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# Recent Developments in the Crystallization Process: Toward the Pharmaceutical Industry

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ABSTRACT

Crystallization is one of the oldest separation and purification unit operations, and has recently contributed to significant improvements in producing higher-value products with specific properties and in building efficient manufacturing processes. In this paper, we review recent developments in crystal engineering and crystallization process design and control in the pharmaceutical industry. We systematically summarize recent methods for understanding and developing new types of crystals such as co-crystals, polymorphs, and solvates, and include several milestones such as the launch of the first co-crystal drug, Entresto (Novartis), and the continuous manufacture of Orkambi (Vertex). Conventional batch and continuous processes, which are becoming increasingly mature, are being coupled with various control strategies and the recently developed crystallizers are thus adapting to the needs of the pharmaceutical industry. The development of crystallization process design and control has led to the appearance of several new and innovative crystallizer geometries for continuous operation and improved performance. This paper also reviews major recent progress in the area of process analytical technology.



## 1. Introduction

The considerable developments in the crystallization process in the pharmaceutical industry have been accelerated by several high-profile cases over the past few decades. For example, thalidomide was marketed as a sedative or hypnotic in the late 1950s and early 1960s and was used by many pregnant women as an anti-nausea agent. However, while (*R*)-(+)-thalidomide served as a sedative, its optical isomer (*S*)-(−)-thalidomide was tragically found to act as a teratogen, resulting in the malformation and death of thousands of infants [1,2]. Another example occurred in 1998, 18 months after the new commercial product ritonavir was launched. A new stable polymorph (form II) was identified in supplies of the drug [3], which greatly reduced ritonavir's solubility compared with the original crystal form, leading to an oral bioavailability problem [4]. In another example in 2008, rotigotine (Neupro) was recalled in the United States and in Europe because of the unexpected appearance of a new polymorph during storage. The topic of maintaining the stability of a solid-state drug in a dosage form has attracted increasingly significant attention in order to ensure product quality [5–7]. Different forms of solid state can lead to variations in product performance, such as a reduction of solubility and dissolution rates or an increase in tablet hardness. Therefore, crystallization technology, as a core technology, was selected as a means of controlling the factors that impact solid-state phase transformations [8]. The US Food and Drug Administration (FDA) and other regulatory agencies have set strict standards to ensure the safety and stability of pharmaceuticals. Further top-down supervision has put forward higher requirements for medicine production, and particularly for the crystallization process. Based on these practices and on advances in nucleation and growth theory at the molecular level [9–12], crystallization is developing from an empirical science to an evidence- and theory-based science.

Because the requirements for improving the efficiency and

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properties of drugs are becoming more stringent, the pharmaceutical manufacturing sector is considering implementing process automation and launching continuous production facilities [13–15]. Precise control of batch processes and the design of continuous processes lead to more reliable products and to a higher production rate. Significant progress has been made in the control of crystallization processes, leading to improvements in different aspects of crystalline product quality including the crystal size distribution (CSD), polymorphic form, morphology, purity, tap density, flowability, compactibility, solubility, and dissolution rate [16–19]. The development of population balance models of crystallization systems has provided a better understanding of the effects of major process variables, such as agglomeration, breakage, additives and impurities, and process control strategies, on the quality of the crystalline material [20]. Two factors promote the research and application of crystallization process control: first, advances in the understanding of the crystallization mechanism; and second, the advent of process analytical technology (PAT) [20–23].

In recent years, continuous crystallization has attracted increasing interest for crystal production. Mixed-suspension mixed-product removal (MSMPR) crystallizer is the most widely used type of continuous crystallizer; it can be coupled with different control strategies, including model-free and model-based approaches [24,25]. The recently developed plug flow crystallizer (PFC), slug flow crystallizer (SFC), microfluidic crystallizer, airlift crystallizer, and impinging jet mixer crystallizer have shown promising results for optimizing crystal qualities. The oscillatory baffled crystallizer (OBC) also exhibits prospects for practical applications [26–29]. In addition, the coupling of other unit operations with the crystallization process and the incorporation of novel designs have enhanced the process efficiency [30–33].

In this review paper, the factors that contribute to the development of the pharmaceutical crystallization process are grouped into two categories: crystal engineering, and advanced solution crystallization process design and control.

## 2. Crystal engineering

The concept of "crystal engineering" was first proposed by Schmidt [34] in 1971. Today, crystal engineering is a powerful tool for designing pharmaceutical solids with desirable physicochemical properties [35]. The diverse structures in pharmaceutical solids, as highlighted by Cherukuvada and Nangia (Fig. 1) [36], provide considerable maneuverability for optimizing product quality. Various intermolecular interactions and packing modes can be used at the molecular level in order to fine-tune the crystal structure with desired physical and chemical properties [34,37]. "Fine-tuning" includes introducing guest molecules to form multiple-component crystals, screening the crystallization condition for different packing arrangements and/or conformations, and promoting preferred crystal nucleation and growth via tailor-made additives and a solid-liquid surface.

### 2.1. Polymorphism

After the issue with ritonavir in 1998 served as a warning to pharmacists and crystal engineers [3], polymorphism became increasingly important in both fundamental research and intellectual property rights. In addition to its effect on drug safety, polymorphism is an important factor in the testing of generic drugs, a huge expansion of which has occurred following the expiration of many patents of original drugs.

The question of how to screen the new polymorphs using a systematic approach rather than by chance has become an important one. Llinàs and Goodman [38] summarized the time scale of different crystallization experiments. The rapid crystallization process is more likely to form metastable polymorphs (Fig. 2) [38]. Mirmehrabi and Rohani [39] developed a method based on atomic electronegativity for selecting a suitable solvent in the preparation of a desired polymorph. Hydrogen-bonding ability can be predicted by calculating the partial charge distribution of solvent and solute molecules. A comprehensive database was explored by Allesø et al. [40], containing 218 organic solvents and 24 property descriptors. Principal component analysis and self-organizing map analyses enable the convenient and rapid selection of diverse solvents. Besides the organized solvent database, high-throughput crystallization platforms such as CrystalMax (TransForm Pharmaceuticals, Inc.) and Crystal16™ (Avantium Technologies, Inc.) were developed to help

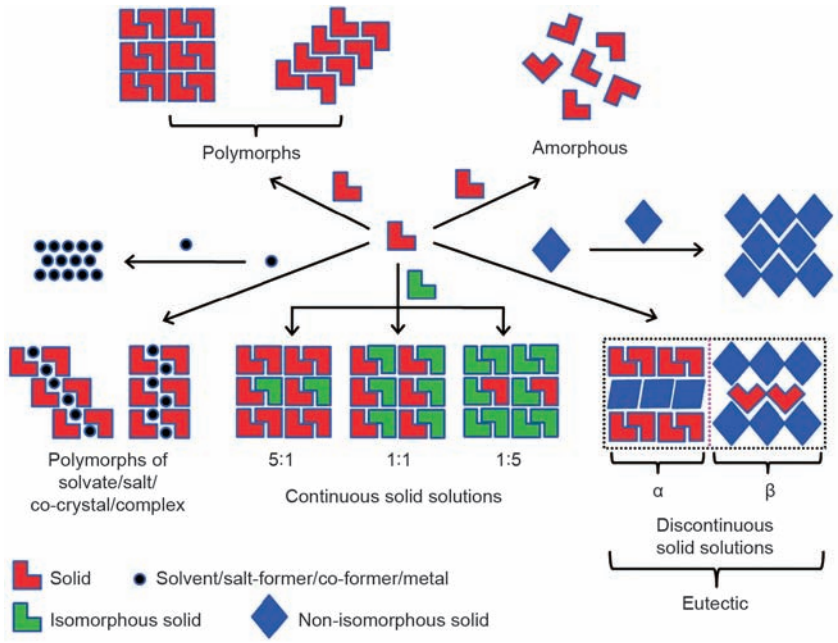


**Fig. 1.** Structural diversity of pharmaceutical solids. (Caption and figure reprinted with permission from Ref. [36])