# Continuous Crystallization of Pharmaceuticals Using a Continuous Oscillatory Baffled Crystallizer

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## Abstract:

**In this paper, we report an investigation into the continuous crystallization of a model active pharmaceutical ingredient (API) using a continuous oscillatory baffled crystallizer (COBC). The results show that continuous crystallization offers significant advantages in terms of process, operation and costs, and delivers the isolation of the model API in just over 12 min compared to the 9 h and 40 min in a batch process.**

## Introduction

Solution crystallization is one of the most widely used separation processes in the chemical and pharmaceutical industries and it is well-known that the latter has traditionally operated in batch mode.[1] Whilst a batch process may appear superficially simple, the underlying science and its control are highly complex, which can lead to problems in achieving consistent product specifications, e.g. size distribution, correct polymorphic form and morphology. These factors have a direct impact on downstream processes such as filtration, and ultimately on formulation into medicines and their performance. Out-of-specification crystals are sometimes encountered, and therefore milling and recrystallization processes are other common unit operations in the pharmaceutical industry.

Continuous reaction, workup and crystallization have been identified as key elements in improving manufacture in the chemical and pharmaceutical industries, through more efficient use of reagents, solvents, energy and space whilst minimising the production of waste materials and reactor downtime for reactor maintenance and cleaning.[2−7]
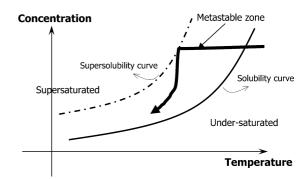


**Figure 1.** General schematic of a typical solution cooling crystallization process.

Solution crystallization can generally be described in two stages: nucleation and crystal growth[8−10] and Figure 1 shows a schematic diagram describing the course of a typical solution cooling crystallization process. Basically, when a hot and under-saturated solution is cooled, it crosses the solubility curve, as shown in Figure 1, and becomes supersaturated. Between the supersolubility and solubility curves, there exists a metastable

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**Table 1.** Scale up rules for mixing in STC

| scale up constant | reference |
|---|---|
| tip impellor velocity | 12 |
| rotational speed of impellor | 13, 14 |
| stirred tank Reynolds number | 15 |
| power input | 14, 16 |
| ratio of impellor to vessel diameters | 17 |
| volume-averaged shear rate | 18 |
| mass transfer coefficient | 19, 20 |
| mean droplet size | 21 |
| mixing time | 22 |
| computational dynamic simulation | 23 |

zone, which provides a region of supersaturation (driving force) where spontaneous nucleation is unlikely to occur. At some point, however, nucleation and crystal growth take place, whilst the concentration of the compound in the solution decreases (desupersaturation).

Whilst solubility of a compound in a solution can be determined experimentally, the supersolubility (Figure 1) or the metastable limit is not well-defined and depends for example on the rate of supersaturation generation (cooling rate), solution history, impurities and fluid dynamics.[11] Some of the parameters listed above are scale dependent. This means that the super-solubility curve, and hence the metastable zone width (illustrated in Figure 1) will change when the reactor's mixing/operation/process conditions vary and when scale up from laboratory to industrial operation is involved. Therefore, on one hand, scale up is necessary to increase production rate, and on the other hand the science of solution crystallization makes it difficult to scale laboratory crystallizations into industrial scale batch operations. An added complication is that our ability and understanding in scaling up a stirred tank crystallizer (STC), typically used in industrial crystallization, is limited as different scale up criteria cannot be met simultaneously, leading to no agreement on a set of parameters to be kept constant in scale up.

Table 1 lists methodologies that have all been used as the scale up parameter in STC. Consequently the process of scaling up STC is case specific. An overview of crystallization scale up can be found elsewhere.[24]

From a fluid mechanics perspective, whilst good mixing can be attained in laboratory reactors, mixing gradients are often found in large scale operations, with better mixing achieved at and near the impeller regimes, and poorer mixing experienced elsewhere.[25−27] This leads to the situation that mixing cannot be linearly scaled-up. In terms of crystallization process, mixing gradients will cause concentration gradients that have direct impact on crystallization process, e.g. supersaturation and metastable zone width. In solution cooling crystallization excellent heat transfer is desirable; however, the specific area per unit volume (m²/m³) for heat transfer decreases dramatically with scale. Therefore, the loss of heat transfer area together with nonuniform mixing on scale up of STCs makes cooling profiles (e.g., linear or parabolic) potentially problematic to implement in any industrial batch STC. Nonetheless open- and closed-loop control of batch crystallization processes have been reported.[28−30]

In terms of monitoring and control, various in-line process analytical technology (PAT) probes are routinely used in laboratory crystallization experiments, e.g. optical turbidometrics for the measurement of metastable zone width;[31] Fourier transform infrared spectroscopy (FTIR) and UV/vis for supersaturation,[32−34] and focused beam reflectance measurement (FBRM) for online chord length of crystals and crystal size

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distribution.[35,36] However, it is still rare to find these probes in industrial-scale operation.

## Oscillatory Baffled Crystallizer

Ideally, a plug flow crystallizer is more desirable, since it can ensure consistent fluid mechanical conditions and superior heat transfer rates. In theory this should lead to a highly reliable environment for the formation of crystals with consistent properties and should allow conditions developed in laboratories to be directly applied to industrial crystallizations. In addition to these advantages, high tonnage products (in pharmaceutical terms >300tonnes/pa) can be achieved in continuous operation rather than a multibatch system, the typical of current operation of the industry.

There are two conventional methods of achieving plug flow: (a) to use a series of continuous stirred tank reactors (CSTR) and (b) to employ a tubular reactor operating under *turbulent* flow conditions. The first method consists of connecting a number of well-stirred tanks of equal volume in series. In theory, when the number of CSTRs becomes infinite, plug flow is achieved. In practice, however, ∼5−10 CSTRs are the norm of most industries. Obviously this arrangement significantly increases inventory in reactors with multiples of controllers, pressure sensors, probes, pumps, flow meters, etc., leading to significantly higher capital and running costs. In terms of the fluid mechanical conditions such an arrangement is still far from plug flow. The pumping solutions in and out of CSTRs may also have serious repercussions on the crystallization products, e.g. by altering the cooling profile and in some cases damaging fragile crystals though attrition.

The second method is to employ a tubular reactor that is operated at turbulent flow, i.e. very high flow rates. When the turbulent flow is reached, near 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 length is required even to accommodate a residence time of just 15 min. Hence, such an operation is practically impossible. As a consequence of this condition, to date, batch STRs have been predominant for industrial crystallization of pharmaceuticals and fine chemicals.

The continuous oscillatory baffled crystallizer (COBC) is a tubular crystallizer containing periodically spaced orifice baffles with oscillatory motion superimposed on the net flow.[37] The mixing in a COBC is provided by the generation and cessation of eddies when flow interacts with baffles, and is thus decoupled from net flow driven turbulence. With the repeating cycles of vortices, strong radial motions are created, giving uniform mixing in each interbaffle zone and cumulatively plug flow conditions along the length of the column at flows that would otherwise result in laminar flow regimes. The fluid mechanical conditions in a COBC are governed by two dimensionless groups, namely, the oscillatory Reynolds number ($Re_o$) and the Strouhal number ($St$), defined as by eqs 1 and 2, respectively

$$Re_o = \frac{2\pi f x_o \rho D}{\mu} \qquad (1)$$

$$St = \frac{D}{4\pi x_o} \qquad (2)$$

where $D$ is the column diameter (m), $\rho$ the fluid density (kg m$^{-3}$), $\mu$ the fluid viscosity (kg m$^{-1}$s$^{-1}$), $x_o$ the oscillation amplitude (m) and $f$ the oscillation frequency (Hz). The oscillatory Reynolds number describes the intensity of mixing applied to the column, while the Strouhal number is the ratio of column diameter to stroke length, measuring the effective eddy propagation.[38]

The motivation of this work was therefore to evaluate the technological and operational merits of continuous crystallization compared to a pharmaceutical batch operation. In particular, the delivery of consistent crystal quality in COBC, such as

- morphology
- size
- size distribution that cannot easily be achieved consistently in large batch operations
- the investigation of additional manufacturing advantages (at development and pilot scale) using COBC,

○ mproved filterability
○ reduced crystallization time
○ reduced space usage
○ reduced utility and energy consumption
○ provided seeding along the flow path if required.

## Materials and Methods

**The Oscillatory Baffled Crystallizer.** Figure 2 shows a photograph and a schematic of the COBC. The COBC was constructed from 25 m long DN25 jacketed glass tubes with a working volume of about 12 L. Baffles were made of PVDF plates and placed periodically along the length of the COBC including bends. The insulation materials were wrapped around the tubes in order to minimise heat loss to the surroundings. The fluid oscillation was achieved using a linear motor and a control box: oscillation frequencies of 1−4 Hz and centre-to-peak oscillation amplitudes of 10−40 mm can be selected, covering the oscillatory Reynolds number from 2300−6150 and Strouhal number of 0.05−0.13. A temperature control unit was designed and used to deliver a cooling rate from 0.25 to 15 °C/min for the process.

The API used in this study was provided by AstraZeneca, which for commercial reasons we are unable to name. The

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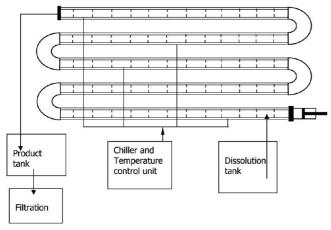
**Figure 2.** Continuous oscillatory baffled crystallizer.



**Figure 3.** The setup of batch OBC.



**Figure 4.** SEM showing rodlike crystal in OBC (cooling rate = 1 °C/min, no seeds).

current batch procedure used to manufacture this compound is as follows: the crude API was dissolved in a solvent and held after dissolution at reflux. After particulate screening, the crystallizer contents were cooled at approximately 10 °C/h under agitation to 20 °C. After a holding period, the contents were cooled to 10 °C under reduced agitation, and held for some further time. The total cycle time of the crystallization process is 9 h and 40 min after which the crystals are filtered, washed with solvent, and dried at 60 °C. The dried crystals are then milled to obtain desired size of the final product. The concentration in the batch process was approximately 6% w/w.

**Analytics.** All of the crystals from the trials were analysed to ensure that they met the API specifications. Base strength was determined by nonaqueous titration using a Metrohm 785 DMP Titrano (Metrohm UK Ltd., Buckingham, UK). Crystal chord length size distributions were measured using a Lasentec focussed beam reflectance measurement (FBRM) probe (Mettler Toledo, Leicester, UK) both in-line and off-line. Optical microscopic images were recorded using the Motic Digital Microscope DMNB1-233 model with Motic Images Plus 2.0 software. Scanning electron microscopic (SEM) images were collected using a Quanta 200 environmental scanning electron microscope (ESEM) (FEI Co. Ltd., Cambridge, UK) and X-ray powder diffraction (XRPD) analysis on the crystals was performed using a Riguku Miniflex (Rigaku Instruments). Filtration studies were performed using a 1 L glass pocket filter (QVF Process Systems Ltd., UK) with a 50 mm diameter sintered Hastelloy filter plate (20 $\mu$m). Filtration was monitored using a digital balance (Sartorius QC35EDE-s, Sartorius, UK) connected to a PC running labworldsoft (IKA, Germany) to collect the weight/time data. Data was collected at three different pressures to assess the dependence of cake resistance upon applied pressure and, he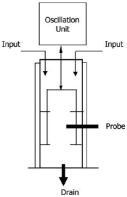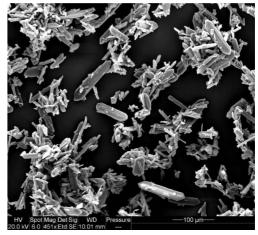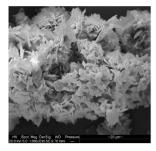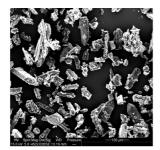nce, compressibility. Data was then processed offline using Microsoft Excel to determine specific cake resistance and medium resistance.

## Results and Discussion

**Batch Tests.** *Screening Tests.* Prior to the continuous crystallization experiments, screening tests were carried out in a 500 mL round-bottom jacketed batch oscillatory baffled crystallizer (OBC) of 50 mm diameter in order to identify the key parameters that influence this crystallization process. Oscillation frequency and amplitude were controlled by a linear motor. Figure 3 is a photo and the schematic of the batch OBC setup. Temperature within the OBC was monitored by a Teflon-coated thermocouple. In addition, a Lasentec FBRM probe was installed in the OBC to monitor crystal growth. A total of 42 experiments were carried out under inert atmosphere, and the following general trends were found:

*a. Effect of Cooling Rate.* Due to the heat transfer rates achievable in the OBC, significant faster cooling rates than 10 °C/h (AstraZeneca's batch process) are attainable for this process, which generated the rod crystals (as shown in Figure 4) that can only be produced by a slow cooling in a traditional batch STC. We also found that aggregates/agglomerates were formed due to the higher nucleation rate in OBC, which then broke up to smaller rods/rod clusters on holding under agitation.

a) Flake-like morphology      b) Plate-like crystals

(crash cool at 3°C/min with no seeds)    (crash cool at 5°C/min with 5% seeds)

**Figure 5.** SEM of crystals obtained in OBC. (a) Flakelike morphology. (b) Platelike crystals (crash cool at 3 °C/min with no seeds) (crash cool at 5 °C/min with 5% seeds).

Agglomeration, as defined by Brunsteiner et al.,[39] is the intergrowth of aggregates formed by particle collisions, through a cementation process that forms an agglomerative bond. The agglomerates were easy to break down.[40] As shown by the work of Alander et al.,[41] supersaturation, particle concentration, hydrodynamics and the solvent all affect agglomeration processes. The agglomerates that form under these conditions in OBC are soft in nature. Platelike morphology was generated as shown in Figure 5 above with a very fast cooling rate (crash cooling, $dT/dt \geq 5$ °C/min).

*b. Effect of Oscillation Intensity.* For mass transfer controlled solution crystallization, one of the mechanisms of transporting the solution to crystal surfaces and then taking part in surface crystallization process is by turbulent mixing.[42] Consequently, the state of mixing in a given crystallizer is an important factor in controlling the uniformity of crystal sizes as well as serving to keep crystals in suspension throughout the process and in some cases preventing segregation of supersaturated solution from causing excessive nucleation.[43] Our results show that, by controlling the experimental conditions, different types of crystals were achieved in the OBC under different experimental conditions as shown in Figure 6, with stronger oscillation giving smaller particle sizes, e.g. the higher the oscillation amplitude or frequency, the smaller the crystal sizes. Note that the vertical axis of Figure 6 is the percentage (0−5.5%) of crystals in each channel of a given size range. Importantly narrow size distributions were maintained (see Figure 6) for all conditions. This indicates that uniform crystal sizes were produced in the OBC for different mean sizes of crystals. The result is unique for OBC, and generated by the uniform mixing environment within the crystallizer.

*c. Effect of Concentration.* In the AstraZeneca's batch process, a ∼6% w/w concentration of the compound was used

for crystallization. It was found that the rod morphology could be generated at higher concentrations with relatively fast cooling rates in the OBC. This is advantageous as this leads to a significant saving on solvent usage. It was also noted that the solution concentration affects crystal sizes, i.e. higher concentrations afforded smaller crystal sizes and vice versa. As an aside, it is possible to elevate the boiling point of the solution by using back-pressure in the flow system, thereby permitting higher concentrations to be used, thus exploiting the power-law behavior of solubility with temperature.

*d. Effect of Holding Time.* From the Lasentec data, it seems that holding time had no significant effect on crystal size distribution at either the nucleation temperature or the end temperature. This observation is again beneficial, since this translates to a substantial reduction in process time.

*e. Effect of Seeding.* Seeding increased the mean particle size. In one experiment, it was found that large rod crystals, as shown in Figure 4, could be generated with crash cooling when 5% w/w seed was added. This finding lends this crystallization process to the adaptation of continuous operation.

All the products obtained were titrated for the measurement of base strength, and were shown to have purities close to that of the seeds material. The XRPD analysis (data not shown) also confirmed that the desired polymorphic form was obtained in all the cases.

**Continuous Mode Trials.** On the basis of the batch data, a COBC was designed and built, and a series of continuous crystallization trials were performed in order to validate the batch results. Two 25 L batch OBCs were used to dissolve the crude starting material and feed it to the COBC using two peristaltic pumps to ensure that the residence time at reflux was less than 40 min to avoid any decomposition. Similar to the batch tests, base strength was analyzed for each run. Crystal size distribution was monitored using a Lasentec probe off-line for samples taken at different temperatures, and optical microscope images were taken at different temperatures in order to follow the crystal growth. Table 2 shows that uniform crystal size can be manipulated by controlling cooling rate, mixing, and concentration in the OBC.

Figure 7 shows an additional filtration study conducted at varying pressures in order to mimic plant performance and the filtration results. Specific cake resistance (a scale up parameter used to assess filtration performance) on the vertical axis is plotted against filtration pressure. Figure 7 also shows that some batches of material (TE-04C and -05C) exhibited incompressible behaviour, indicated by an asymptotic increase in cake resistances with applied pressure once initial consolidation had been overcome, whilst other batches (TE-01C and -02C) were compressible. This behaviour is related to the degree of agglomeration, and hence the applied cooling rate for the crystallization phase, with the more agglomerated material from the faster cool being more compressible. It should be noted that even though some of the material was seen to be compressible, the specific cake resistances observed were all significantly lower than those seen in many pharmaceutical development compounds, being ∼$10^6$ m/kg compared to a typical values of $10^7−10^9$ m/kg.
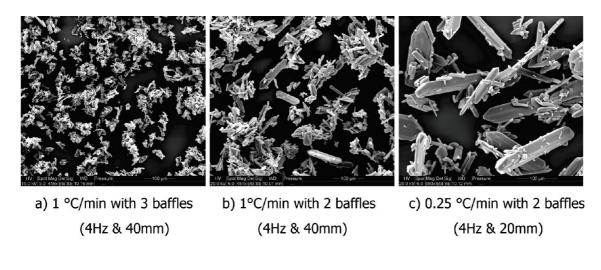
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a) 1 °C/min with 3 baffles
(4Hz & 40mm)

b) 1°C/min with 2 baffles
(4Hz & 40mm)

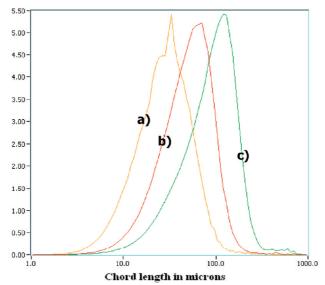c) 0.25 °C/min with 2 baffles
(4Hz & 20mm)

**Figure 6.** SEM of crystals and the corresponding crystal chord size distributions under three experimental conditions. (a) 1 °C/min with 3 baffles; (b) 1 °C/min with two baffles; (c) 0.25 °C/min with two baffles (4 Hz and 40 mm), (4 Hz and 40 mm), (4 Hz and 20 mm).

**Table 2.** Continuous crystallization trials design

| target | cooling | agitation | concentration | seeding |
|--------|---------|-----------|---------------|---------|
| small | fast | high | high | none |
| large rods | slow | low | standard | none |
| large agglomerates | fast | low | standard | none |
| mid size | 1 °C/min | standard | high | none |
| small | fast | high | high | 10% w/w @70 °C |

With COBC a model API was isolated in just over 12 min compared to the 9 h and 40 min in a batch process. Therefore, it would be feasible to replace two 6.3 m³ dissolution vessels and four 6.3 m³ crystallizers by two skid-mounted COBCs in an overall continuous process that could deliver acceptable material in a much faster time.

**Comparing Investment and Operating Costs.** Comparisons can be made of both estimated capital costs and operating costs for a continuous isolation process exploiting COBC as opposed to a traditional batch isolation process.

For the model substance, flow sheets were developed for a batch process and also for an equivalent overall continuous purification and isolation process incorporating continuous
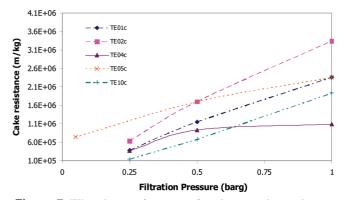


**Figure 7.** Filtration performance for the experimental runs (TE-01C and -02C: cooling rate = 5 °C/min; TE-04C and -05C: cooling rate = 1 °C/min).

dissolution and crystallization. Two dissolution vessels and four crystallizers on the batch process flow sheet were replaced by two COBC units, one for dissolution and one for crystallization, and appropriate materials charging, filtration, and drying equipment selected for the different scenarios. Where possible, similar

equipment was considered in both flow sheets, in order to ensure that differences due to the COBC elements in the design were emphasized.

*a. A New Build.* Approximate capital costs for a new installation were estimated using factorial methods based on known capital equipment costs for major plant items, e.g. batch vessels, service requirements, significant ancillary equipment, and quoted equipment costs for COBC equipment.

This comparison for the purification and isolation steps only indicated that the capital costs for a new installation could be approx 20% lower for the continuous option than a typical $3−5 million batch process.

*b. Infrastructure Consideration.* The capital cost estimating technique did not take into account other factors that would impact favorably on the continuous option such as reduced asset footprint, reduced complexity, and overall reduced number of plant items. Some of these factors were, however, reflected in estimated operating costs for the two options. On the basis of the flow sheets, it was estimated that the operating team for the continuous installation could be about half the size as that required to run the batch operation. On the basis of the scale and complexity of the batch plant this potential saving was considered to be in excess of £300k per annum. Reduced energy costs and increased opportunities for heat recovery could potentially further enable a lower cost of goods to be achieved, although this was not quantified.

Other benefits quantified included operating the process under slightly elevated pressure and temperatures, facilitated by the equipment configuration and the reduced inventory of the continuous system. At scale, a predicted 10% solvent consumption reduction would result in £400k per annum savings.

*c. Crystal Engineering without Milling.* A further cost evaluation was carried out, considering the scenario where the continuous process exploiting COBC could be controlled to engineer the crystals, efficiently delivering a reproducible, right size and shape material, suitable for downstream processing and formulation without the need for milling. Whilst this capability was not tested during the trials, observations during the trials indicated potential opportunities in this area.

Avoiding the need for a milling processing plant using COBC, as opposed to the overall batch processing including milling, represented an estimated 50% reduction in capital costs, and further avoidance of >£300k per annum costs in personnel, milling losses and other inefficiencies. Table 3 below summarizes the comparison.

The biggest perceived benefits, however, were estimated to be in areas of lean production. It was anticipated that the

**Table 3.** Summary of comparison

| | potential saving (£) from traditional batch operation |
|---|---|
| new build | 20% lower |
| operating costs | 300k per annum |
| crystal engineering without milling | 50% lower + >300k per annum |

continuous option would allow production to increase/decrease output easily, with a fast response. Production could be linked to a demand-driven lean supply chain, presenting different options in operating modes, e.g. start/stop vs rate turndown. It was also anticipated that for a new facility a lower investment could be required for a unit with greater flexibility in terms of increasing capacity. The continuous option was estimated to have a wider capacity range for a given equipment configuration.

In summary, for a new installation, significant reductions in both capital outlay and operating costs were identified for the continuous option exploiting COBC as compared to the batch equivalent.

## Conclusions

The results from both batch and continuous experiments using commercial drug substance demonstrated that the continuous crystallization using COBC overcomes the problems facing traditional batch operations, due to the unique features of the increased specific area per volume for heat transfer together with the plug flow conditions in the COBC. The scale up of COBC is linear and involves very small changes in diameter of the tubular crystallization, which ensures that the governing science of solution crystallization remains the same in the scale up, a very important factor that cannot be achieved in the scaling up of batch STC. The combination of these aspects in COBC offers more controls over crystallization process and delivers the isolation of the model API in just over 12 min compared to the 9 h and 40 min in current batch process.

## Nomenclature

$D$ = column diameter (m)
$f$ = oscillation frequency (Hz)
$Re_o$ = the oscillatory Reynolds number
$St$ = the Strouhal number
$x_o$ = oscillation amplitude (m)
$\mu$ = fluid viscosity (kg m$^{-1}$ s$^{-1}$)
$\rho$ = fluid density (kg m$^{-3}$)