**Project aims**

- To better understand the fundamentals of crystal nucleation mechanisms of pharmaceutical compounds under flow conditions.
- To design continuous crystal nucleation units which enable to achieve control over the particles attributes like particles size, yield, polymorphism, purity etc. using the model pharmaceutical compounds.

**CONTINUOUS CRYSTALLISATION**

![Diagram of mixing, nucleation, and growth stages](image)

**Crystal nucleation mechanism in cooling crystallisation of glycine**

The crucial features of the crystal such as purity, morphology, crystal lattice organisation, size and size distribution are defined by condition during the earliest stage of crystallisation–nucleation. To be able to manage and control the process of the crystal formation (especially in terms of flow), the mechanism of crystals nucleation should be better understood.

**NUCLEATION PATHS**

- **Non-productive nucleation**: Small nanodroplets d
- **Productive nucleation**: Water

**Antisolvent crystallisation – nucleation setups**

**Setup 1:**
- mixing and solution using static mixers (T, X, Y mixers and introducing mixture into a nucleator with an additional agitation element and heating jacket (prevent fouling).
- Continuous crystallisation upon small microcrystals is continuously transferred to the crystal growth unit (tubular crystalliser, OBC etc).

**Setup 2:**
- cold antisolvent is mixed with (warm) solution in a nucleator with a heating jacket (prevent fouling).
- Continuous crystallisation upon small microcrystals is continuously transferred to the crystal growth unit (tubular crystalliser, OBC etc).

**Setup 3:**
- (warm) solution is introduced into the flowing in tubular nucleator cold antisolvent. The solution containing small microcrystals is continuously transferred to the crystal growth unit.

**Initial batch screening tests were done using acetone/isopropanol water solvents and model compound (paracetamol) (Figure 4). The results show strong influence of sample preparation techniques and the type of antisolvent in the final crystal size and the level of agglomeration (Figure 6).**

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**Model compound (paracetamol) – batch screening**

![Diagram of nucleation growth and solvent](image)

**Paracetamol – continuous antisolvent nucleation – setup 1**

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**Paracetamol – continuous antisolvent nucleation – setup 1**

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**Conclusions**

- Higher supersaturation required for larger nucleation rate.
- Too large crystals’ nuclei formed – higher supersaturation/shorter residence time.
- Static mixer – dissolving blockage problem.
- Fouling – heating nucleator walls.
- Operation in fully continuous mode (continuous pipe setup).