Modular test bench for continuous crystallisation

EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

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Project aims

- To better understand the fundamentals of crystal nucleation mechanism 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

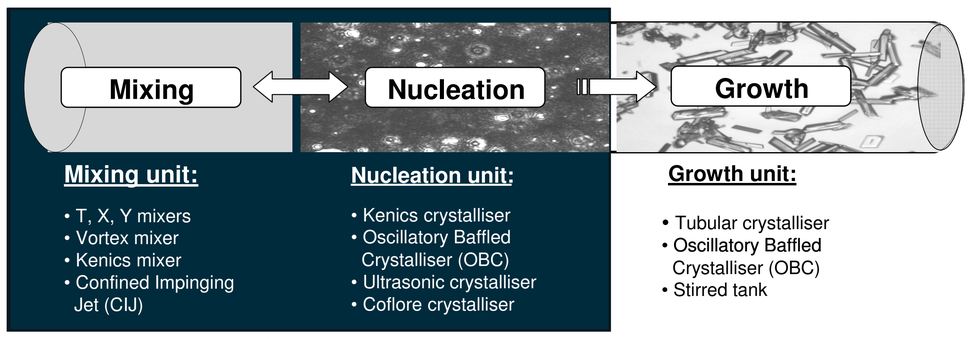


Figure 1. Continuous crystallisation process –pipeline.

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 / control the process of the crystal formation (especially in terms of flow), the mechanism of crystals nucleation should be better understood.

NUCLEATION PATHS

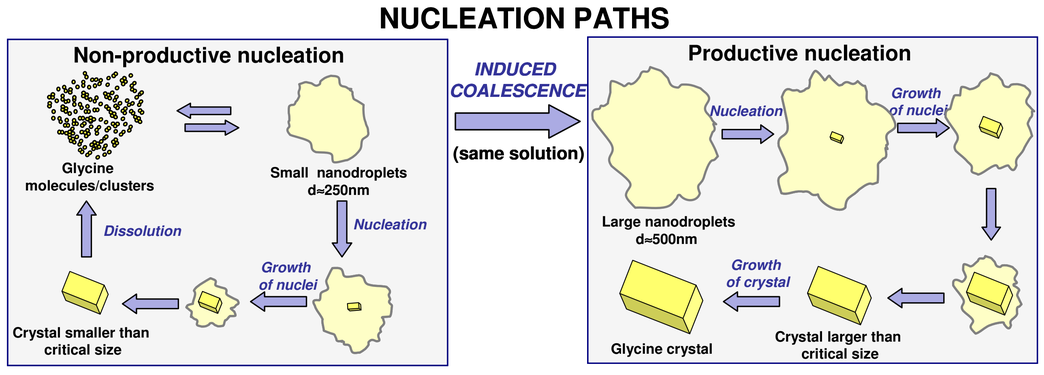
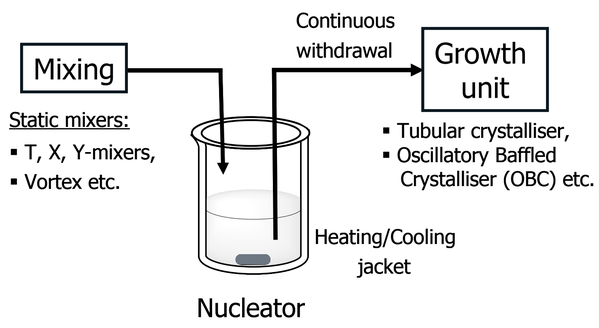


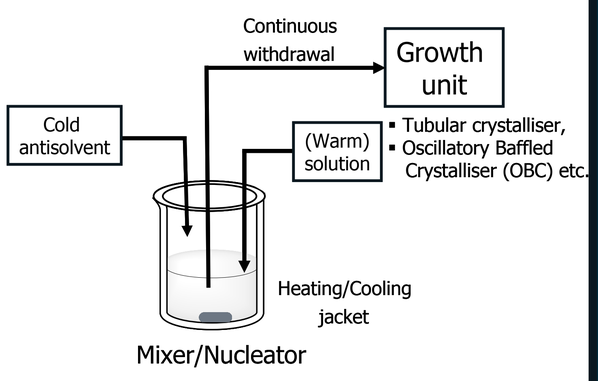
Figure 2. Effect of nanodroplet size on the outcome of nucleation.

Our experimental studies have proposed a two-step mechanism for crystal formation in which crystal nucleation is preceded by formation of disordered molecular assemblies (nanodroplets). By employing scattering techniques sensitive to the presence of much larger species we were able to show that dissolution of glycine crystals leads directly to a small but thermodynamically stable population of ~250 nm diameter glycine-rich nanodroplets. These small nanodroplets were found not to lie on a successful nucleation pathway. Only when larger nanodroplets (>500 nm) were produced, via mechanical coalescence of the smaller nanospecies was the rate of nucleation significantly enhanced. It is proposed that productive crystal growth requires nucleation to occur within a critical-sized solute-rich nanodroplet, i.e. one containing sufficient mass of concentrated solute. Otherwise the nascent crystals produced from the solute-rich nanodroplet will be too small to survive exposure to the more dilute surrounding bulk solution and will simply redissolve (Figure2).

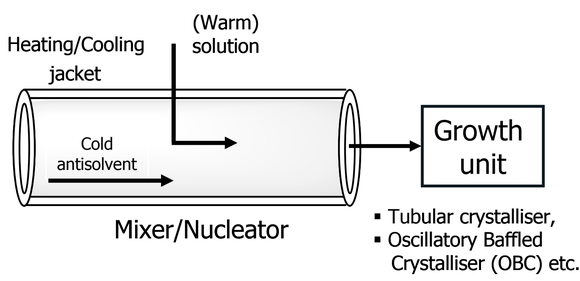
Antisolvent crystallisation – nucleation setups



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



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



Setup 3: the (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.

Figure 3. Continuous antisolvent crystallisation setups.

Model compound (paracetamol) – batch screening

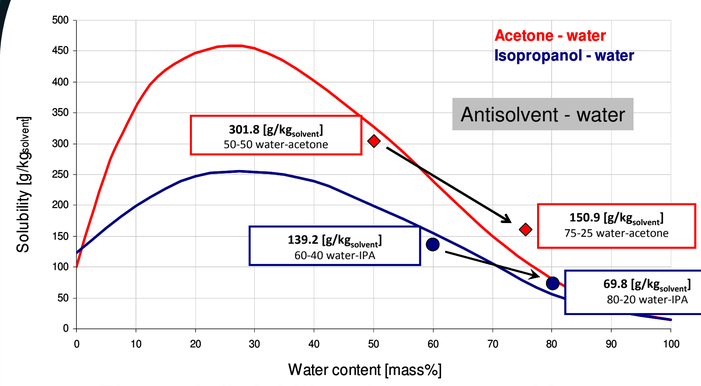


Figure 4. Solubility of paracetamol in acetone /isopropanol – water solvent[1,2]

Initial batch screening test 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).

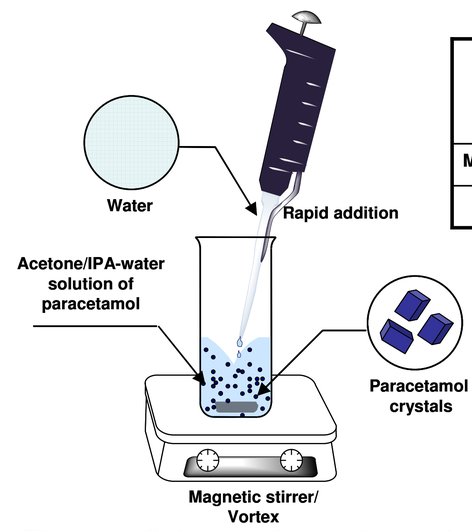


Figure 5. Schema of experimental setup –batch screening.

Table 1. Induction time and solid recovery – batch.

	Acetone-Water Supersaturation 1.45		IPA-Water Supersaturation 1.50	
	Induction time [s]	Solid recovery [%]	Induction time [s]	Solid recovery [%]
Magnetic mixer	55±20	74.4 ±3.0	140 ±83	46.2 ±16.4
Vortex	120 ±36	10.1±2.2	84 ±30	42.3±12.9

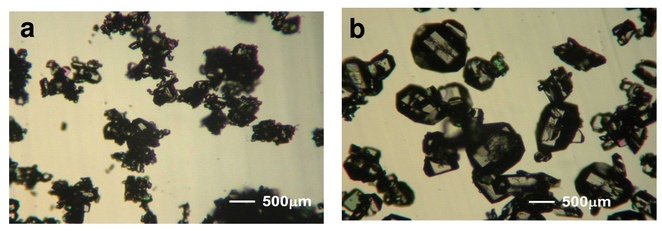


Figure 6. Microscope image of paracetamol microcrystals crystallised from acetone/water solvent a) magnetic mixing, b) vortex.

Paracetamol – continuous antisolvent nucleation – setup 1

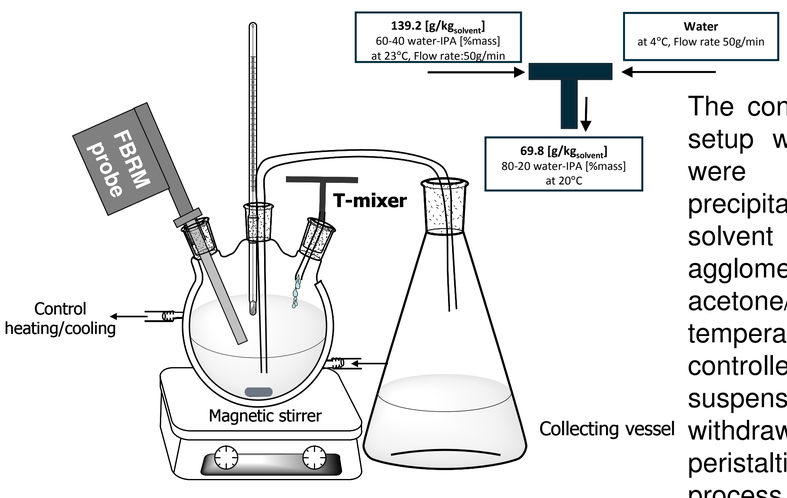


Figure 7. Schema of experimental setup –continuous nucleation (setup1).

The continuous antisolvent nucleation setup with pre-mixing unit (T-mixer) were used for paracetamol precipitation form isopropanol/water solvent (less fouling and agglomeration in comparison with acetone/water systems). The temperature of the nucleator was controlled and microcrystals suspension was continuously withdrawn into collecting vessel using peristaltic pump. The nucleation process was monitored using FBRM (Figure 7).

Paracetamol – continuous antisolvent nucleation – setup 1

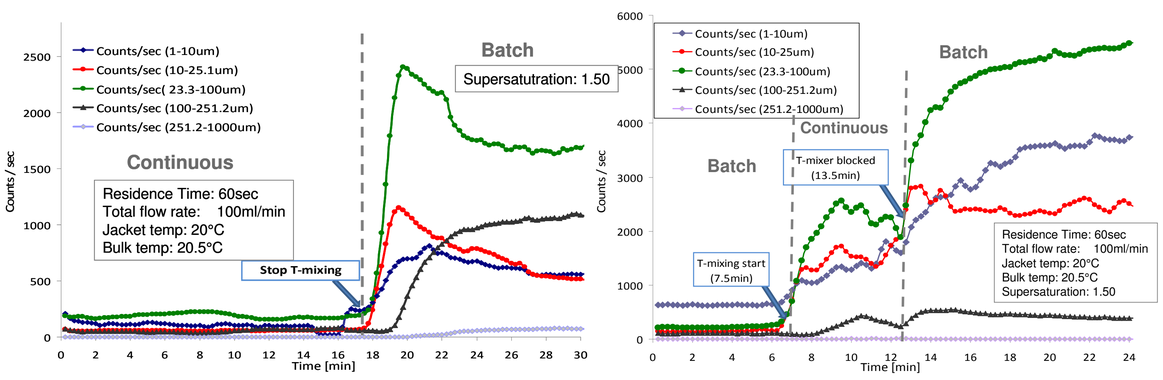


Figure 8. FBRM monitoring of nucleation, a) process-1, b) process-2.

Antisolvent crystallisation of paracetamol (supersaturation 1.5) using the first configuration not shown nuclation after 17 minutes (in a continuous process FBRM). But soon after stopping the continuous withdrawal of nucleai began to appear, and after about 20 minutes steady state was achieved in batch mode (Figure 8a). As it turned out that the pre-mixing is not sufficient to induce crystal nucleation the batch mode was used to generate first nucleai. After about 7.5min the first nucleai was observed and continuous process was started. The nucleator seemed to obtain a continuous steady state mode after about 9min, but T-mixer blocked after 14min (Figure 8b).

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)

References

[1] Roger A. Granberg, Ake C. Rasmuson; '*Solubility of Paracetamol in Binary and Ternary Mixtures of Water+ Acetone + Toluene', J. Chem. Eng. Data* **2000**, *45,* 478-483.

[2] H. Hojjati, S. Rohani; '*Measurement and Prediction of Solubility of Paracetamol in Water-Isopropanol Solution. Part 1. Measurement and Data Analysis', Organic Process Research&Development* **2006**, *10,* 1101-1109.