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2. Analyze The Crystallization Path That Occurs During Cooling

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ABSTRACT

The pharmaceutical and fine chemical industries rely heavily on crystallisation for the separation and purification of substances. In pharmaceutical active ingredient manufacturing, crystallisation procedures have generally been recipe-based operations, with minimal room for dynamic process control or modification. Traditional crystallisation techniques for pharmaceutical active ingredients were recipe-based, leaving little room for process control and modification. As the regulatory climate shifts from quality-by-testing (QbT) to quality-by-design (QbD) and the process analytical technology (PAT) push takes hold, now is an ideal time to investigate the impact of such quality-based attention on crystallisation control.

KEYWORDS:

Crystallization, super saturation, ATR-FTIR, spectroscopy, crystal characterization image analysis.

Introduction:

Everyone's life is affected by crystallisation, from our food to our medicine to the fuels that power our cities. While in development and production, most agrochemicals and pharmaceuticals go through a number of crystallisation stages. Petrochemical companies are concerned about the dangers of gas hydrates crystallising in deep sea pipes, which are used to produce key food ingredients like lactose and lysine. [1] If the atoms and molecules of an object are arranged into an ordered three-dimensional lattice, then crystallisation has occurred. This arrangement reduces the total energy of the system. During crystallisation, atoms and molecules of a substance come together to form a solid structure with clearly defined angles.

Adding and stirring a solid into liquid results in the material dissolving. Adding more and more solid to the liquid eventually reaches a point where no more solid dissolves. [2] The fluid is considered to as a saturation solution when it reaches this threshold. The crystal size distribution is perhaps the most critical factor in the end product's quality and effectiveness, despite the fact that crystals contain numerous other important characteristics (and the process needed to deliver it). Filtration and drying performance are particularly sensitive to changes in the size and shape of the crystals that come out of the crystallizer. [3] Furthermore, the final crystal size has a direct impact on the end product's quality. Bioavailability and efficacy in pharmaceuticals generally depend on the particle size, with smaller particles preferred because of their higher solubility and dissolving properties. This can be done by selecting the right crystallisation conditions and process parameters to maximise and regulate the size distribution of the crystals. Researchers can build and produce crystals with the appropriate properties and efficiency if they understand how process parameters affect important transformations, such as nucleation, growth, and breaking. [4]

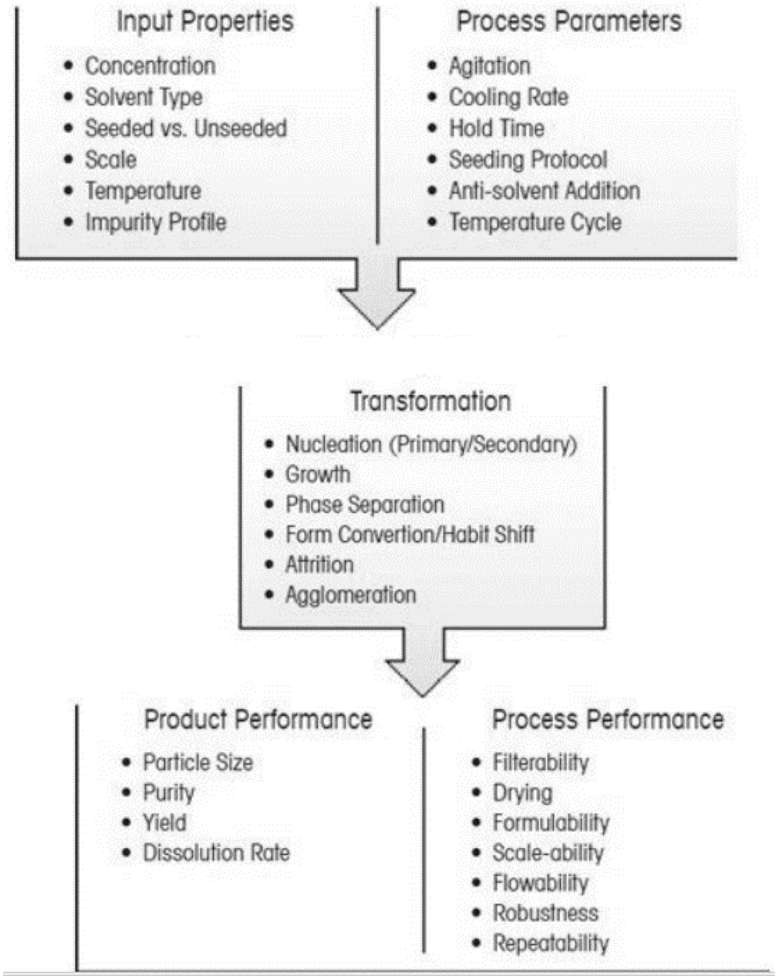

Fig. 1: Crystlization Input Properties, Process Parameter and Performance

Application of Crystallization:

- Water purification from the sea
- Separation of alum crystals from unpurified samples
- To synthesise and isolate co-crystals, purify active pharmaceutical ingredients (API), distribute controlled-release pulmonary drugs, and separate chiral isomers in pharmaceutical drugs, crystallisation is employed as a separation and purification procedure [5].

Review of Literature:

QbD's emphasis on process knowledge has led to the introduction and development of the latest generation of state-of-the-art PAT (process analytical technology) tools and procedures, which open up tremendous new prospects for process control. There has been a review of the use of PAT in crystallisation by Yu et al. 2004[6]. By developing mathematical models for the cooling crystallisation of potassium sulphate and ammonium sulphate, Mullin and Nyvlt (1971) [7] were able to produce 'programmed cooling' profiles. Accordingly, a constant supersaturation was maintained throughout the crystallisation process. Supersaturation does not have to be constant and can fluctuate within the meta-stable zone if secondary nucleation is prevented, according to some researchers (Jones and Mullin, 1974) [8]

As a result, a specific control objective is defined in terms of desired properties of final crystal products such as maximum average size, narrow crystal size distribution, minimum mass ratio of newly-formed crystals to grown seeds, the shortest batch time, or any other combination of these. Nucleation and growth rates as a function of super saturation are used to determine the temperature trajectory that will achieve the goal.

Objectives:

- To investigate the significance of crystallisation and its function
- The effect of cooling rate on crystal size will be studied
- To examine the properties of the inputs, the parameters of the process, and the results.
- Crystallizer factors are examined in this study

Research Methodology:

A research technique is a method for resolving a research issue in a methodical manner. It can be viewed as a branch of science that focuses on the mechanics of scientific investigation. In it, we examine the numerous approaches researchers commonly use to examining their research questions, as well as the reasoning that underlies each one. Research methods/techniques and methodology are essential for the researcher to understand. Secondary sources must be thoroughly reviewed and analysed in order to use analytical and descriptive methodologies to the research. Close study of a few secondary items would be necessary to expand the textual analysis and this would necessitate close reading of secondary materials.

Result and Discussion:

Secondary nucleation occurs at the end of the batch as a result of the cooling rate, resulting in a large number of tiny particles. Supersaturation is consumed faster when the cooling rate is increased, rather than when it grows. Crystal size distribution can only be achieved with precise control over cooling rate. [10]

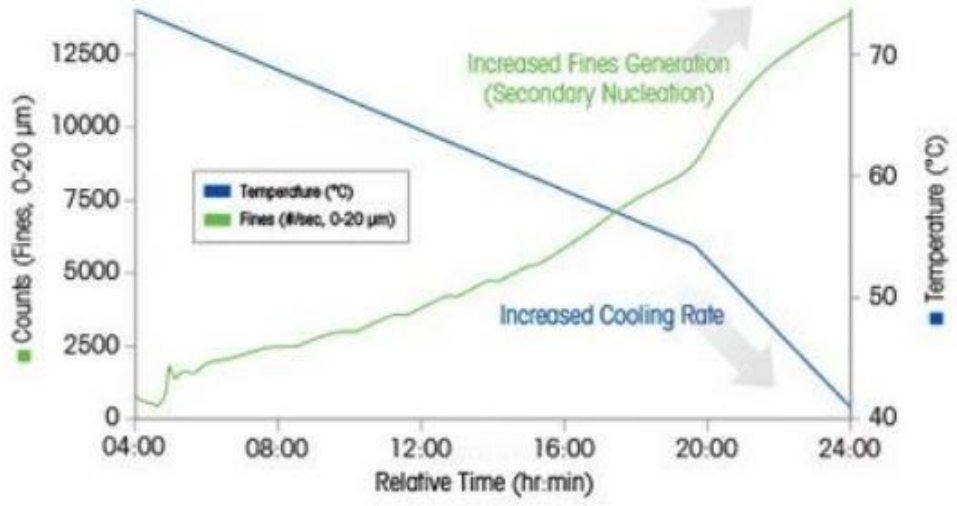

Fig. 2: Analysis of Cooling Rate

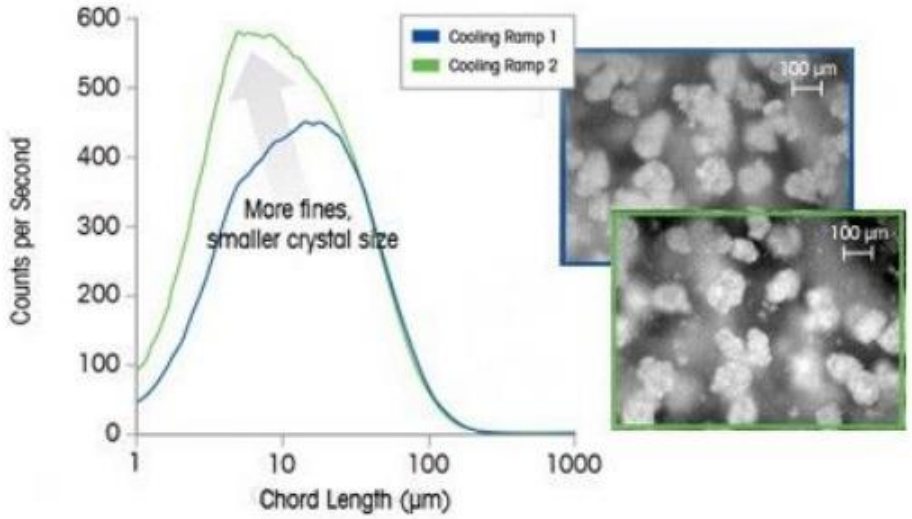

Fig. 3: Analysis of Crystal Size

Crystals smaller than 50 μm are superior than crystals larger than 100 μm in terms of ice cream flavour and consistency. It is critical that agrochemical particles are small enough to be sprayed without clogging nozzles, but large enough to avoid drifting into adjoining fields. [11] However, controlling crystal size distribution across different sizes can be difficult, but understanding crystallisation processes can help assure a cost-effective procedure with the best possible quality. [12-13]

State variables influence crystal quality during crystallisation as depicted schematically in Fig. 4. Notched arrows are used to represent the interaction network. [14]

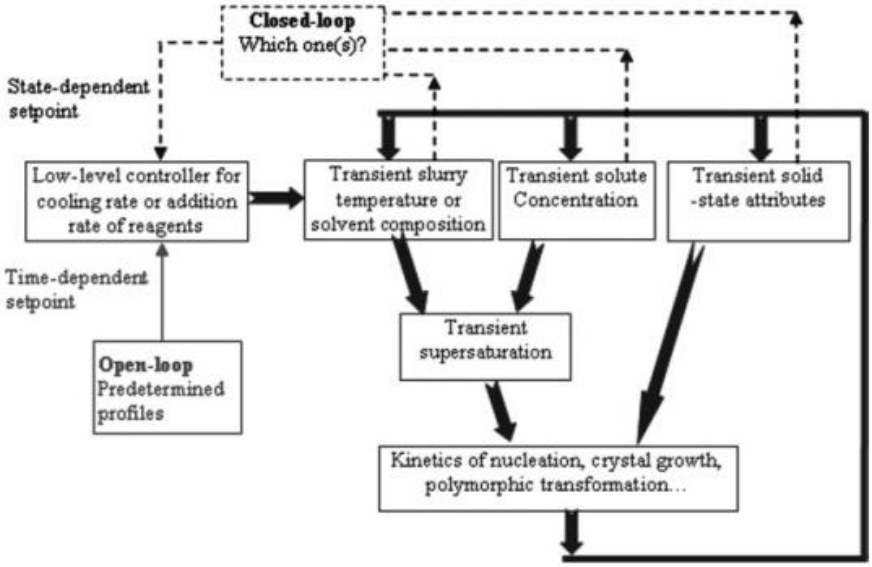

Fig.4: Interplay Among State Variables of The Crystallizer.

It is possible to employ open loop or closed loop control strategies for crystallizers, and which state variables are used as feedback signals in closed loop, or which state variable is handled as the controlled variable in closed loop (solid-state attributes or super saturation). [15]

Conclusion:

Crystallization is a common outcome of rapid cooling in industrial processes. Integral control of crystal formation was observed in all systems studied, notably at greater super saturation levels produced by faster cooling rates.

Lower cooling rates emphasised crystal size enlargement more because of longer retention times and modest de super saturation. Although secondary nucleation was observed in all systems studied, the agglomeration of crystals was more severe in systems with higher cooling rates. Regardless of the crystallizer's impeller type, massive, consistently shaped crystals can be made at low cooling rates.

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