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# Advances in Pharmaceutical Crystals: Control over Nucleation and Polymorphism

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The Special Issue “Advances in Pharmaceutical Crystals: Control over Nucleation and Polymorphism” collects eight papers focusing on different aspects of crystallization processes for pharmaceuticals. Insightful investigations concerning applied aspects, such as manufacturing and process monitoring, as well as more fundamental aspects, such as polymorphic transformations and co-crystallization, are covered. Innovative solutions to current problems in the production of crystalline drugs, as well as for the improvement in the physicochemical properties of crystal-based pharmaceutical preparations are presented. Additionally, new challenges in drug crystallization have been identified, opening new and interesting research directions in this field.

Crystallization is a widespread unit operation in the pharmaceutical industry, often used as a separation method to obtain highly pure drug substances or intermediates. The process is generally operated in batches, but a shift to continuous crystallization processes is desirable. Kufner et al. [1] proposed an end-to-end continuous manufacturing process involving separated nucleation and crystal growth units. The nucleator allows for the continuous production of nuclei, allowing for long-term operations, as well as a reduced risk of contamination and fueling. An important aspect of any crystallization process is indeed the presence of impurities, which can precipitate alongside the target molecule during crystallization and potentially result in toxicity. Paoletto et al. [2] report that the undesired crystallization of a poorly soluble impurity, i.e., curcumin, can be kinetically hindered by seeding. They coupled a regression model with a population balance model to explore the impact of different process conditions, i.e., seed amount and purity and total crude concentration, on the acetaminophen product purity in the presence of curcumin. The seeds’ purity was found to mostly affect the acetaminophen purity.

Polymorphism is of crucial importance in the pharmaceutical field, as the crystal form of a drug affects many properties, such as stability and bioavailability. Therefore, the phase transformations during the crystallization process, but also during storage, have to be monitored through appropriate characterization methods to understand the impact of the process parameters on drug stability. Li et al. [3] studied the solution-mediated phase transformation of the metastable  $\alpha$ -form of glycine to the stable  $\gamma$ -form using different operating parameters, i.e., agitation speed, temperature, seeding, and salt concentration. The phase transformation was monitored through in situ Attenuated Total-Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) and Raman spectroscopy. Nevertheless, the polymorphic behavior of a substance can also support understanding of the specific interactions occurring between molecules inside the crystals. Salinas-García et al. [4] discovered that the ionization of aspartate and glutamate impacts the crystal form of a postsynaptic density protein, i.e., PSD95-PDZ3. Their results pointed out that the electrostatic interactions are the preferred protein–protein interactions, and that the pH of the precipitant solution determines the obtained polymorph.



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The targeted crystallization of Active Pharmaceutical Ingredients (APIs) is a key aspect because of the huge impact the crystals' characteristics have over their use in the pharmaceutical industry. Specifically, to obtain enantiomerically pure crystal phases from racemic mixtures is desirable. Herbst and co-workers [5] have systematically studied the crystallization and multicomponent crystal formation of the gamma aminobutyric acid (GABA) structurally related chiral drugs Baclofen and Phenibut, searching for a relatively simple method to obtain eutomer pure crystals. Their study found that the formation of multicomponent species with both tartaric acid and malic acid is possible in all cases, but challenges arise in obtaining single crystals and pure microcrystalline phases due to the presence of intermediate hydrates. They emphasize the challenges in achieving phase purity due to molecular influences such as chirality, propensity to form hydrates, and low solubility of Baclofen and Phenibut.

Cocrystals are valuable crystalline solids that can tune the physical properties of an API without changing its chemical identity or biological activity. For the analgesic Diclofenac, co-crystallization has been deeply explored to compensate for its extremely poor aqueous solubility. Mirocki et al. report a novel mechanochemical approach to obtain a new 1:1 Acridine-Diclofenac salt [6]. The liquid-assisted grinding (LAG) method they employed has allowed to efficiently produce the cocrystal salt in high yield. The authors have also communicated that the synergistic interaction of both molecules generates a cocrystal with a higher melting point than the melting point of each single component. The procedure has been designed to reduce waste and energy consumption, making it suitable for industrial application.

Cocrystals can be obtained as a result of the crystallization of compounds made of the stoichiometric non-covalent bonding of two (or more) molecular independent moieties, also known as supramolecular compounds. The production of supramolecular compounds cocrystals containing APIs can be interesting for the development of novel pharmaceutical forms with improved properties. Tinidazole (TNZ) is a well-known antiparasitic drug widely used for the treatment of amebic and parasitic infections, but there is still room for improvement regarding its stability. To face this challenge, Li and coworkers have synthesized three supramolecular compounds made of TNZ with three different hydroxy-carboxylic acids [7]. The authors prepared high-quality rod-like cocrystals by slow evaporation of acetone-dissolved mixtures. The crystal structure analysis showed that non-covalent interactions generate the three-dimensional framework which demonstrates the supramolecular nature of the obtained novel compounds. A thermogravimetric analysis (TGA) confirmed that the combination of TNZ with the hydroxy-carboxylic acids resulted in an increase in the thermal stability of the raw acids. Even if no increase in thermal stability of TNZ was observed, the new strategy developed to produce TNZ cocrystals and the principles found by the authors are encouraging for further exploration of co-crystallization trials with other additives.

The improvement in drugs' water solubility is a major aim in pharmaceutical research. Different approaches have been explored for this purpose; for example, using excipients that facilitate drug release, or other strategies based on crystallization such as co-crystallization (as seen above) or polymorph screening. The study presented by Zámotný et al. aims to improve the dissolution properties of poorly water-soluble drugs by impregnating a hydrophilic matrix with hydrophobic drugs [8]. The authors chose Meloxicam as a model of an extremely insoluble drug and microcrystalline cellulose as a carrier. The results indicate that the dissolution rate can be optimized by controlling the quantity of the impregnated drug and the number of impregnation cycles. An optimum is identified for maximizing the Meloxicam release rate, allowing for superior dissolution behavior compared to tablets made from a physical mixture. Polymorphism is relevant in the properties of a crystalline API, as it can determine if a crystal form is acceptable for pharmaceutical use. In this work, the authors demonstrated the presence of the polymorph I of Meloxicam in the optimized dosage form, which is currently allowed in pharma, making this work of special relevance for further industrial application.

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