# Multistage, multi-zones antisolvent-cooling crystallisation of a proprietary API: Experimental comparison of effect of geometry and hydrodynamics in four batch crystallisers

CMAC FUTURE MANUFACTURING RESEARCH HUB

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## Background

- Early decision making of batch vs continuous and which type of crystalliser to select is a key decision point.
- Four different lab-scale (100's ml) crystallisers were investigated and compared for multistage, multi--zone, antisolvent-cooling crystallisation of a proprietary anticancer active pharmaceutical ingredient (API).
- The seeding load (1&5%), antisolvent addition rate and residence times were fixed across all four platforms based on fixed process conditions.

## Objectives

- This work aims to enable decision making earlier in the development cycle by understanding how batch reactors compare to their continuous counterparts.
- Investigate how to run small scale "batch" experiments to replicate continuous performance.
- Develop a comparative basis to select an ideal crystalliser for early stage development with less material than is currently possible.

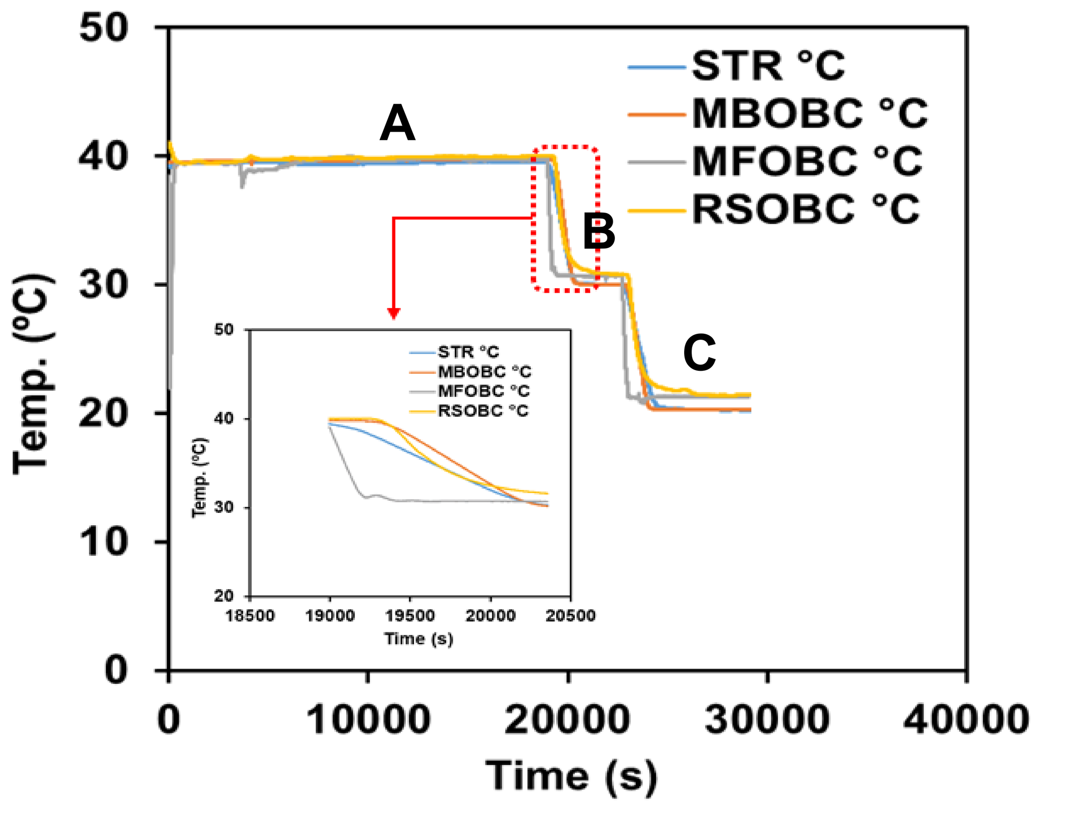



**Figure 1**: Temperature profiles implemented across all the four crystallisers. STR (aka – **STC**) – Stirred tank crystalliser, **MBOBC** – Moving baffled oscillatory baffle crystalliser, **MFOBC** – NiTech DN15 – batch moving fluid oscillatory baffled crystalliser, **RSOBC** – Cambridge reactor design (rattle-snake equivalence) batch moving fluid OBC.

## Process Translation from Continuous to Batch

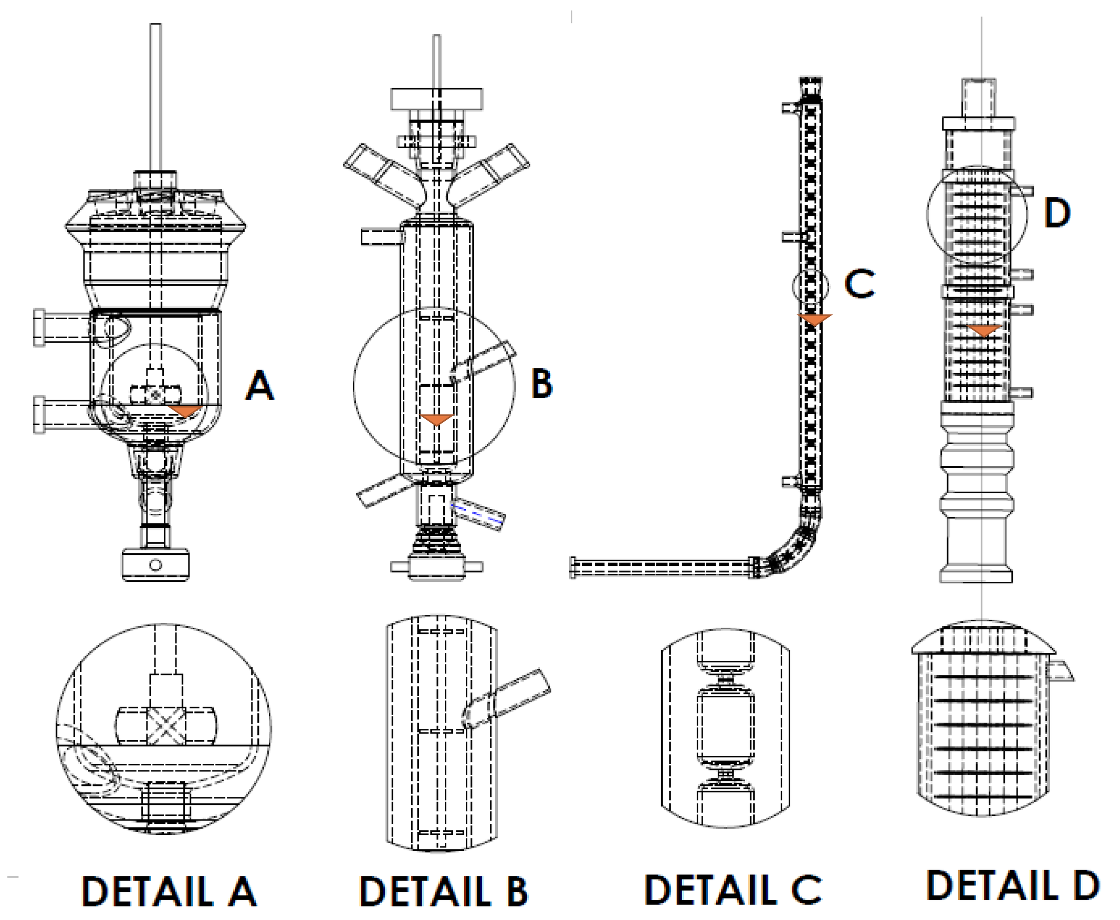
### Process Conditions

- As shown in Figure 1 and Table 1 below, the process conditions implemented were fixed across all the four crystalliser types.
- Antisolvent addition was continuous from stage 1 to 5 at different flow rates.
- Initial investigation using recirculation loop to mimic plug-flow condition in the STR was discontinued due to attrition caused by the peristaltic pump head.

**Table 1**: Process information

| Process Information | | | | | | | |
|---|---|---|---|---|---|---|---|
| Plot regions | | A | | | B | C | |
| Stages | *ID | 1 | 2 | 3 | 4 | 5 | *FD |
| Operating temperatures C | 40 | 40 | 40 | 40 | 30 | 20 | 20 |
| Cryst. time (min) | 60 | 91 | 94 | 71 | 63 | 46 | 60 |

*ID – initial desupersaturation.*FD – final desupersaturation.




**Figures 2:** Parallel comparison of batch reactor geometries used for the multizones and multistage AS-cooling crystallisation of an API. (A) stirred tank crystalliser (STC), (B) MBOBC, (C) MFOBC, (D) RSOBC

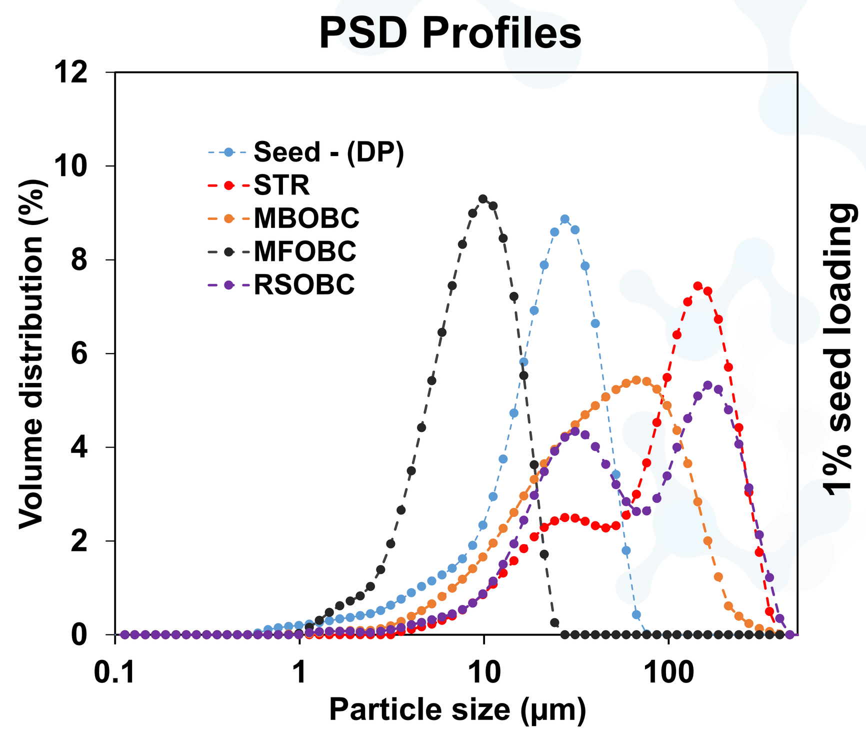
Represents the antisolvent addition point in the crystallisers.

- Previous investigations were carried-out in CMAC comparing the continuous equivalence of the STR – MSMPR and the MFOBC – COBC at multi-kilo scale.
- Similar study was also reported by [1] for STR and MBOBC

**Table 2:** Batch reactors specifications

| Reactor Geometry Specifications | STC | MBOBC | MFOBC | RSOBC |
|---|---|---|---|---|
| Base shape | Conical | Conical | Flat | Flat |
| Inner diameter (mm) | 62 | 40 | 15 | 69 |
| Total vessel height (mm) (excluding the bend) | 100 | 200 | 700 | 500 |
| Total volume (mL) | 250 | 250 | 185 | 1800 |
| Working volume (mL) plus sample volume | 221 | 221 | 221 | 1574 |
| Impeller/Baffle diameter (mm) | 38 | 23 | 3.5 | 69 |
| Baffle orifice/constriction diameter (mm) | NA | 10.5 | 3.5 | 6 |
| Jacketed | Yes | Yes | Yes | Yes |
| Baffle spacing/Impeller height (mm) | 20 | 37.4 | 30.0 | 18 |
| Baffle numbers / Segments (#) | NA | 3 | 33.3 | 23 |
| Number of orifice (#) | NA | 1 | 1 | 33 |

## PSD Profiles



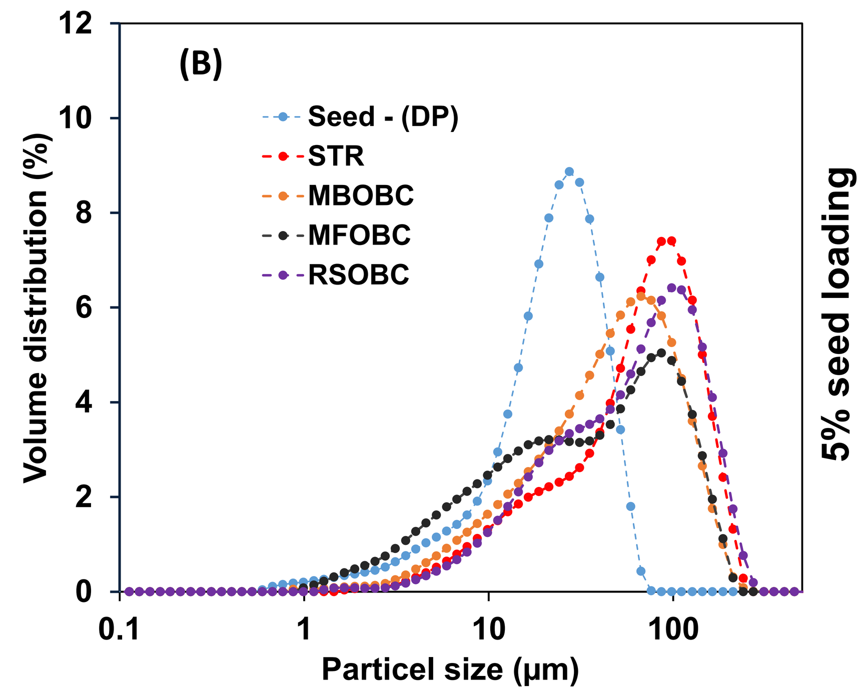




**Figure 3:** Parallel comparison of PSD profiles for AS-cooling crystallisation in four reactor geometries at conditions of 1&5% seed loading. (A) & (B) represent the PSD of the final dried product respectively. See Figures on the right-hand side

**Comments: (A)** RSOBC product's bimodality were more pronounced compared to the STR. A narrower span would have been expected for the MBOBC, but a suspected nucleation effect seems to broaden the span. **(B)** The final dry samples trends were similar with to what was observed in the wet samples. STR and RSOBC resulted in comparable $d_{50}$ with varying degree of fines. The same was observed for MFOBC and MBOBC.

## Microscopic Images of the Final Product

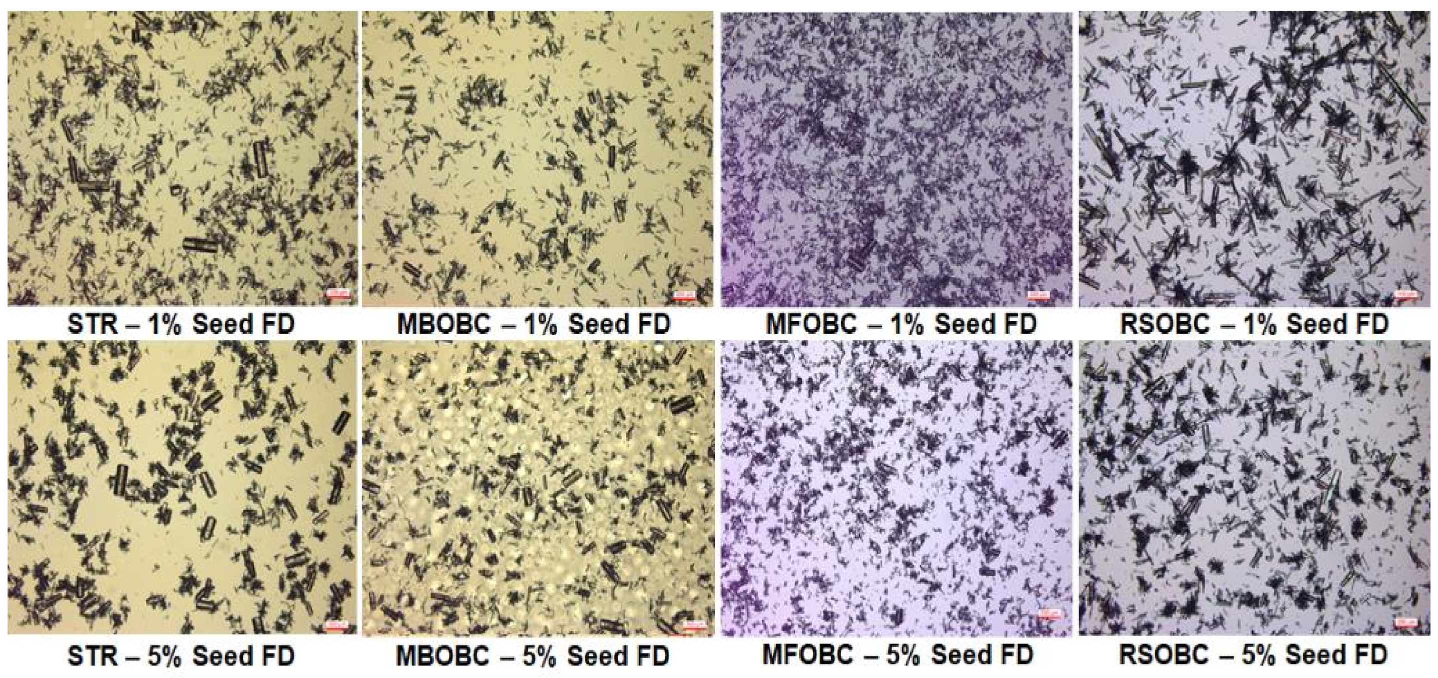



**Figure6**: SEM images of the final crystal from the all the four reactor types at 1 & 5% seed loading.

- **Comments:** From the microscopic optical images shown in Figure 6, mixed agglomerates with short rod-like grown crystals could be observed in the STR, MBOBC and RSOBC.
- MFOBC showed significant presence of agglomerated fines as a result of secondary nucleation. For API with slow growth kinetics[2], efficient heat transfer coupled with high surface area to volume ration may result in supersaturation spikes leading to nucleation.
- It may mean that the better the growth achieved, the less the agglomeration observed. Also, nucleation effect tends to contribute more to the extent of agglomeration.

## Tabularised Comparison of Process Outcomes in Batch and Continuous Platforms

**Table 3**: Comparison of process performance between the batch and continuous crystallisation platforms.

| | Batch Crystallisers | | | | Continuous Crystallisers | |
|---|---|---|---|---|---|---|
| Dimensions | STC | MBOBC | MFOBC | RSOBC | COBC (MFOBC) | MSMPR (STC) |
| Technology Readiness Level | System is well understood and adopted as reference for other newer technologies | System has not been routinely reported for batch crystallisation and might require further engineering characterisation and impact of system hydrodynamics and geometry on product attributes | | | Development unit built for flexibility, not production unit. Easy to change number and position of AS addition points or temp profile | More established technology, more plant-ready |
| Process/Product evaluation | • Notable fouling on the headspace but no crystal settling observed.<br>• 5% seed loading had higher impurity rejection (~90%) compared to 1% (87%).<br>• Bimodality of product PSD observed at 1% seed loading.<br>• Process was optimised for STC. | • Reduced fouling and encrustation observed on the crystalliser.<br>• Comparable impurity rejection with STR.<br>• Higher span compared to STR with unimodal PSD.<br>• Process is non-optimised with more observed agglomeration compared to STC. | • Notable fouling and encrustation observed around the region of AS delivery and settled crystals on the oscillator region.<br>• Impurity rejection are comparable with other platforms.<br>• Process is non-optimised and therefore resulting in notable agglomerated fines. | • Significant encrustation and fouling on the upper half region of the reactor.<br>• PSD were similar to STR.<br>• Impurity rejection are comparable with other platforms.<br>• Process is non-optimised with observed agglomeration. | • Significant fouling observed at the Seed/AS inlet/straights.<br>• At fixed seed loading (~5%) impurity rejection of 76% was achieved.<br>• Process was non-optimised, however, less agglomerated crystals with improved flowability obtained.<br>• Approximately 98% yield comparable to the batch systems was obtained. | • Headspace encrustation and fouling similar to batch equivalence (STC).<br>• At fixed seed loading (~5%) impurity rejection of 79% was achieved.<br>• Process was optimised for MSMPR but obtained crystals were agglomerated.<br>• Yield was slightly lower. |

## Conclusion

- The seed loading directly impacts on the final crystal attributes as observed in the STC and RSOBC, and the overall ease of process handling. An example of an early stage process understanding to foresee likely challenges going from batch to continuous.
- While the implementation of the multistage continuous antisolvent addition and multizones temperature regime were successfully mimicked in the batch systems, mimicking the continuous platform plug flow conditions in the batch crystallisers will require further investigations particularly for the MFOBC.
- Pros and cons were identified for each batch crystalliser. However, optimisation of the process conditions (mixing conditions, temperature, hydrodynamics, and antisolvent addition design in the batch OBC systems should result in improved product attributes with translatable process understanding to continuous platforms.

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## Reference

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