THE SCT APPROACH TO CRYSTALLIZATION

In a White Paper we described earlier what the advantages of the use of Secoya's Crystallization Technology (SCT) are to tame the nucleation of a material in solution inside a crystallization reactor as designed by Secoya[1]. Several advantages do exist: control of final crystal size, correct crystal form, inherent narrow size distributions, etc. But how exactly do you start using the technology, and how long does it take to develop a crystallization routine using the SCT technology?

From the first tests we have ever done, the aim was to increase nucleation and subsequently overall crystallization rate, using small sized reactors, with a strong philosophy to decrease complexity of crystallization. For example, the use of solids during a seeding step was ruled out of the equation as blockages are expected to occur at one point or another. However, aiming for spontaneous nucleation requires a (very) rapid change in thermodynamics in order to reach high supersaturation levels. Nucleation is a stochastic process, it depends on the amount of successful creations of nuclei of a critical size that may persist and grow to a crystal. The larger a volume where nucleation may take place, the larger the possibility of successful events: indeed, nucleation is dependent on volume. Therefore, while we are lowering the overall reactor volume to gain control of conditions - flow rate, reactor evacuation, temperature evolution – an increase in nucleation events, and therefore the nucleation rate, becomes primordial.

Luckily, when using our SCT reactors, two approaches are possible to reach the desired supersaturation state: either with mixing with e.g. antisolvents or by very fast cooling. Depending on mixing efficiency, different supersaturation values can be obtained while using the principle of antisolvent addition. On the other hand, simple cooling crystallization strategies are for many applications sufficient to obtain crystalline material in the order of 50 to 100 µm average size. Let us look more closely to develop a crystallization routine using cooling crystallization.

[1] Find this white paper at: https://secoya-tech.com/documents/crystallization/

The practical approach to conduct cooling crystallization experiments largely depends on the position of the metastable zonewidth (MSZW) under ruling thermodynamic and kinetic environment. The MSZW (or undercooling) is the thermodynamical instability that needs to be overcome to create these critical nuclei, and is specific for any combination of solute / solvent / reactor / contact time. If you look for example to the theoretical solubility and MSZW curves in Figure 1, the MSZW is positioned at a certain distance from the solubility curve. When a solution is able to be cooled down inside the reactor to a temperature below this MSZW (like the red-to-blue arrow indicates), nucleation may take place and a crystalline slurry is obtained afterwards[2].

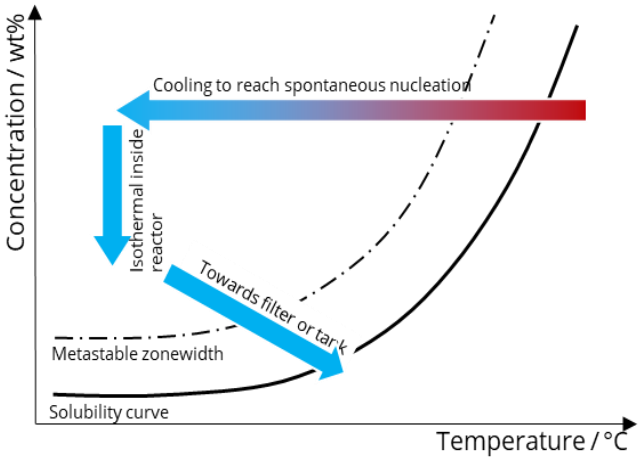

Figure 1: Theoretical phase diagram of a solute in solution, with a typical cooling crystallization scenario.

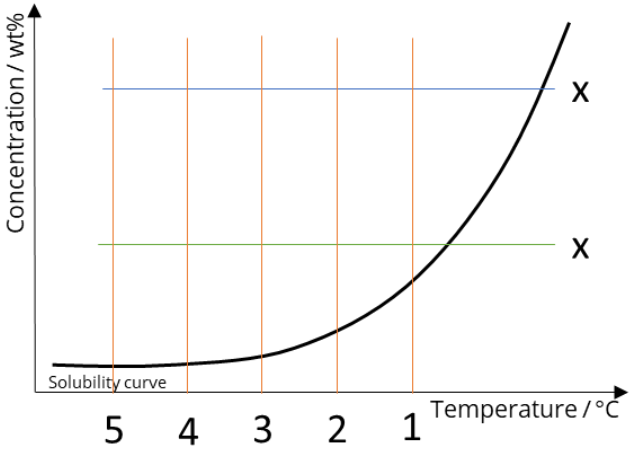

Figure 2: Schematic approach to screen the MSZW and lower limit of the operational zone using SCT.

For a new screening of the crystallization of a solute in solution, we typically dissolve the molecule in two distinct concentrations, given by the x's in Figure 2. In a first approach, we keep the temperature identical for both solutions. We also propose the use of a 3mL reactor, as it is sufficient to cool down the material to the set nucleation temperature (which is in fact the temperature of the water/oil batch in which the reactor is plunged into)[3]. For flow rate, anything between 10 and 30 mL/min is advised in this initial exploratory study.

[2] As a rule of thumb, we decided that crystals need to be observed in a vial maximum 5 minutes after a passage through the reactor, otherwise we conclude that for a given test the nucleation occurred inside the vial.
[3] Rimez et al. Journal of Flow Chemistry, **9,** 237-249 (2019)

Now, both solutions are injected subsequently into the reactor, while the nucleation temperature, T_N, is set at a temperature right below solubility of the solution with the lowest concentration, in the example of Figure 3 at temperature 1. In between every test the reactor is cleaned with the same solvent and flushed several times with air. Then, the temperature of the reactor is decreased with incremental steps, e.g. -5 degrees C per step. At each set T_N fresh solution is injected (10 to 20 mL), and the product is collected. When crystals are observed within a couple of minutes, the MSZW has been overcome for that solution under those conditions. The MSZW line is then in between the tests where crystals did not occur and the tests where crystallization occurred; marked with a black dot. If a more refined value is needed, a smaller temperature interval in this zone can be set for new tests. Arguably, an exponential dependency of MSZW as a function of concentration and temperature can be extrapolated. While dropping the temperature for subsequent tests, the crystals observed in the vials will become smaller and smaller as the nucleation rate increases.

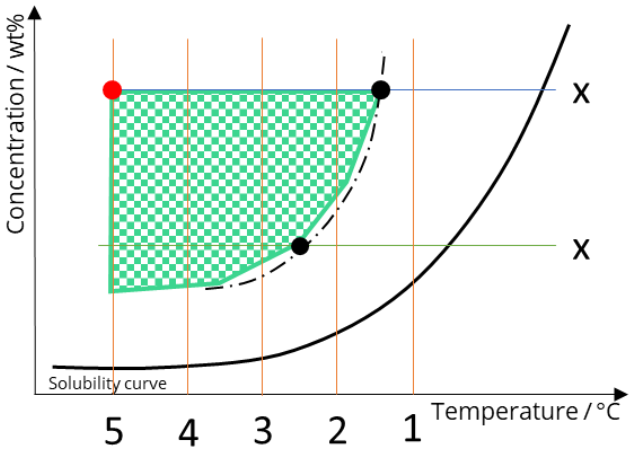

Figure 3: schematic representation of the position of screening tests leading to the determination of the MSZW (dotted line), temperature lower limit for screening (red dot) and operational zone for screening (checkered zone).

It is worthwhile to let the crystals mature under these conditions up to the next day, filter the material, and then take microscopic images to see this evolution. At a certain (too) large undercooling, nucleation will be so fast that the reactor will block during the test. No worries however, heating the water or oil bath will unclog the reactor. On the other hand, this test indicates the lower limit of the operational zone that you want to study (red dot). This operational zone where the nucleation rate can be studied until a sufficient nucleation rate is obtained is then given in the green zone.

Practical example: the crystallization of adipic acid in water

The solubility curve of adipic acid in water is given in Figure 4 as the black line. Two solutions were prepared, at 60 mg/mL (green line) and at 100 mg/mL (blue line). Starting dissolution temperature was set at 65°C for both solutions, the samples were injected at a rate of 30 mL/min inside the 3 mL SCT reactor. The nucleation temperature was stepwise decreased

with a first nucleation temperature (T_N) set at 40 °C. The results of the crystallization tests are shown in

Table 1 as a function of decreasing nucleation temperature. Already at 40 °C, a concentration of 100 mg/mL results in crystallization. Therefore, the MSZW at this concentration is set at this temperature[4]. For the 60 mg/mL samples the MSZW value is estimated to be in between 35 and 40 °C; no further refinement is required as this MSZW value is rather close to the solubility. Both MSZW values are shown as black dots in Figure 4.

T_N [°C]	60 mg/mL	100 mg/mL
40	No	Yes
35	Yes	Yes
32.5	Yes	Blocked
30	Yes	
27.5	Yes	
25	Yes	
22.5	Yes	
20	Yes	
17.5	Yes	
15	Blocked	

Table 1: tested nucleation temperatures T_N for two different concentrations of the adipic acid/water system.

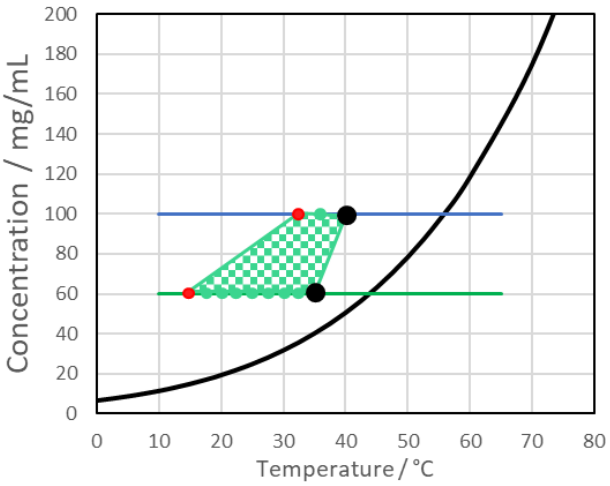

Figure 4: solubility line of adipic acid in water (black line), together with tested concentrations, experimental validated metastable zonewidth (black dots), temperature lower limit for the two concentrations and operational zonewidth for screening (green checkered zone)

Already at a T_N of 32.5°C does the tubing block due to a too fast nucleation of adipic acid, therefore a red dot is put into the graph. For a lower concentration of 60 mg/mL this occurs at 15°C. The operational zone for optimization screening is therefore given by the combination of concentration and temperature in between the black and red dots in the graph, indicated by the checkered zone.

We let the material crystallize inside a vial overnight, filtered the slurry and then took microscopic images of the dried crystals. For the test at concentration of 60 mg/mL with T_N set at 20°C, two different magnifications are shown in Figure 5.

[4] Arguably, the true MSZW value at a concentration of 100 mg/mL is probably at an even higher temperature. Given the fact that a concentration of 100 mg/mL results also at high T_N values into a blockage of the reactor due to uncontrolled nucleation, we did not consider this concentration in further studies.

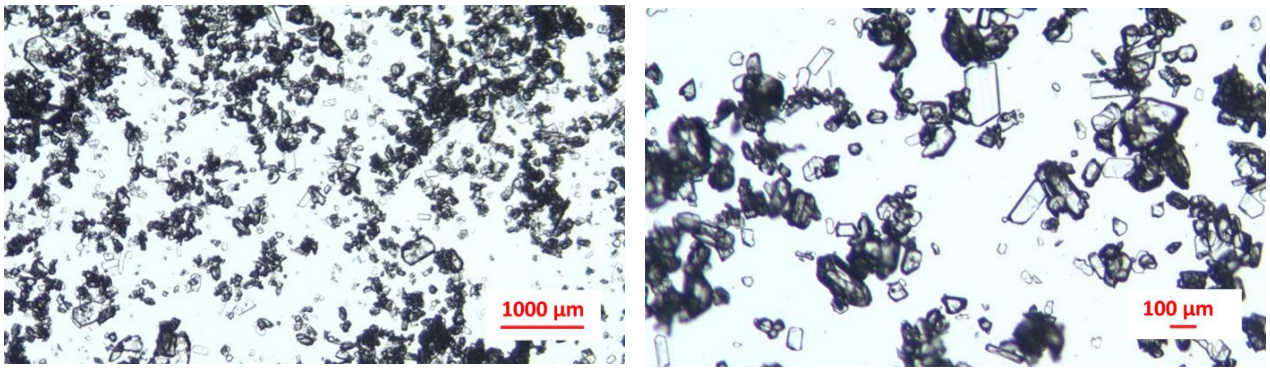

Figure 5: Microscopic images of adipic acid crystallized in water. Starting concentration of 60 mg/mL set at a temperature of 65°C, 3mL reactor, flow rate of 30 mL/min, nucleation temperature of 20 °C.

It is always very useful for this first analysis to also measure the length of, for example, 100 to 200 crystals to have an idea of the size change as a function of the set nucleation temperature. This evolution is shown in Figure 6. Once a temperature below 25 °C is set, the nucleation rate drastically increases and smaller and smaller crystals are observed.

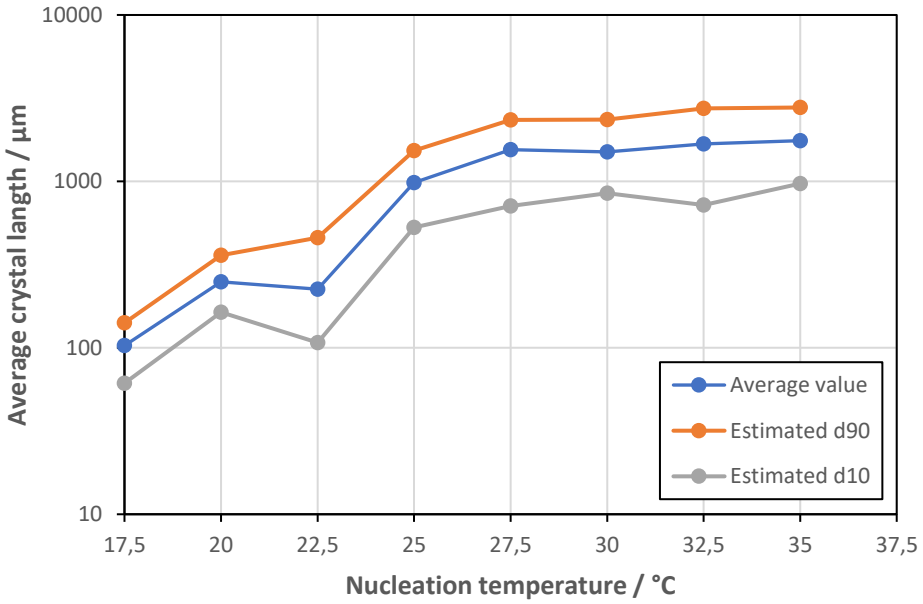

Figure 6: Adipic acid crystal size as a function of nucleation temperature, estimated average crystal length and 10 and 90th percentile in size, respectively d10 and d90, are shown. Measured on a total of 200 individual crystals, longest observable distance per crystal from side to side was always measured. Starting concentration was 60 mg/mL, set at a temperature of 65°C.

What's next then?

After this first screening, we are ready in roughly one week time to optimize further the crystallization parameter set by the creation of a test matrix: tests at different concentrations, *e.g.* 70 – 80 - 90 mg/mL, different flow rates, longer reactors, change the flow path using different inserts, etc., as shown in Table 2. It is strongly advisable to look first for the extremes in every parameter, on the other hand, a 1 degree difference in nucleation temperature can have a drastic impact on nucleation rate. The use of the different inserts to look for the impact of hydrodynamics is advised at the end of the tests when the influence of thermodynamics on the nucleation rate is fully mapped. For several selected parameter sets that result in good crystalline material, we advise to reproduce several times some particular tests to check on the robustness of the conditions. Additionally, this allows to perform XRDs, more robust sample size analysis like diffractions, check on the powder flowability, etc.

Initial concentration (mg/mL)	Reactor volume (mL)	Flow rate (mL/min)	T_N (°C)	inserts
60	2	10	15	0
70	3	20	16	2
80	4	30	17	4
90	5		18	
			19	
			20	

Table 2: Setup of a Design of Experiments for Adipic acid crystallization

Still hungry for more nucleation or any questions?

Do not hesitate to contact me !

Greetings

Bart Rimez