

Growing large crystals from solution

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This document provides basic information about growing large (a few mm to a few cm) crystals of soluble (solubility $c_{\text{eq}} > 1$ mg/mL) small molecular mass ($M_w < 0.5$ kDa) organic and metalorganic molecular and ionic compounds as well as inorganic salts from solution.

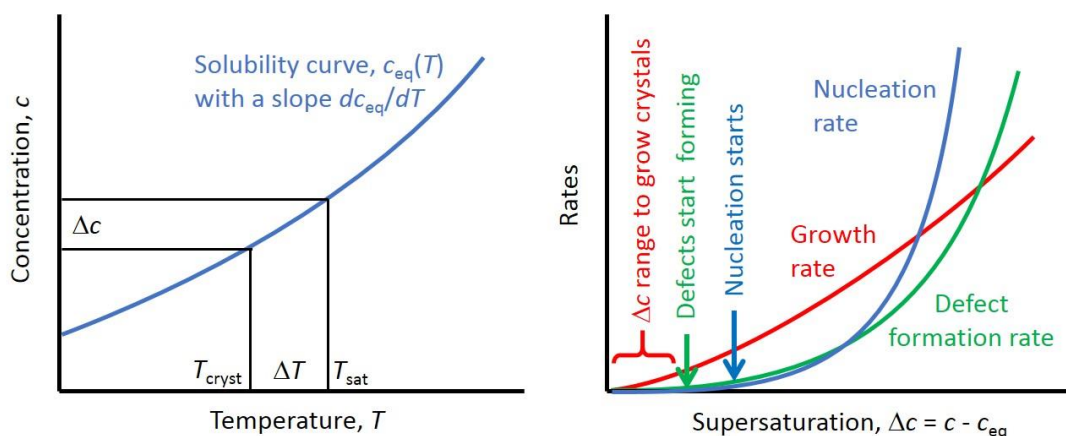
There are several crystallization techniques, which can do the job successfully, however, only the temperature lowering technique is considered here as the simplest and most straightforward approach for those, who are not focusing on crystallization itself but just need to grow some large and relatively high quality crystals using only limited resources.

Principles

- The driving force for crystallization from solution is the difference between the current solution concentration, c , and its equilibrium concentration (solubility, c_{eq} , here expressed as mass of solute per 100 mL of solvent) at a given temperature T . It can be expressed through absolute supersaturation, $\Delta c = c - c_{\text{eq}}$, or relative supersaturation, $\sigma = \Delta c / c_{\text{eq}} = (c - c_{\text{eq}}) / c_{\text{eq}}$.
- As supersaturation increases:
 - Material deposits faster on the existing crystals (growth rate increases)
 - New crystals form faster in solution (nucleation rate increases)
 - Crystals get lower quality (defect formation rate increases).
- All these rates increase non-linearly with supersaturation and are system dependent. The challenge is to find and maintain supersaturation, at which growth is sufficiently fast but nucleation is absent and crystal quality is high enough.
- Sometimes the suitable range of supersaturations is large and easy to determine, sometimes it does not exist. The most important factor that determines this range is solubility and its temperature dependence $c_{\text{eq}}(T)$.
- Mass of material, which can precipitate from solution at given temperature can be estimated as: $\Delta m = V\Delta c = V(c - c_{\text{eq}}) = V(dc_{\text{eq}}/dT)\Delta T \approx V\alpha c_{\text{eq}}\Delta T$, where V is volume of solvent, ΔT is the temperature difference between crystallization temperature and temperature, at which solution is saturated, and coefficient $\alpha \ll 1$.
- The practical outcome: to grow large high quality crystals better to have high but not very high solubility.
- Problems with very high solubility:
 - Easier results in not-crystallizing “syrups”
 - Requires more precise temperature control
 - Requires more material
- Problems with low solubility
 - One needs to use high relative supersaturation σ
 - Requires larger volume of solution, temperature range and/or time
 - High probability of nucleation
 - High probability of crystal imperfections
- In the following example three compounds are crystallized from aqueous solution with volume of water $V = 100$ mL at 40°C .

Material	c_{eq} , mg/mL	dc_{eq}/dT , mg/mL/°C	α , 1/°C	ΔT , °C to crystallize $\Delta m = 1$ g	Initial σ to crystallize $\Delta m = 1$ g
Sodium chlorate	1153	11	0.0095	0.9	0.0087
Potassium alum	255	8	0.031	1.3	0.039
Paracetamol	25	0.8	0.032	12.5	0.40

One can see that paracetamol has much smaller solubility than two other compounds. In order to get the same amount of crystals one needs to use much higher supercooling ΔT and relative supersaturation σ . This problem can be alleviated by a gradual cooling over a large temperature range and/or by using a larger volume of solution, however, both approaches are technically more challenging.



Procedure

Materials and equipment

- Solvent and solubility
 - The solvent should provide high solubility of the material. Some target value is 200 mg/mL (20 g/100 mL) but solubility in the range 50 to 1000 mg/mL can be good too.
 - In the extreme cases, when available solvents provide only either very low or very high solubility, a suitable solubility can be achieved by mixing “good” and “bad” solvents. However, this method has a lot of drawbacks and should be avoided. In particular, in the presence of solute even miscible solvents sometimes lead to liquid-liquid phase separation and no stable crystallization.
 - It is highly recommended to determine or obtain from the literature the solubility curve in the desired temperature range.
- Temperature control
 - Growth at room temperature from solutions saturated at higher temperature without additional temperature control and cooling steps is possible for some materials.
 - In most cases solution should be placed into a thermostat, in which temperature can be maintained and changed with an accuracy 0.1 °C or better.
- Crystallizer
 - Should contain enough solution $V = \Delta m / (dc_{eq}/dT) / \Delta T$ to supply mass of crystallizing material Δm ; ΔT is a whole temperature range, over which crystallization is performed.

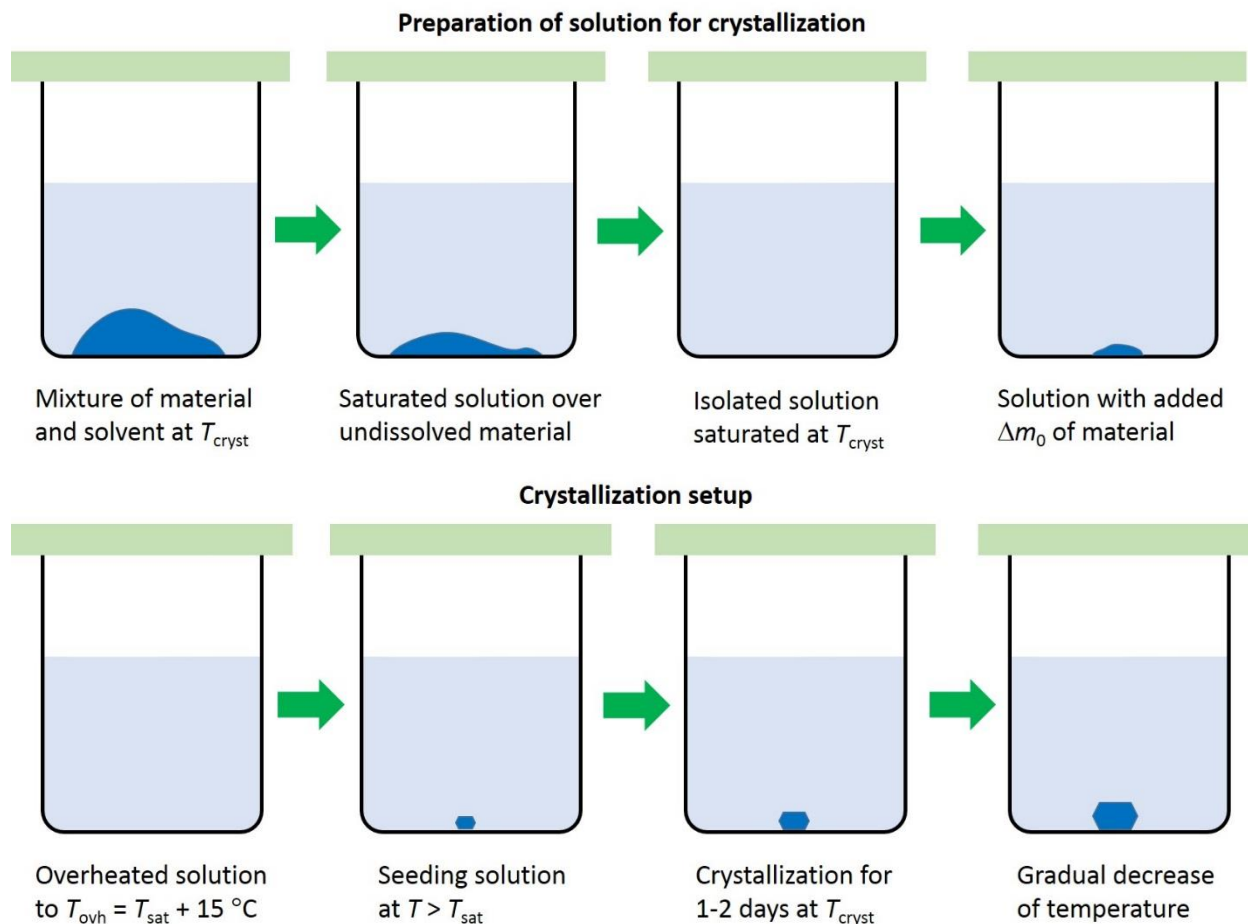
- Should provide enough space around growing crystal for unrestricted convective mass transport (at least 3 times larger than the final crystal size in all dimensions). To grow crystals 1-2 cm in size, a crystallizer of 100-500 mL volume is a reasonable option.
- Shape is typically a cylinder, ideally with the height ~ 1.5 times larger than the diameter.
- Should have a lid to prevent evaporation of solvent and contamination from the environment.

Preparation of seed crystals

- Growth of large crystals should be performed at low supersaturation, at which spontaneous nucleation does not occur but crystal growth is fast enough. In order to make crystallization happen one needs to introduce small crystals of this material, which will work as seeds for the subsequent crystallization.
- Seed crystals should be not intergrown single crystals of high perfection 1-5 mm in size.
- Seed crystals should be obtained in advance from the same material. Growth method and growth conditions are not that important.
- The simplest way to get seed crystals is to prepare solution in the same way as explained below but using larger initial supersaturation ($\Delta m_0 > 1$ g of material for volume of solvent $V = 100\text{-}500$ mL). Dissolve everything at $T_{\text{sat}} + 15^\circ\text{C}$, cool solution to T_{cryst} and wait for a day for nucleation and growth of crystals.
 - If crystals are too small (and there are too many of them), decrease initial supersaturation (simply remove some of the crystals and redissolve the rest) and repeat crystallization.
 - If crystals do not form in a supersaturated solution, one can increase initial supersaturation by adding more material or seed solution cooled to T_{cryst} with a tiny amount ($\ll 1$ mg) of material.

Preparation of solution

- Prepare solution at a constant temperature with the excess of material, so that some material cannot dissolve and remains on a bottom. Stir solution occasionally and allow enough time (a day or two) to equilibrate solution with undissolved material.
- Solution temperature should correspond to crystallization temperature T_{cryst} . For crystallization under gradual cooling, the temperature should correspond to the initial (highest) crystallization temperature.
- The temperature range should be far from freezing and boiling points of the solvent.
- If after equilibration amount of undissolved material is < 50 mg (for solvent volume $V = 100\text{-}500$ mL), proceed to the next step.
- If amount of undissolved material is large, then solution without undissolved material should be carefully transferred into a clean container.
- Add $\Delta m_0 = 50\text{-}100$ mg of material (for $V = 100\text{-}500$ mL). This material is expected to crystallize during the first day of crystallization. This solution will be saturated at $T_{\text{sat}} > T_{\text{cryst}}$.

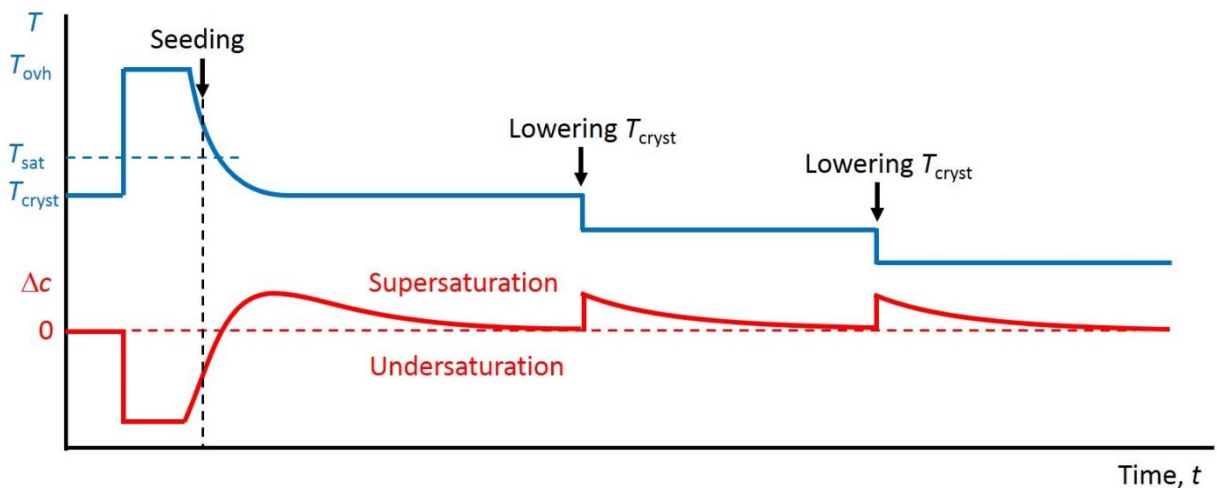


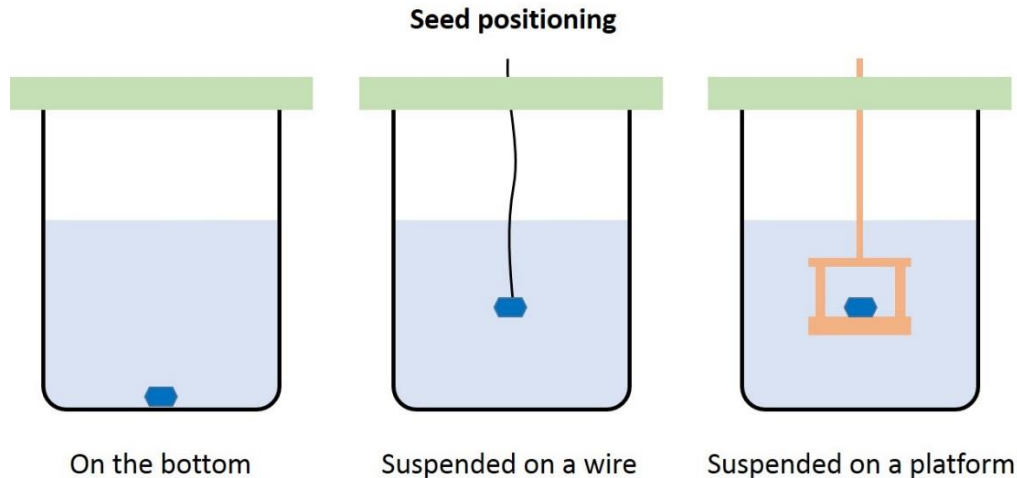
Crystallization

- Overheat solution for several minutes ($T_{\text{ovh}} > T_{\text{sat}}$ by 15-20 $^{\circ}\text{C}$) in a closed container to dissolve all remaining material and stabilize solution against spontaneous nucleation. Now solution is ready for the crystallization experiment.
- If dissolution and overheating is performed in a different container (sometimes it is more convenient but not necessary), solution should be poured into a crystallizer at $T \approx T_{\text{ovh}} > T_{\text{sat}}$. The crystallizer and its lid should be rinsed with the pure solvent and not dried to prevent formation of crystallization centers.
- The overheated undersaturated solution in a crystallizer should be moved to a place, a bench or a thermostat, where crystallization will be performed. This location should not experience much vibrations.
- Take a seed crystal, rinse it with a pure solvent to remove dust of the material from the crystal surface and prevent additional nucleation.
- Carefully place a wet seed crystal into an overheated solution. Ideally, the seed should land in the middle of the crystallizer. Do not touch solution with any tools, just drop the seed. Close the lid immediately.
- While solution is still overheated, the remaining small (a submicron crystal is large enough to grow on its own) crystals will dissolve. The seed itself will dissolve too but its size should be large enough to avoid complete dissolution.

- Within several minutes solution cools down to the starting crystallization temperature. As crystallization proceeds the supersaturation gradually decreases from the initial value to zero. Typically one-two days is enough to exhaust initial supersaturation almost completely.
- If solution is placed in a thermostat and can be cooled in a controlled way, on a first day no additional cooling should be performed. Once it is clear that the seed is growing nicely and additional “parasitic” crystals do not form, the solution cooling can be set up, either continuously or step wise. The cooling rate or cooling step should be determined empirically and can be adjusted as crystallization proceeds.
 - The goal is to have maximally fast growth without spontaneous nucleation, formation of solution inclusions, crystal branching and other defects.
 - If the number of crystals does not increase and the observed crystal quality is fine but growth is too slow, then supersaturation is too low and one can try to increase the cooling rate.
 - If new crystals spontaneously nucleate and/or crystal quality worsen then the supersaturation was too large. At this moment the crystallization experiment should be stopped and then repeated using an adjusted cooling rate.
- To avoid spontaneous nucleation it is recommended not to touch crystallizer and not to open its lid during the whole crystallization process.
- Due to better mass transport conditions higher growth rate and better crystal quality can be achieved if a seed crystal is suspended in solution. This can be done by attaching a thread or a fishing line or implanting a metal wire (if crystal melting point is not too high a wire can be heated and directly melt-in inside a seed crystal).
- In more advanced setups one can mount a crystal on a platform or a rigid rod and rotate during crystallization. This helps a lot to grow larger and more perfect crystals but requires more sophisticated equipment. Do not stir solution using a magnetic stir bar because this often results in a massive crystal nucleation.

Temperature and supersaturation evolution before and during crystallization





Troubleshooting

Every system is unique and therefore there is no way to describe every possible situation. Several common scenarios are summarized below.

- After cooling to T_{cryst} the seed crystal dissolved and no crystallization occurred. If it is not absolutely clear that solution is supersaturated, add a tiny piece of material and see within several hours if crystallization starts.
 - If the added material dissolves, then solution was not supersaturated, more material should be added to make solution saturated at T_{cryst} , so that the whole experiment should be repeated from the beginning.
 - If crystallization starts then the solution was supersaturated. Repeat the experiment with the same solution using a slightly larger seed crystal or place it in solution when solution temperature is slightly lower.
- There is one crystal in the crystallizer and it is growing. The crystal quality is good in the beginning but as crystal size increases, the crystal starts incorporating solution inclusions. This happens because mass transport condition worsen as crystal size increases. Solution stirring (if possible for a given setup) and decreasing of supersaturation usually help.
- There is one crystal in the crystallizer and it is growing. The crystal quality is good in the beginning but as crystal size increases, the crystal starts forming misoriented blocks and cracks. Formation of defects does not happen immediately because it requires some induction time. Decreasing of supersaturation may help.
- There is one crystal in the crystallizer and it is growing but its quality is bad from the beginning. Reduce initial supersaturation. If this does not help, there is no easy solution. Try a different solvent or a different crystallization method.
- There is one crystal in the crystallizer but it grows extremely slow. Likely the solution contains a growth inhibiting impurity. Purification of starting material is a possible remedy but usually it is very challenging. An alternative is to increase supersaturation. Sometimes it helps but it is often accompanied by a lower crystal quality and spontaneous nucleation.
- New crystals nucleate on the bottom.
 - Perform a solution overheating at higher temperature and for longer time. Very often this can help stabilize solution against spontaneous nucleation.

- Better rinse/partially dissolve a seed crystal to avoid additional nuclei coming into a crystallizer.
- If none of these options works, decrease initial supersaturation (remove some crystallized material and perform crystallization again).
- New crystals nucleate on walls above solution level. Likely the solvent is evaporating during crystallization. Seal the crystallizer better.