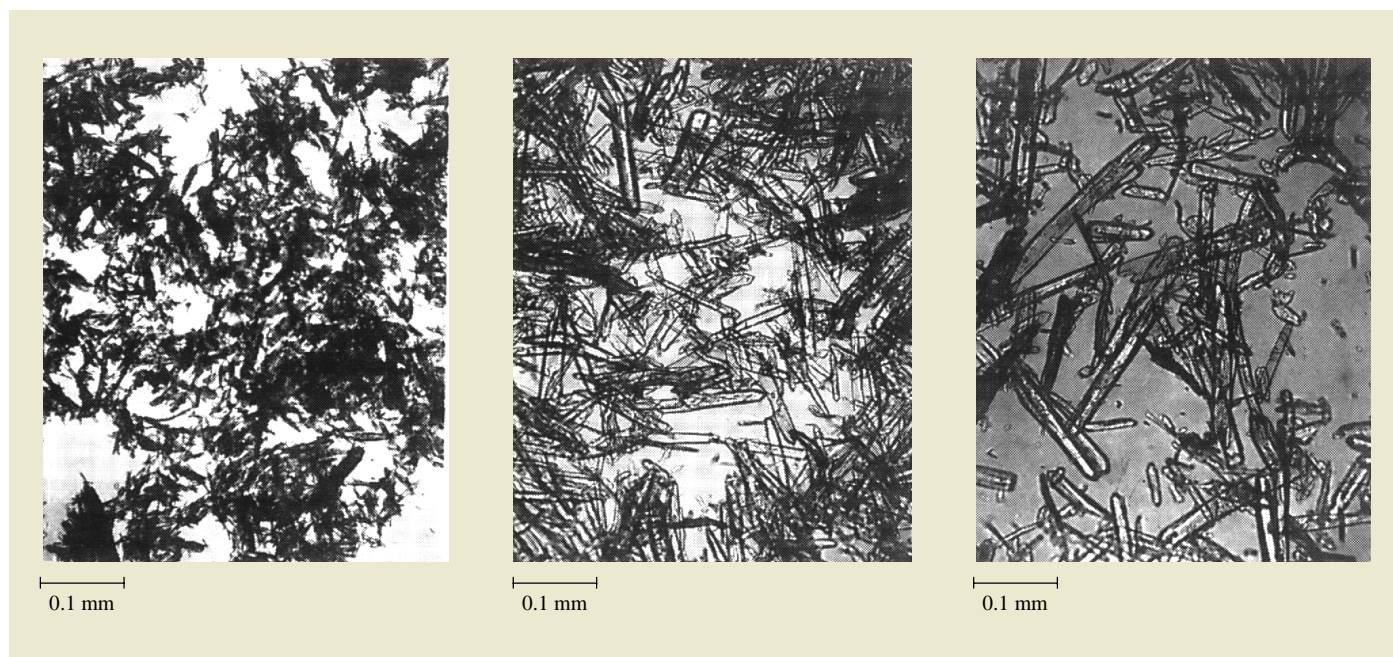


Figure 10: Quality of the crystals as a function of the cooling profile. From left to right natural, linear, optimum cooling profile. The width of the photo corresponds to 0.45 mm in each case.

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