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Application of FBRM Technology in the Crystallization Process (A perspective)

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Crystallisation is a two-step process, Step 1 being Nucleation (commencement of the new phase) & Step 2 being subsequent growth of nuclei to crystals. The pre-requisite for crystallisation to occur is the formation of a super-saturated solution, which is in a non-equilibrium state. From this point forward, the process is all about moving towards an equilibrium point, to achieve crystal formation.

The typical steps involved in making a particular crystallisation application more robust & with better control, can be grouped into 4 major categories:

- Solvent Selection
- Solubility
- Seeding
- PAT Techniques

Seeding is essential to initiate nucleation and make crystal growth the dominant process. It is often performed to control particle size or polymorphic form. Factors affecting seeding are Temperature, Quantity of seed, Quality of seed & the cooling rate. It is normally easy to add seed as a slurry or create the seed in situ.

Process Analytical Techniques as defined by the USFDA is "A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality".

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Subsequent sections of this Article focus on the aspect of PAT in greater depth.

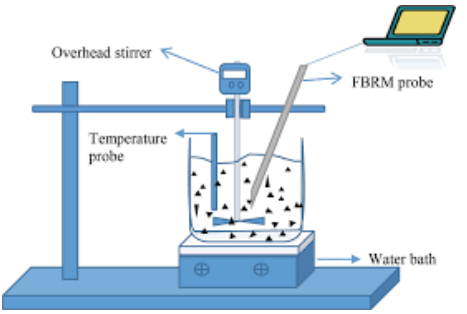
1. Process Analytical Techniques

The USFDA is increasingly interested in PAT, as applied to crystallisation processes, owing to the scope of real time processing and monitoring.

In crystallisation, there are numerous types of PAT that exist. To highlight a few:

- Turbidity (Crystal16 or Labmax)
- **FBRM- Lasentec**
- PVM (for in situ observation)
- ATR UV/Vis spectroscopy
- ATR FTIR spectroscopy
- Raman spectroscopy (useful for polymorphs)

The FBRM or Lasentec has a laser beam that rotates and when it hits a particle, the light back scatters. The time of the back scattering is measured and turned into a chord length. FBRM collects real time data across the size ranges. Statistics can be either number or volume weighted to track fine and coarse particle populations respectively. Particle size distributions at any point in time are displayed as an output.



Particle track with FBRM technology

FBRM - Lasentec is a very important PAT tool in crystallisation development, understanding and control. It conveys information about critical crystallisation sub-processes such as growth,

agglomeration and attrition. Under certain circumstances, it can be used in conjunction with other PAT tools for a more comprehensive understanding. It can also be deployed at various scales, e.g. 50mL to plant scale.

Amongst the many benefits of PAT, there are a few that are worth highlighting:

- Enhanced process understanding - reduced process failures
- Optimal design, continuous monitoring and feedback control – ensured quality
- Reduced cycle time - improved manufacturing efficiency
- Identify the root causes of process deviations – effective troubleshooting

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