

Bridging the gap

Continuous crystallisation smoothes the step from lab to industrial scale crystallisation, finds **Ni Xiong Wei**



CRYSTALLISATION is one of the oldest unit operations and is widely used in fine and speciality chemicals and pharmaceutical industries. Almost eight out of ten pharmaceutical products and six out of ten fine and speciality chemicals are produced via crystallisation. Examples of products include antibiotics, cancer drugs, healthy food ingredients, food additives, beauty products, and personal products, to name but a few. These products can be highly complex and in large manufacturing plants are often difficult to process to the standards demanded by consumers and regulators. These difficulties have made batch crystallisation a very active research area in past decades.

fundamentals of crystallisation

Crystallisation is the formation of solid particles within a homogeneous phase. It may occur as the formation of solid particles in a vapour, as in snow; as solidification from a liquid melt, as in the manufacture of large single crystals; or as crystallisation from liquid solution. The latter is the main focus of this article, as it is important industrially because of the range of materials in speciality and pharmaceutical industries that are marketed in the crystalline form.

Generally, solution crystallisation consists of two major steps: nucleation and growth. In order for crystallisation to take place a solution must be supersaturated. Supersaturation refers to a state in which the liquid (solvent) contains more dissolved solids (solute) than can ordinarily be accommodated at that temperature. As with any separation method, equilibrium plays an important role in crystallisation. Let's

consider an example that is fairly easy to envisage. Take a cup of boiling water and add sugar while stirring to make a water-sugar solution. Continue adding sugar until no more sugar will be dissolved in the solution: the solution is now saturated. If we add one final teaspoon of sugar, the sugar that will not dissolve will help the first step in crystallisation, ie nucleation.

When working on an industrial scale, we know that a large supersaturation force is needed to drive nucleation, however, what actually initiates the nucleation is not well understood. Among different initiation mechanisms, the most important is that of collision breeding: when a crystal touches another crystal or any other solid object, such as the walls of a crystalliser, this produces fresh crystal nuclei. This is a very rapid process, in fact it often is too fast to be reliably controlled.

Once the nucleation has been initiated, crystal growth depends on mass transfer and requires turbulent mixing to take the solution to the crystal surface, where it takes part in the surface crystallisation process. Consequently, the state of the mixing in a given crystalliser is an important factor in controlling the uniformity of the crystal sizes. Mixing also keeps crystals in suspension throughout the process, and in some cases prevents segregation of the supersaturated solution from causing excessive nucleation.

Cooling is one of the most common methods of achieving supersaturation. In the water-sugar example, since the solubility of sugar in water decreases with decreasing temperature, as the solution cools, its saturation increases until it reaches supersaturation and crystallisation begins. Figure 1 is the typical diagram describing a solution crystallisation process. When a hot and under-saturated or saturated solution is cooled, the solution crosses the solubility curve as shown in Figure 1 and becomes supersaturated. As the cooling continues, the solution enters the "metastable" zone where nucleation begins via either induction or seeding. The crystal growth takes place as the

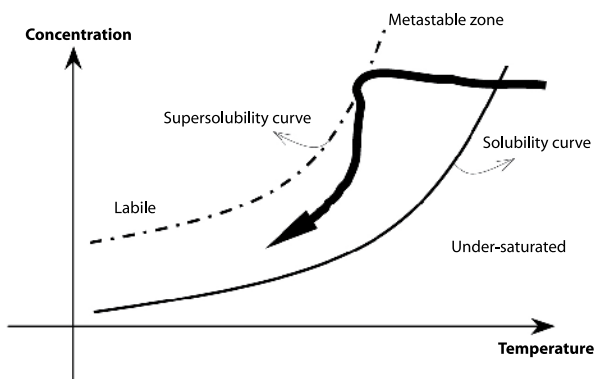
concentration decreases. The main cooling cycle is in the supersaturated state within the "metastable zone". In order to obtain the desirable crystal specification, industrial-scale batch crystallisation operations have to follow the "concentration-temperature path" of the bold arrow as shown in Figure 1. However, this is still not a trivial task.

challenges in industrial batch crystallisation

The following process variables affect solution crystallisation process: supersaturation, solute concentration, temperature, mixing, cooling profile, solvent/additives, seeding, materials of crystalliser and etc. Since no complete theory is available to model nucleation and crystallisation, their behaviours can only be anticipated by experimentation, making accurate measurements essential to understanding crystallisation processes. A number of techniques have been used to monitor the process variables at lab scale. Optical turbidometric UVvis probes measure the metastable zone width, X-ray diffraction (XRD) monitors polymorphism, Fourier transform infrared spectroscopy (FTIR) gauges supersaturation, ultra sound spectroscopy (USS) assesses crystal size, focused beam reflectance measurement (FBRM) records the chord length and chord size distribution of the crystals online while particle vision measurement (PVM) gives online data on crystal shape, and particle image velocimetry (PIV) evaluates local velocities, and so on. These techniques have promoted significant advances in understanding batch crystallisation at the lab scale and helped design better crystallisation processes.

However, these advances at the lab scale have not been matched by an equivalent increase in our understanding of scaling up stirred tank reactors (STR), the workhorse of industrial crystallisation. The scale-up of crystallisation processes involves a net result of several independent, but interrelated, steps. A crystallisation vessel is three-dimensional, so as the linear dimensions increase, the capacity of the system increases as the cube of the linear dimension. With this increase in scale, other variables rise on the linear scale with different exponents,

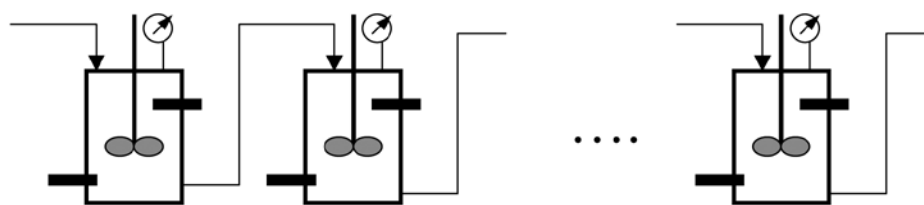
Figure 1: General schematic of a typical solution crystallisation process



which may vary from negative to zero to three and higher. As a result, it has always been difficult to scale up STRs. In addition, experts don't agree which parameters need to be kept constant during scale-up. This has led to some of the problems that beset industrial crystallisation processes today: very long heating and cooling cycles due to the huge batch mass and volumes involved, large concentration and temperature gradients in plant scale crystallisers due to the non-uniform mixing, and large velocity gradients, making the required "concentration-temperature path" as shown in Figure 1 uncontrollable. Inconsistent crystal morphology, long filtration time and inconsistent product quality are some of the direct outcomes of these problems.

In addition, the measuring techniques mentioned above only measure local conditions, ie events at either a point or a very small area within a given crystallisation vessel. The principle of such measurements is based on the assumption that the vessel is well mixed, so that local events can be used to represent the overall measurement of the whole system. The assumption may well be valid at lab and small scales, but both the confidence and capability of measuring techniques decrease substantially with the increase in scale. As a result, instrumentation that has widely been used in lab and small-scale crystallisers is seldom found in batch industrial crystallisation. Even when some measuring probes are employed in large scales, the probes have to be very carefully placed, otherwise, the measurements might not be wholly representative. In other cases, the local fluid mechanical conditions are so poor that the faces of probes are fully covered or in some cases stuck by crystals, making measurements impossible. On top of that, much of the measurement equipment is simply impractical to use in industrial scale crystallisation.

From an operational point of view, obtaining a linear cooling profile, ie a linear relationship between cooling temperature and time, has been shown to



be key to achieving the "concentration-temperature path" of the bold arrow as shown in Figure 1. Whilst it is fairly easy to do so in small STR, it is still a nearly impossible mission in an industrial-scale batch STR due to the huge volume, inherited non-uniform mixing and significant concentration and temperature gradients. Clearly, there is still a gulf between the laboratory understanding and industrial-scale crystallisation. The benefits being realised in laboratory STR cannot be translated into the large industrial operations.

the theoretical solution

In theory, a plug flow crystalliser would be a good solution, as it creates consistent fluid mechanical conditions that create a reliable environment for measurements and consistent crystal properties. A plug flow crystalliser ensures that the radial mixing is uniform, and the axial dispersion is kept to a minimum. It is worth mentioning that plug flow can **only** be achieved in **continuous** operation.

There are two textbook methods of achieving plug flow: firstly, by using a series of continuous stirred tank reactors (CSTR), or secondly, through a tubular reactor operating at turbulent flow.

The first method means connecting a number of well-stirred tanks of equal volume in series. Figure 2 shows the schematic of this type of operation. In theory, when the number of CSTR goes to infinite, plug flow is achieved. In practice, five to ten CSTRs are the norm in most industries today. This arrangement significantly increases inventory in reactors with multiples of controllers, pressure sensors, probes, pumps, flow meters etc, which significantly increases capital and running costs; not to mention that the

fluid mechanical conditions are still far from plug flow.

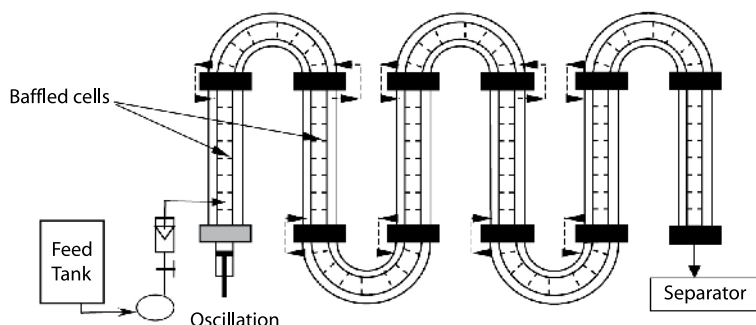
The second method is to employ a smooth tubular reactor that is operated at turbulent flow, ie very high flow rates at a given tube diameter. When the flow becomes turbulent, near to plug flow conditions can be obtained. However, as the mixing in such tubular reactors is driven by the net flow, this means that a very long tube (in a magnitude of miles) is required even to accommodate a crystallisation of just 15 minutes! Hence, such an operation is practically impossible. As a consequence of this, all industrial crystallisation to date has been carried out in batch STR.

continuous oscillatory baffled crystalliser

Now, a new crystalliser may offer a third way. Developed by Scottish technology company NiTech Solutions, the continuous oscillatory baffled crystalliser (COBC) consists of a jacketed tubular device containing periodically-placed orifice baffles superimposed with fluid oscillation. The

Figure 2: Schematic of a series of continuous stirred tank reactors (CSTR)

(Below left to right) Figure 3: The schematic of continuous oscillatory baffled crystalliser
Figure 4: The set up of the COBC



filtration and separation 1

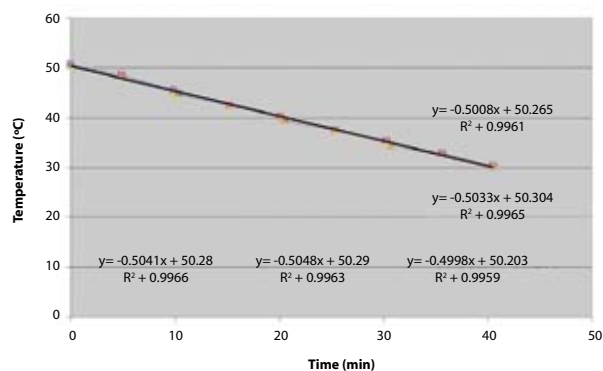


Figure 5: Cooling profile from 50 to 30 °C (cooling rate = 0.5 °C/min, flow rate = 0.3 l/min)

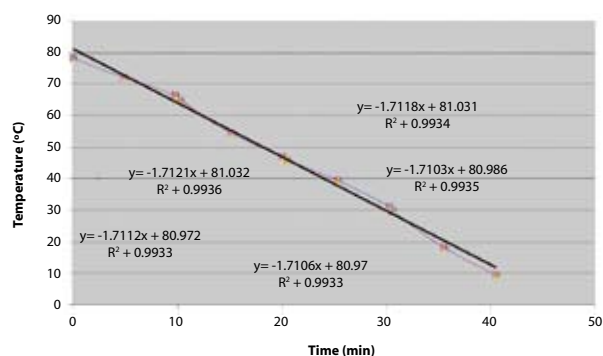


Figure 6: Cooling profile from 80 to 10 °C (cooling rate = 2 °C/min, flow rate = 0.3 l/min)

crystalliser mixes its contents by the generation and cessation of eddies that are formed when fluid flows through the baffles. The mixing in COBC is uniform and highly reproducible in each baffled cell. Each cell effectively acts like a CSTR; when a large number of cells in series is used, as shown in Figure 3, plug flow conditions are achieved under laminar flows (low flow rates). The key differences between the COBC and other tubular devices in the market are a) the mixing in the COBC is governed by the oscillation, **not** the net flow, allowing plug flow conditions under laminar flows, making the crystalliser design and configuration much more compact, significantly reducing the amount of space required, and b) superior heat transfer coefficients are obtained under plug flow. In order to achieve continuous crystallisation, synchronised global and local temperature controls obtain the desired heat transfer and temperature profiles. This results in precise linear cooling profiles in terms of either °C/min or °C/m, along the length of the COBC. Figure 4 shows the set up of the COBC.

Figures 5 and 6 are some of the typical examples of linear cooling profiles achievable in COBC, eg cooling linearly from 50 °C to 30 °C over 40 minutes at a cooling rate of 0.5 °C/min in Figure 5 and from 80 to 10 °C about

40 minutes at a cooling rate of 2 °C/min in Figure 6. In fact, with the set up of COBC, any form/function of cooling profiles can easily be implemented, and profiles can be linear, non-linear, continuous, stepwise or discontinuous.

In addition, any of the aforementioned measuring instruments can easily be implemented along the COBC. As the mixing in each baffled cell along the COBC is uniform, the environment for process monitoring and measuring is very reliable.

At industrial scales, the diameter of COBC is seldom greater than 200 mm. Measuring equipment can be used to its full extent, and process engineers can be much more confident that their local measurements can represent the whole system.

real examples

The following are some of the real cases of crystallisation using COBC. The names of companies and the chemistry used have been excluded to protect commercial confidentiality.

- A global US food company was interested in decreasing the filtration time in one of their products. Their current batch crystallisation operation is carried out in a large STR, typically 20–40 m³, together with either a drum or belt filter operating under strong vacuum. The filtration time is usually 10 hours. The crystallisation process in the COBC was divided into two cooling sections: a cooling rate of 17 °C/min was used from 60 to 33 °C in the first section; followed by a cooling rate of 0.2 °C/min from 33 to 23 °C so that large crystals could develop. Our results indicate that COBC cut crystallisation time from 7 hours to 40 minutes, and the filtration time to 25 mins.
- A large chemical company wanted to increase its filtration index of one of its pharmaceutical products. The filtration index is defined as the ratio of a product of the volume by the height of a filter cake over a product of the pressure applied by the time taken for filtration.

A filtration index less than 1 indicates badly-filtered products; for an index between 1 and 10, the filterability is average; while an index figure of 11 to 100, shows good filterability. Currently, the filtration index for one of the company's APIs varies daily from below 1 to over 10. Their process involves heating up the solution to ~80 °C, and then cooling it to ~50 °C in a 3 m³ STR over 5 hours, without controlling the cooling rate. The company would then cool the solution further to room temperature

and held for a period of time to allow it to separate.

Using the COBC at a controlled linear cooling rate of 1 °C/min reduced the crystallisation time from over 5 hours to less than 10 minutes and raised the filtration index to 23.

- A pharmaceutical company needed to achieve a consistent mean crystal size of ~100 µm. Its current operation uses two 2 m³ STRs, in which it carries out a catalysed reaction followed by a crystallisation step once the catalyst has been removed.

Crash cooling was the only available means in its operations, resulting in much wider size distributions than desired. In some campaigns, crystals stuck to the walls of the vessel and the surfaces of the impeller.

Applying the linear cooling profiles and the appropriate mixing using NiTech's technology resulted crystals that consistently conformed to the desired particle size range. There were also no more cases of crystal-sticking, significantly reducing the down-times.

- Among the pharmaceutical crystals we have tested, one has two crystalline polymorphs, α , which is metastable, and β , which is stable. The objective was to obtain α crystals. In a traditional STR, the operation would encourage α to transform into β , so that most runs would produce primarily β crystals.

Applying the linear cooling profiles together with the appropriate temperature ranges in the COBC resulted in the crystallisation process following the "concentration-temperature path" as shown in Figure 1 throughout. As a result, it consistently and continuously yielded α crystals.

The examples of actual industrial crystallisations illustrate the benefits that can result from using continuous oscillatory baffled crystallisation, eg consistent crystal morphology and size, better filterability, significantly reduced crystallisation time, better use of space and reduced energy consumption.

The message is clear: the process, though still fairly new, is both commercially and technically viable, and provides a unique means of bridging the gap between lab understanding and industrial operation. I hope the article will stimulate interesting discussions, and result in renewed confidence to identify new, useful and perhaps unexpected crystallisation applications using COBC. **tce**

References available from the author

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