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Review

Solution Cocrystallization: A Scalable Approach for Cocrystal Production

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Abstract: With an increasing interest in cocrystals due to various advantages, demand for large-scale cocrystallization techniques is rising. Solution cocrystallization is a solvent-based approach that utilizes several single-component crystallization concepts as well as equipment for generating cocrystals. Solution-based techniques can produce cocrystals with reasonable control on purity, size distribution, morphology, and polymorphic form. Many of them also offer a scalable solution for the industrial production of cocrystals. However, the complexity of the thermodynamic landscape and the kinetics of cocrystallization offers fresh challenges which are not encountered in single component crystallization. This review focuses on the recent developments in different solution cocrystallization techniques for the production of pharmaceutically relevant cocrystals. The review consists of two sections. The first section describes the various solution cocrystallization methods, highlighting their benefits and limitations. The second section emphasizes the challenges in developing these techniques to an industrial scale and identifies the major thrust areas where further research is required.

Keywords: cocrystals; solution cocrystallization; scale-up; cocrystallization kinetics; modeling; PAT tools

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1. Introduction

Cocrystallization is the process of producing cocrystals, i.e., crystals with two or more molecular species in a specific stoichiometric ratio within a crystal lattice. The different molecular species associated with forming the cocrystal are referred to as the coformers. The coformer molecules are associated together primarily by noncovalent interactions such as hydrogen or halogen bonds. Among pharmaceutical and nutraceutical compounds, cocrystals are chosen to ameliorate the physicochemical properties such as dissolution rate, bioavailability, and aqueous solubility, in comparison with single component crystals [1]. Cocrystals also exhibit different stability, melting points, mechanical properties, and polymorphism with respect to the coformers [2–4]. Various cocrystallization methods in the literature can be categorized into two major classes, solution-based and solid-state processes. Solid-state methods involve using a little or no solvent, while solution-based methods use copious amounts of solvent, necessitating subsequent separation of the crystalline product from the mother liquor [5]. An appropriate method for cocrystal production can be chosen based on the requirement of final crystal properties, like crystal size, morphology, and purity i.e., critical crystal attributes. These crystal attributes are affected by the cocrystallization strategy, and thus, selection of suitable method is the primary step in production. The major advantages and disadvantages associated with solution-based and solid-state methods are listed in Table 1.

Table 1. Advantages and disadvantages of the solution and solid-state cocrystallization.

Solution Cocrystallization	Solid-State Cocrystallization
• Use of solvent for cocrystallization.	• Use of negligible or no solvent for crystallization.
• The driving force required is supersaturation.	• Crystal formation is forced through shear mixing or by melting and resolidification.
• Examples: evaporation, cooling, antisolvent, slurry crystallization techniques.	• Examples: grinding, extrusion, spray congealing techniques.
Advantages	**Advantages**
• Well established methodology and apparatus.	• Green technique due to avoidance of solvent.
• Reasonable control on control size, morphology, and polymorphic form is possible.	• Avoids formation of solvates.
• High purity of cocrystals.	• Single-step process.
• Easily scalable, both for batch and continuous mode.	**Disadvantages**
• Efficacy in screening.	• Poor control on crystal properties.
• Established PAT (process analytical technology) tools for monitoring.	• Difficulty in real-time monitoring using PAT.
Disadvantages	• Not appropriate for thermally labile drugs.
• Separation of crystals from the mother liquor.	
• Solvent disposal or recycling.	

The solution cocrystallization is advantageous over solid-state methods in various aspects, including better control on crystal properties, high purity, and industrial scale-up. Solid-state methods often lack control over crystal properties, need high thermal or mechanical energy, and many are difficult to scale-up [6]. Energy intensive solid-state methods have to address the challenges associated with crystal defects and amorphization, which affect crystal purity [7]. However, solution cocrystallization could enable the complete removal of impurity from the crystallized product and help to overcome challenges to selective polymorphic crystallization [8–11]. It is also a convincing strategy for producing cocrystals on an industrial scale as equipment required for large scale production (e.g., stirred tank reactors) are already in widespread use in the pharmaceutical, food, and agrochemical production centers. Potentially, solution cocrystallization can be applied at various steps of cocrystal manufacturing, ranging from preliminary screening to scale-up for commercial production [12]. Although the first cocrystal drug Beta-Chlor® reached the markets in 1963, there has been only a handful of approved pharmaceutical cocrystals since then [13]. Nonetheless, the number of cocrystals reported in the literature has increased significantly over the last decade and many are in the pipeline for commercialization [14–18]. Recently, reports on drug–drug cocrystals gain traction due to the added benefit of incorporating multiple drugs in a single solid form [19–22]. Looking ahead, the focus has to be on the development of robust and scalable cocrystallization techniques that can cater to the needs of industrial production.

The scale-up of solution cocrystallization is a tedious task, considering critical target qualities of the cocrystal such as yield, average size, morphology, and purity. The complexity is exacerbated as scarce information is available in the literature on the crystallization kinetics and the thermodynamic landscape of many cocrystals. This limits the quantitative and qualitative analysis of cocrystallization for detailed process investigations required for plant-scale manufacturing. Appropriate information on the impact of process parameters on the critical product attributes needs to be established to develop a quality-by-design (QbD) approach for cocrystallization techniques [23]. The application of modelling and advanced process analytical technologies can also help in the design, development, monitoring, and control of cocrystallization. This review focuses on recent examples on solution cocrystallization and the challenges to industrial production, highlighting the need for modeling and application process analytical technologies. This information could help researchers to explore cocrystallization in the context of scale-up for the efficient production of cocrystals on commercial scales.

2. Types of Solution Cocrystallization

Solution crystallization has been used in both batch and continuous modes for industrial crystallization for several decades. Solution cocrystallization is often used on a laboratory scale due to its familiarity, simple design, ease of operation, process monitoring, and control. Solvent selection and the mode of supersaturation generation are the two factors that are crucial at the early stages of solution crystallization. For cocrystallization, the solubility of coformers in a given solvent is key factor in solvent selection. Additionally, other operational parameters such as the crystallizer design, mode of agitation, cooling rate/antisolvent addition rate, seeding, or nucleation control can impact final crystal properties such as shape, size, and desired polymorphic form [7,24]. Zhu et al. investigated the impact of solvent on the growth and morphology of cocrystal through computational and experimental techniques. Comparison of binding energy between the coformers and that with the solvent revealed that the solvent interactions play a cooperative role in forming good quality cocrystals [24]. A cocrystal ternary phase diagram, developed based on cocrystal solubility, can be an effective solvent selection tool to secure high crystallization yield. Using this approach, Holaň et al. examined various organic solvents for the production of agomelatine-citric acid cocrystal. Based on experimental results, methyl ethyl ketone was chosen as a suitable solvent for cocrystallization as it gave the highest process yield (about 90%) and produced large rod-shaped cocrystals [25]. The solvent selection also plays a significant role in the production of the specific stoichiometry of cocrystals. For example, ethyl acetate enables the production of 2:1 cocrystal of caffeine-maleic acid while acetone enables the formation of 1:1 cocrystal [26]. Hence, the solvent used for cocrystallization needs to be selected based on the required cocrystals and the desired crystal attributes.

Examples of the solution cocrystallization methods used in order to obtain cocrystals composed of various coformers are given in Table 2. Commonly reported solution cocrystallization techniques could be divided into four major classes, as highlighted in Figure 1. Methodologies and findings from various solution cocrystallization studies are discussed further in this section.

Table 2. Application of various solution cocrystallization for the synthesis of cocrystals.

Reference	Model Compound	Coformer	Synthesis Method	Remark
Yu et al., (2021) [27]	Urea	Succinic acid	Cooling	Achieved desired polymorphic form
Huang et al., (2019) [28]	Theophylline	Benzoic acid	Cooling	-
Thakor et al., (2020) [29]	Carbamazepine	Nicotinamide	Antisolvent	Synthesized nano-sized cocrystals
Yang et al., (2020) [30]	1,3,5-Trinitrobenzene	1-methyl-2,4-dinitroimidazole	Antisolvent	Production of energetic cocrystals
Guo et al., (2020) [31]	Nicorandil	1-hydroxy-2-naphthoic acid and salicylic acid	Evaporation	Enhanced chemical stability and dissolution rate of cocrystals
Wu et al., (2020) [32]	Quercetin	Nicotinamide	Evaporation	Higher dissolution rate and improved bioavailability
Luo et al., (2018) [33]	Naringenin	Isonicotinamide, picolinic acid, and betaine	Slurry method	Improved equilibrium solubility of cocrystals
Inam et al., (2018) [34]	Ticagrelor	Nicotinamide	Slurry method	Improved solubility and dissolution rate of cocrystals
Cuadra et al., (2018) [35]	Carbamazepine	Saccharin	Supercritical fluid	Higher dissolution efficiency of cocrystal.
Apshingekar et al., (2017) [36]	Caffeine	Maleic acid	Ultrasound-assisted	Improved dissolution rates of the cocrystals.
Liu et al., (2016) [37]	Myricetin	Proline	Ultrasound-assisted	Improved dissolution rate and bioavailability

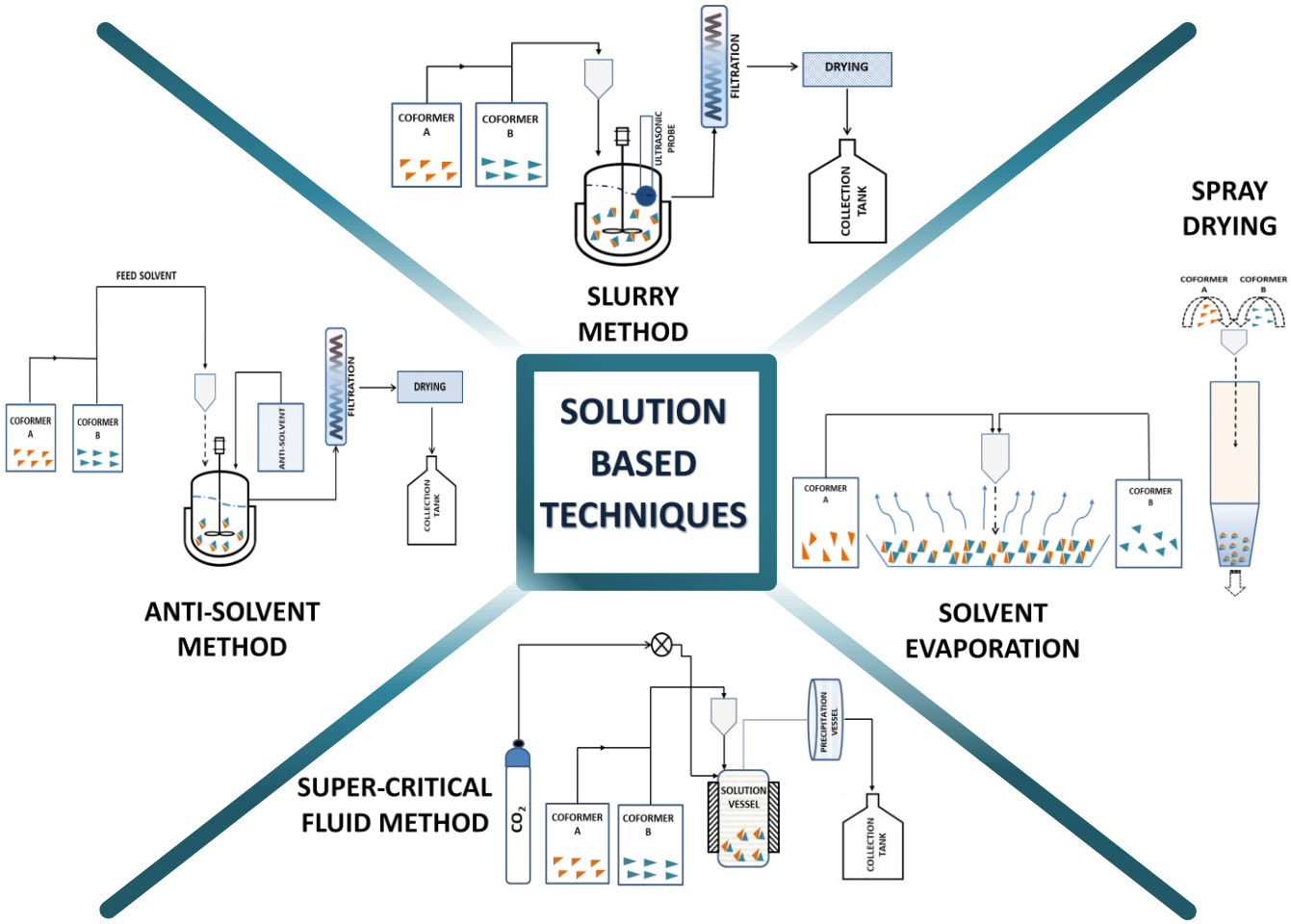

Figure 1. Schematic representation of the commonly used solution based cocrystallization techniques.

2.1. Evaporative Cocrystallization

This method involves the dissolution of the coformers in a suitable solvent, followed by solvent evaporation. As evaporation proceeds, supersaturation is generated, leading to cocrystal nucleation and growth. This is a widely used experimental screening method for possible cocrystal formation due to its simplicity and efficiency in determining the suitable conditions for cocrystal formation. Several authors have successfully used this technique for identifying cocrystals. Some of the cocrystals are carbamazepine-aminobenzoic acid, curcumin-phloroglucinol, curcumin-ascorbic acid, carbamazepine-itaconic acid, and acyclovir-succinic acid [38–42]. Cocrystals of the antiviral drug acyclovir with four dicarboxylic acids have been reported through the solvent evaporation technique. Interestingly, acyclovir did not form cocrystal with malonic acid through the solid-state grinding method [43]. All cocrystals exhibited better solubility and dissolution rate than parent materials. In general, the solvent evaporation method is suitable for low volume screening processes and can be easy to set-up and monitor. However, this method may also lead to the precipitation or crystallization of the pure components or eutectic crystals and undesirable solvate formation. These can be identified by routine analytical techniques such as powder X-ray crystallography or differential scanning calorimetry.

For the cocrystal screening process using solvent evaporation, the solution of coformers can be evaporated quickly using a rotary evaporator or left open in a controlled environment such as an incubator or a fumehood until crystals appear [32,44,45]. Hence, the duration of solvent removal may range from a few minutes to a few weeks. However, the rate of evaporation can significantly affect the formation of crystals. For example, at

low evaporation rates, isoniazid forms eutectic crystals with curcumin while they form 2:1 cocrystal at high evaporation rates [46]. Similarly, the evaporation temperature may affect the thermodynamic landscape of the cocrystal in relation to the pure crystals of the coformers. Phase diagrams can be helpful to identify the conditions that will lead to the production of cocrystals or pure coformer crystals [38,47]. In addition to these factors, the presence of external components such as heteronuclei may also affect the selective crystallization of cocrystal forms [11]. Although solvent evaporation is widely used in the screening process, this technique is less likely to be used in an industrial scale production. The significant challenge for scale-up is the longer batch time required for a large amount of solvent and the massive energy demand for the same [30]. Nonetheless, rapid solvent removing equipment such as spray dryers and rotary dryers have been in industrial use for decades. Thereby, these techniques can be used as preferred kinetic methods for the production of cocrystals, especially when they are the metastable solid form. For example, caffeine-dapsone, saccharin-carbamazepine, paracetamol-oxalic acid, and ascorbic acid-isonicotinamide cocrystals have been produced via rapid solvent removal method [48,49].

2.2. Cooling Cocrystallization

Cooling cocrystallization relies on the temperature-dependent solubility change to achieve cocrystal formation. Both the coformers are initially dissolved in a solvent, and then supersaturation is achieved by reducing the temperature of the solution. Cooling crystallization has been employed on an industrial level for a large number of organic molecules in the pharmaceutical and allied industries. Hence, extensive research has been done on the effect of various operating parameters, control strategies, and process integration steps for this technique, both in batch and continuous modes [50–52]. However, in cooling cocrystallization, the phase diagram of the components at different temperatures is essential for process design [53]. The operating region for producing a specific cocrystal has to be determined based on the relative stability of all the crystal forms and their relative nucleation and growth kinetics. This makes the design and operation of cooling cocrystallization more complex than a single solute cooling crystallization. The purity of the cocrystal would be affected if operated beyond the safe operating conditions. He et al. have reported that the cooling crystallization of caffeine and p-hydroxybenzoic acid can produce single-component crystals or two cocrystals with different stoichiometry based on the relative coformer concentrations [54]. Observations using Pulsed Gradient Spin−Echo Nuclear Magnetic Resonance technique revealed that the variations occur due to the difference in intermolecular interactions between the coformer molecules at various concentration ratios. A similar impact of incongruent coformer solubility and coformer concentrations in cooling cocrystallization has been observed during slow cooling crystallization of carbamazepine and acetamide from acetone and toluene [55]. While carbamazepine dihydrate crystals were formed when the carbamazepine mole fraction was above 0.5, a lower concentration resulted in cocrystals. However, using a 1:1 solvent mixture of acetone-toluene cocrystal was produced at carbamazepine mole fractions in the range of 0.25–0.67. The relative concentration of the coformers is also reported to affect the crystal size distribution of the product cocrystals for the cooling cocrystallization process [56].

Industrial cooling crystallizers are often equipped with agitators or other mechanisms for mixing and flow to keep the crystals suspended during operation. However, fluid flow conditions can affect crystal nucleation [57,58]. In the case of cocrystallization too, the nature of agitation can impact the formation of various crystal forms. For instance, Li et al. reported that in a conventional mixed tank cooling crystallizer nucleation of the metastable 2:1 cocrystal of caffeine-malic acid occurs first, followed by the nucleation of stable 1:1 form. However, a rotating disc crystallizer following a similar cooling regime can directly generate the nuclei of the stable form crystals due to periodic vortex motion [59].

Similarly, induction time, yield, and crystal composition of benzoic acid-sodium benzoate cocrystals in cooling crystallization are affected by the mixing condition [60].

Scale-up for cooling crystallization of carbamazepine-saccharin cocrystal to multi-gram scale has been reported by Hickey et al. in 2007 [61]. Since then, several studies have focused on scaling up cooling cocrystallization of various products to establish the impact of process parameters on product attributes [7,9]. The application of unconventional parameters such as heteronucleants on cooling cocrystallization has also been reported in the literature. Recently, Yu et al. investigated the cooling crystallization of urea-succinic acid cocrystal in the presence of nano-porous glass [27]. It was reported that the stable 2:1 cocrystal formed in the bulk while a mixture of 2:1 and metastable 1:1 cocrystals formed in pores above 100 nm. However, when the pore size was below 60 nm, only 1:1 cocrystals formed.

Cooling crystallizers have been considered as the "workhorse" of industrial crystallization [62]. Hence, it is unsurprising that cooling cocrystallization is a preferred method to produce potential cocrystals from small-scale laboratory manufacturing to commercial-scale production.

2.3. Antisolvent Cocrystallization

Antisolvent cocrystallization utilizes an antisolvent to reduce the solubility of coformers in the solvent, leading to cocrystal formation. Generally, the solvent and the antisolvent must be miscible, creating a single phase. The most commonly used solvent-antisolvent combination is an organic solvent-water combination. Antisolvent cocrystallization is a suitable alternative to the evaporative and cooling cocrystallization for the cocrystals having lower solubility. Besides, the process can be operated at ambient temperature, consuming less energy than solvent evaporation and cooling. Several studies have explored antisolvent cocrystallization for better control of crystal characteristics with enhanced purity and yield. Selection of the solvent-antisolvent combination suitable for the cocrystallization is the first step in this method. However, with two coformers and a solvent mixture, assessing the solubility of the cocrystal and the component crystals at various solvent ratios becomes a challenging task [63]. Often, such data is nonexistent and has to be determined experimentally or computationally before the suitable solvent-antisolvent combination can be selected. Lange et al. used a combined approach of utilizing thermodynamic model prediction and experimental data to account for the nonideal solubility of the nicotinamide-succinic acid cocrystal system for identifying the solvent-antisolvent combination [64]. Others have also utilized similar approaches for the estimation of ternary phase diagrams of various APIs and coformers in different solvents [65,66]. Such calculations can aid the screening process for the selection of suitable solvent systems for antisolvent crystallization.

The rate of addition of antisolvent is the second major factor that has to be considered in antisolvent cocrystallization. For example, Wang et al. initially reported the formation of carbamazepine-saccharin cocrystal by the addition of water into a methanol solution of the coformers [67]. However, it was later reported that the metastable form II cocrystal was formed when a high rate of antisolvent addition and agitation rate is maintained while similar chemical condition with a low rate of antisolvent addition and agitation rate produces the stable form I crystals [68]. For scale up, an optimized addition rate of the antisolvent would ensure that the composition will remain within the critical operating region where the cocrystal would be the stable form [69]. Additionally, antisolvent cocrystallization may be combined with cooling cocrystallization to achieve a higher yield of cocrystals [70].

Antisolvent cocrystallization has also been used for the production of nano-sized cocrystals. Thakor et al. investigated several solvents, antisolvent, and stabilizers for the production of nano cocrystals of the carbamazepine-nicotinamide system [29]. The impact of the operating parameters such as the concentration of stabilizer, temperature, sonication time, and agitation speed on the cocrystal size was also explored. The study revealed that cocrystal size was affected by the stabilizer concentration and a wide range of nano-cocrystals could be produced from coformers having different solubilities. Based

on the results, the authors have suggested a generalized decision tree involving solvent-antisolvent and stabilizer selection process that can be useful in the production of nano cocrystals. With further work on antisolvent cocrystallization, this technique has the potential to provide a bottom-up approach for the production of nano cocrystals. This would enhance the application of cocrystals of poorly water soluble drugs, providing a boost to the dissolution rate and bioavailability [71].

2.4. Slurry Cocrystallization

Slurry cocrystallization is an alternative approach for producing cocrystals whose coformers have incongruent solubilities. The process starts with a suspension of either or both of the coformer crystals in a small amount of solvent, creating a slurry. As the stable cocrystal nucleates and grows, the single component crystals dissolve, akin to the solution-mediated polymorphic transformation process. Slurry cocrystallization was first proposed as an effective cocrystal screening technique by Zhang et al. [72]. Once established, this approach is easy to operate and involves crystallization of pure cocrystal utilizing small quantities of solvents. However, this method can be chosen for cocrystal production only when the required cocrystal is the most stable thermodynamic form in comparison to other crystal forms. Hence, the technique may also be used to screen for the most stable form of the crystals [73]. Further, slurry cocrystallization could also be used to establish the ternary phase diagram, which is an essential component for the process design during scale-up. Hong et al. utilized the method to determine the phase solubility diagram of four cocrystals of myricetin, which was subsequently verified with conventional techniques [74]. The major advantage of the method is that the cocrystals can be generated even without the knowledge of the required stoichiometric ratio of the cocrystal.

Recently, Ahuja et al. reported three new cocrystals (sulfamethazine–nicotinamide, sulfamerazine–salicylamide, and sulfamerazine–anthranilic acid) using the slurry cocrystallization technique. The authors reported that the rate of cocrystal formation was higher when microwave was used as the heating source [75]. Similar enhancement on slurry cocrystallization of caffeine-maleic acid cocrystal has also been reported with the use of high power ultrasound [36,76]. The temperature of the slurry during crystal transformation plays a crucial role in determining both the thermodynamic and kinetic parameters of the process. Soares and Carneiro reported that carbamazepine-nicotinamide cocrystals formed only when the slurry temperature was above 60 °C [77]. While the complete conversion occurred when the slurry temperature was 80 °C, cocrystal nucleation was optimal at 60 °C, inferred from the large number of small cocrystals produced. Furthermore, unconventional phase transitions may also occur during slurry cocrystallization. Qu et al. reported that the formation of pyraclostrobin-thiophanate methyl cocrystal through slurry cocrystallization undergoes a gelation and hardening phase before the suspension of cocrystal is formed [78].

Slurry cocrystallization is a screening as well as a production technique for cocrystals. However, the batch time of the technique is limited by the solution-mediated conversion kinetics. Hence, the production of pure cocrystals would require conditions that ensure complete conversion of other crystal forms within the batch time. Subsequently, while the method is beneficial for batch operation due to low solvent requirement, continuous single-stage operation could produce a mixture of crystal forms.

2.5. Ultrasound-Assisted Cocrystallization

Solution cocrystallization has been explored along with sonication as process intensification in cocrystal formation. The sonication induces the formation of cavity bubbles inside the solution, which acts as sites for nucleation and leads to nucleation events at lower superstations. The sonication can enhance nucleation rate and reduce induction time and agglomeration of cocrystals [79]. Apshingekar et al. used ultrasound in slurry cocrystallization of caffeine-maleic acid cocrystal using water as a solvent [36]. The authors emphasized the impact of sonication on the ternary phase diagram of the cocrystal. It was reported that the aqueous solubility of both the coformers increased significantly on soni-

cation. Consequently, the stable region of pure cocrystal on the phase diagram decreased, resulting in the solvent-mediated transformation to pure coformer crystals. Similar to other solution cocrystallization techniques, the molar ratio of the coformers is an essential parameter in producing pure cocrystals. Ultrasound can be applied as a process intensification parameter along with cooling or slurry cocrystallization to produce pure cocrystals under conditions that might result in crystal mixtures in conventional processes [76]. Nonetheless, Rodrigues et al. have utilized ultrasound-assisted cocrystallization for high-throughput screening of cocrystals of hydrochlorothiazide [80]. Out of the six coformers tested, the screening was able to identify nicotinamide and p-aminobenzoic acid as coformers that produced cocrystal with the solute.

Sonication can be a process intensification tool that can increase nucleation rate and alter the phase diagram. However, industrial scale-up of the process would be difficult due to the requirement of high sonication power, which could enhance the operating cost of cocrystal formation.

2.6. Supercritical Fluid Cocrystallization

Supercritical fluid cocrystallization has been tested in recent years as a green approach to produce high purity cocrystals. The supercritical fluid can be used as an antisolvent, solvent, or cosolvent. The process often used is analogous to the antisolvent cocrystallization process, where the supercritical fluid is the antisolvent. In this technology, a fluid (most commonly—carbon dioxide (CO_2)) is pressurized and heated above its critical point, thereby creating a supercritical phase. Beyond the critical point, fluid has the diffusivity of gas and the solvating property of liquid. The supercritical fluid is then added to the solution, containing a solvent in which the supercritical fluid is miscible. This addition causes a reduction in solubility and crystal nucleation. The low solubility of many solutes in supercritical CO_2 and the low critical conditions of CO_2 make it an excellent choice for the supercritical crystallization process [81]. Solvent selection, CO_2 addition rate, contact time, temperature, pressure, agitation rate, and coformer concentration are process parameters that can be utilized for achieving required product attributes. Wichianphong and Charoenchaitrakool used Box–Behnken design approach to optimize operating temperature, coformer concentration ratio, and drug saturation for the production of mefenamic acid–nicotinamide cocrystals with a high dissolution rate [82]. Similarly, cocrystal of the resveratrol-nicotinamide system with high dissolution rate has been produced by using supercritical CO_2 as an antisolvent for organic solvents [83].

However, the supercritical fluid may also be used as the single solvent or the favored solvent in the solvent-antisolvent process. Ribas et al. investigated the production of curcumin-nicotinamide cocrystal by using CO_2 as the supercritical solvent [84]. The cocrystals exhibited a significant increase in the dissolution rate in comparison to pure curcumin crystals. Additionally, it was found that utilizing acetone as a cosolvent in the supercritical process produced smaller crystals with a weaker crystalline structure, thereby increasing the dissolution rate of the cocrystals. Padrela et al. used supercritical CO_2 as a green solvent for the cocrystallization of six APIs (theophylline, indomethacin, sulfamethazine, caffeine, acetylsalicylic acid, and carbamazepine) with saccharin [85]. They reported the formation of pure cocrystals for theophylline, indomethacin, and carbamazepine. The investigation revealed that stirring played an important role in determining the rate of cocrystallization. Without stirring, the cocrystallization was significantly limited. Further, the cocrystallization rate was higher when the dissolution rate and the solubility of the coformers were high. In this study too, the addition of ethanol as a cosolvent resulted in the formation of new cocrystals that were not produced otherwise.

Supercritical cocrystallization can be a potential candidate for screening as well as production of cocrystals. This technique is a single-step scalable method and allows to control morphology and size of cocrystal [86]. Supercritical fluids can also be used for cocrystallization of heat-sensitive products and is an eco-friendly method, reducing the use of hazardous solvents. However, there are several challenges that need to be overcome.

For example, estimation of coformer and cocrystal solubility in a supercritical fluid is more complex than for a simple fluid. Several different experimental and computational approaches have been reported in the literature towards this [87]. In-line measurement tools for monitoring product quality need to be developed specifically for the operating conditions that require high pressure. Moreover, the contact time required for the production of pure cocrystals is typically in the range of a few hours, with additional time required for pressurizing and depressurizing the system. The process is typically conducted batch-wise, challenging continuous product removal from the pressurized crystallizer vessel. The continuous operation would require further adaptation of techniques such as modified atomization or spray drying processes that utilize supercritical fluid [88]. Furthermore, setting up an industrial-scale operation for supercritical crystallization requires heavy capital investment for handling and recovery of the supercritical fluid.

3. Challenges to Industrial Cocrystallization

Each of the solution cocrystallization techniques discussed above has its own benefits and drawbacks. Nonetheless, the conventional cooling and antisolvent crystallization are favored for large-scale manufacturing of cocrystals as these are a scalable process which has been utilized on an industrial scale for many years. The major challenges that are to be addressed to take cocrystallization as a mainstream industrial process are discussed in this section.

3.1. Kinetics of Cocrystallization

The study on nucleation and growth of cocrystals formed by combining various stoichiometries of coformers is a key component of cocrystallization. On the whole, cocrystallization research has focused more on identifying and characterizing new cocrystal phases. In comparison, only a few reports have focused on studying the nucleation and growth kinetics of cocrystals. While the laboratory scale production of new cocrystals may be readily achieved using the various solution-based or solid-state techniques, the large-scale manufacturing of cocrystals requires a detailed understanding of the nucleation and growth of cocrystal to develop an efficient and scalable cocrystallization process.

When coformers in a solution achieve supersaturation, the nucleation of various cocrystal forms and pure coformer crystals compete with each other. The solubilities of the coformers and cocrystals and their metastable width influence the relative nucleation and growth rates [89]. This can alter the nucleation order of the crystal forms under different rates of supersaturation generation. For example, different cocrystals of the curcumin-isoniazid system were formed at different evaporation rates [46]. Similarly, different polymorphs of carbamazepine-saccharin cocrystals form at different antisolvent addition rates [68]. Similar nucleation rates between the metastable and stable forms could make the production of pure metastable cocrystal form difficult. For example, the production of pure 1:2 maleic acid-caffeine cocrystal is a challenge from most solvents. Both 1:1 and 1:2 forms nucleate almost concomitantly, initially leading to an impure cocrystal mixture which eventually converts to 1:1 form. Hence, most of the crystallization attempts to produce pure 1:2 cocrystal rely on fast kinetic approaches. However, identification of the kinetic and thermodynamic limitations have prompted the development of exceptional conditions or unconventional steps for the production of the metastable cocrystal form [26,90].

Metastable zone width and induction time are the two most common factors that are studied for identifying nucleation kinetics in cooling crystallization. Mohammad et al. investigated the nucleation kinetics of carbamazepine–saccharin cocrystals in cooling cocrystallization [91]. The authors determined the metastable zone width and the nucleation order of the cocrystal via slow cooling crystallization. Induction time, critical size, and interfacial energy of the nucleus were determined using fast cooling cocrystallization. It was found that the nucleation kinetics could be established solely based on the slow cooling crystallization process. The nucleation order for the cocrystal was in the range of organic compounds. Although the metastable zone width established from slow cooling

experiments exhibited a strong correlation with the cooling rate, the results also suggested that the width was not affected by the carbamazepine concentration in the solution. Ternary phase diagrams could be useful in the case of kinetic studies to understand the order of nucleation and the impact of coformer molar ratios. Croker et al. studied the nucleation of p-toluenesulfonamide-triphenylphosphine oxide cocrystals at various stoichiometric ratios during cooling cocrystallization [92]. Cooling crystallization of mixtures which is within the stable region of a cocrystal in the ternary phase diagram, generated the cocrystal. However, cocrystallization in the mixed-phase region resulted in the nucleation of one cocrystal, followed by the nucleation of the second form. The relative amount of cocrystals in the mixture changed over the course of crystallization. This suggests nonconcomitant nucleation of the crystals or significant difference in their growth rates at specific coformer combination. Overall, the nucleation order would be determined by the kinetic parameters and not the stability conveyed by the phase diagram. Sheikh et al. also determined nucleation and growth kinetics of carbamazepine-nicotinamide cocrystal in cooling cocrystallization [93]. Based on the results, the authors suggested a general approach for scaling up of solution cocrystallization for coformers with significantly different solubilities. The approach utilizes knowledge of nucleation and growth kinetics to produce the required crystal form through suitable seeding strategy.

Though ternary phase diagrams provide information on the stable crystal form, it is the nucleation and growth kinetics of the crystal forms that decide the progress of cocrystallization. Knowledge of these parameters is essential to develop a strategy to control them for producing the required cocrystals with suitable size distribution. The minimum batch time or the residence time required to produce pure cocrystals will be influenced by the growth as well as dissolution kinetics. Additionally, relative coformer concentrations can alter the growth rate of crystal facets, thereby affecting the crystal morphology [92,93]. Process integration, such as the application of ultrasound or heteronuclei along with other processes for cocrystallization, also works based on their impact on the nucleation kinetics. Hence, knowledge of the nucleation and growth kinetics of the cocrystal as well as the coformer crystals is crucial for the efficient production of cocrystals on a larger scale.

3.2. Scalable Methods

For industrial manufacturing, cocrystallization has to be scalable from lab scale to commercial production without compromising attributes such as product purity, crystal size and morphology, and process yield. Several authors reported successful scale-up of lab-scale solution cocrystallization. Yang et al. developed a scalable process for the production of two energetic cocrystals through an antisolvent cocrystallization process [30]. Thermodynamic and kinetic data were used to access the choice of coformer ratio and process design of antisolvent cocrystallization. The scaled-up processes provided above 65% for both the cocrystals, suggesting a scalable process. In batch cooling cocrystallization, Yu et al. studied the scalability of caffeine-glutaric acid cocrystal production [94]. The authors employed the first-principles modeling process to identify the design space and assess the risks for the cocrystal production where the polymorphic purity was the critical crystal attribute. Impact of operational parameters such as coformer concentration, seed size, loading, temperature, and cooling profile was studied along with the scale-up from a 1 L vessel to 10 L vessel. Established knowledge from large-scale crystallization of single components could also be adapted for cocrystallization. Impact of process parameters such as solvent selection and seeding strategy on controlling the crystal attributes such as purity and crystal size distribution of cocrystals has been reported by Sheikh et al. [93]. Scale-up strategy for cooling cocrystallization for cocrystals was suggested based on carbamazepine-nicotinamide cocrystallization at a 1 L scale, which resulted in the process yield of more than 90% with a throughput of 14 L kg^{-1}.

Out of the solution cocrystallization techniques discussed in this article, cooling, antisolvent, and slurry cocrystallization are the most promising methods for scale-up. They are favored as they have been used extensively in large-scale single component crystalliza-

tion. Hence, principles of scale-up, crystallizer designs, monitoring techniques, and major process parameters are all reported widely. Additionally, large-scale vessels and trained manpower for their operation are available for these methods. Nonetheless, cocrystallization brings its own set of challenges due to the varied crystal forms that need to be handled during the production of cocrystals. Hence scale-up studies on these cocrystallization techniques need to be studied further to gain the confidence for industrial application.

Although solvent evaporation is a common screening process for cocrystal discovery, it is not often used on a larger scale due to the slow process. However, fast-drying techniques such as spray drying and rotatory evaporation are scalable processes that are used in industries. Weng et al. reported the production of itraconazole-suberic acid cocrystals through both rotatory evaporation and spray drying techniques [95]. Fast evaporation helped the production of pure cocrystal, which was not formed during slow solvent evaporation screening. Spray drying also produced small cocrystal particles within a narrow size range and better morphology, resulting in a better dissolution rate for inhalation application. However, the coformer molar ratio required for the production of pure cocrystals in a spray drying process may vary from that in a simple solution cocrystallization. For example, isolation of pure niclosamide-urea cocrystal from solution cocrystallization techniques would require an excess of urea, based on the ternary phase diagram. However, pure cocrystal can be produced through the spray drying process even without the need for excess coformer [96]. Additionally, spray drying of the cocrystal can also be performed along with an excipient component to alter the physical properties of the cocrystal particles produced through the process [97]. Being an existing industrial process, spray drying is also a scalable solution cocrystallization technique that can produce small particles with narrow size distribution.

Scale-up of the cocrystallization methods also requires simultaneous development of mathematical models and in-line monitoring tools specific to the cocrystallization process. The difference in the kinetics with simple crystallization needs to be acknowledged. This would also call for different control strategies for ensuring the purity of products. Hence study on novel cocrystallization techniques and process intensification of existing methods are essential to establish scalable cocrystallization processes.

3.3. Continuous Manufacturing

The conventional crystallization processes are mostly operated in batch mode. Batch processes are often considered simple and are flexible to respond rapidly to changing market demands. However, operation and control of batch crystallizers are difficult, leading to batch-to-batch variations, increased manufacturing costs, and high human intervention [98]. Continuous crystallization is gaining considerable attention in industrial manufacturing. Continuous crystallization can overcome several limitations of the batch process and offer better control of the process, consistent product quality, less human intervention, reduced production costs, and robust scale-up of the process [99–101].

Most studies on continuous cocrystallization have utilized solid-state processes [102–105]. However, solution cocrystallization can also be used for the continuous production of cocrystals. Only a few researchers have explored cooling cocrystallization for continuous manufacturing. Lee et al. reported the continuous generation of phenazine-vanillin cocrystal using the cooling cocrystallization technique [106]. The crystallizer consisted of a simple tubular reactor maintained at three different temperature zones. In comparison with the batch process, the nucleation rate was enhanced in continuous crystallizer due to the rapid decrease in temperature, thereby altering the crystal size distribution of the final product. Powell et al. utilized periodic mixed suspension mixed product removal crystallizer for the production of the polymorphic urea-barbituric cocrystals [10]. The crystallizer utilized a hybrid operational approach, switching between batch and continuous operation, enabling the production of the pure polymorphic form of the cocrystal. Oscillatory baffled crystallizer is one of the preferred crystallizers for continuous crystallization studies. They operate under steady state conditions following a plug flow pattern which is efficient

at handling slurries and provide good rates of heat and mass transfer [107]. Zhao et al. investigated the performance of the continuous oscillatory baffled crystallizer for the synthesis of α-lipoic acid-nicotinamide cocrystal. They reported the process development of cocrystal manufacturing from batch to continuous mode using a cooling crystallization approach. About a kilogram of the 99% pure cocrystal was produced via continuous operation cocrystallization at a throughput of 350 g h^{-1} [108]. Antisolvent cocrystallization is also a method that can be utilized for continuous manufacturing. Nishimaru et al. studied the continuous production of carbamazepine-saccharin cocrystal via the antisolvent cocrystallization route [109]. Utilizing a multicomponent phase diagram, the operating condition for the production of pure cocrystal was established. The study revealed that the stability of the operating conditions during continuous operation depended on the addition rate of the coformers, antisolvent, and the kinetics of cocrystal formation. Furthermore, the mixing rate of the antisolvent can alter the nucleation kinetics and thereby affect the particle size distribution. Continuous antisolvent cocrystallization of benzoic acid-isonicotinamide 1:1 cocrystal in tubular flow crystallizer resulted in different crystal size distributions at different flow rates due to difference in their mixing regime [110]. However, with appropriate control of flow rate and coformer concentrations, both 1:1 and 1:2 cocrystals were produced successfully under continuous operation.

In comparison to continuous crystallization of single component crystals, research on continuous cocrystallization techniques is yet to pick up the pace, especially in utilizing solution-based methods. Improving solid-phase yield, monitoring and avoiding presence on undesired crystal forms, and development of kinetic models that enable a quality-by-design approach are important factors that have to be addressed in the development of continuous cocrystallization techniques.

3.4. Application of Modeling and Process Analytical Technology (PAT)

In recent years, considerable effort has been given to develop a detailed outline of the cocrystallization mechanisms as well as to model and control cocrystal formation. Developments have occurred in the modeling, simulation, and application of process analytical technologies (PAT) for novel cocrystallization routes. Progress in the modeling and application of PAT would help in the timely measurement of critical quality attributes during the operation, with the aim of achieving better and consistent product quality. The application of modeling and PAT enables the implementation of Quality-by-Design (QbD) concepts in the industrial crystallization process. These key enablers are highly associated with the scale-up of the cocrystallization process for commercial production.

Mathematical modeling for the batch cooling crystallization of agomelatine–citric acid cocrystal has been studied by Holan et al. They employed different linear cooling profiles for unseeded and seeded cocrystallization to study the impact on crystal size. The focused beam reflectance measurement (FBRM), a common PAT tool in crystallization, was applied to monitor the particle size distribution in real-time. A mathematical model comprising the population balance and mass balance equations was developed and solved using the finite difference method. Such models can be used as a building block for the process design, development, and scale-up of the cocrystallization process [111]. A similar study was conducted by Yu et al. to develop a mathematical model for batch cooling crystallization of caffeine-glutaric acid cocrystal and was solved by the method of moments. The model was based on three equations, one each for mass balance, 1D population balance, and cooling profile. Assumptions included size-independent growth rate, absence of nucleation, agglomeration, and breakage, and ideal mixing. The model centered on ensuring the polymorphic purity of the cocrystal through control on supersaturation. Experimental data were fitted with the model to estimate the growth rate and a crystal growth order. Appropriate seeding time, seed loading, seed size, and cooling profile were determined using experimental and simulation to avoid the formation of undesired polymorph. Advanced PAT tools, including attenuated total reflectance−Fourier transform infrared (ATR-FTIR) and particle vision measurement (videography) was used for monitoring solute concen-

tration and cocrystal morphology, respectively. The uncertainty in model parameter and process variability was determined by the Monte Carlo simulations and the batch model was validated with experimental results. Additionally, the model developed based on 1 L vessel was further validated with a scaled-up 10 L crystallizer [94].

Antisolvent cocrystallization of naproxen-nicotinamide cocrystal using compressed CO_2 as an antisolvent has been modeled by Erriguible et al. [112]. Nucleation and growth parameters were estimated by fitting the predicted data of particle size distribution with experimental data. Neurohr et al. modeled supercritical CO_2 antisolvent cocrystallization of the same cocrystals, using a similar approach, considering both primary and secondary nucleation [113].

While modeling helps in process understanding and design, efficient quality control requires continuous monitoring of the critical process parameter and the critical quality attributes. These are essential parameters in QbD implementation [114]. Solution composition and the solid form morphology and size are the most commonly monitored attributes in the crystallization process. ATR-FTIR, attenuated total reflectance ultraviolet/visible spectroscopy (ATR-UV/vis), FTIR spectroscopy, and near-infrared spectroscopy can be used for monitoring the solution composition. Particle vision microscopy (PVM), Raman spectroscopy, FBRM, and turbidity can be used to record the production and nature of the solid form [115]. Powell et al. coupled Raman spectroscopy, ATR-UV/vis, FBRM, and PVM techniques along with a crystallization process informatics software tool to monitor and control the operation of a cascaded periodic-MSMPR for cooling cocrystallization of urea-barbituric acid (UBA). The in-line PAT tools were used to identify process conditions like nucleation event, solute concentration, and particle size distribution to achieve QbD manufacturing of specific polymorphic cocrystals [10]. Later, Powel et al. investigated the cocrystallization of p-toluene sulfonamide-triphenylphosphine oxide cocrystal in acetonitrile using batch and semibatch crystallizers. Pure 1:1 and 3:2 cocrystal forms were produced by control strategy aided by PAT tools which were used for real-time monitoring of the cocrystallization process. It was reported that required crystal form could be generated even when operating in a mixture region by utilizing thermal cycling along with appropriate Raman spectroscopy. Thereby, PAT tools can aid in monitoring and controlling crystal transformation between cocrystals [116]. In-line Raman spectroscopy is also useful for identifying the complete conversion of coformer crystals to the cocrystal in slurry cocrystallization. Soares and Carneiro coupled multivariate curve resolution–alternating least squares method with Raman spectroscopy to quantify product formation in the slurry cocrystallization of carbamazepine-nicotinamide system [77]. Similarly, Huang et al. used the Raman spectroscopy to study the impact of coformer density and temperature on cocrystallization of theophylline-benzoic acid cocrystal via slurry and cooling crystallization. The real-time data was also able to identify nucleation temperature and the cooling end point [28].

Due to the similarity with the conventional crystallization process, solution cocrystallization techniques can be the same base of PAT tools that are reported for single component crystallization. However, cocrystallization brings in a complex challenge of distinguishing and controlling the formation of different solid forms simultaneously. Hence, the process models and control strategies required for cocrystallization can be significantly different. Thus, more studies are required in this aspect to develop robust models for the cocrystallization process with process parameters and product attributes that can be monitored with existing PAT tools. Close monitoring and real-time process tuning enabled by PAT tools would be more effective in continuous cocrystallization techniques over batch processes to maintain product quality [117]. With the development of accurate models for cocrystallization, real-time monitoring using PAT tools, and active process control, continuous cocrystallization techniques can move ahead to the Quality-by-Control (QbC) regime, with high process robustness and efficiency [118].

4. Concluding Remarks

Solution cocrystallization provides a scalable solution for the industrial-scale production of cocrystals. Product attributes such as phase purity, yield, and crystal size distribution can be effectively controlled using solution cocrystallization techniques. While conventional evaporation cocrystallization is routinely used for cocrystal screening, it might not be directly scalable. Nonetheless, other rapid solvent removal techniques such as spray drying can be used on an industrial scale. However, kinetics plays an important role in maintaining the purity of cocrystal formation. Cooling-, slurry-, and antisolvent cocrystallization can be easily modified to generate the required supersaturation and thereby regulate the crystallization kinetics. Other techniques such as ultrasound-assisted cocrystallization or supercritical fluid cocrystallization require further research to develop to an industrial scale. Irrespective of the crystallization technique, the development of accurate mathematical models that capture the nucleation and growth kinetics of the cocrystallization process is a major challenge that needs to be overcome. PAT tools and active control schemes specifically for cocrystallization need to be researched to establish a QbD strategy for cocrystal production. These would also accelerate the adaptation of continuous cocrystallization techniques with high throughput and efficiency. Understanding the process kinetics, developing numerical models, and real-time process monitoring and control are the major thrust areas identified for future research in solution cocrystallization.

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References

1. Sinha, A.S.; Maguire, A.R.; Lawrence, S.E. Cocrystallization of Nutraceuticals. *Cryst. Growth Des.* **2015**, *15*, 984–1009. [CrossRef]
2. Aakeröy, C. Is There Any Point in Making Co-Crystals? *Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater.* **2015**, *71*, 387–391. [CrossRef]
3. Mazzeo, P.P.; Carraro, C.; Monica, A.; Capucci, D.; Pelagatti, P.; Bianchi, F.; Agazzi, S.; Careri, M.; Raio, A.; Carta, M.; et al. Designing a Palette of Cocrystals Based on Essential Oil Constituents for Agricultural Applications. *ACS Sustain. Chem. Eng.* **2019**, *7*, 17929–17940. [CrossRef]
4. Aakeröy, C.B.; Wijethunga, T.K.; Benton, J.; Desper, J. Stabilizing Volatile Liquid Chemicals Using Co-Crystallization. *Chem. Commun.* **2015**, *51*, 2425–2428. [CrossRef] [PubMed]
5. Karagianni, A.; Malamatari, M.; Kachrimanis, K. Pharmaceutical Cocrystals: New Solid Phase Modification Approaches for the Formulation of APIs. *Pharmaceutics* **2018**, *10*, 18. [CrossRef]
6. Rodrigues, M.; Baptista, B.; Lopes, J.A.; Sarraguça, M.C. Pharmaceutical Cocrystallization Techniques. Advances and Challenges. *Int. J. Pharm.* **2018**, *547*, 404–420. [CrossRef]
7. Malamatari, M.; Ross, S.A.; Douroumis, D.; Velaga, S.P. Experimental Cocrystal Screening and Solution Based Scale-up Cocrystallization Methods. *Adv. Drug Deliv. Rev.* **2017**, *117*, 162–177. [CrossRef]
8. Hsi, K.H.-Y.; Chadwick, K.; Fried, A.; Kenny, M.; Myerson, A.S. Separation of Impurities from Solution by Selective Co-Crystal Formation. *CrystEngComm* **2012**, *14*, 2386–2388. [CrossRef]
9. Billot, P.; Hosek, P.; Perrin, M.A. Efficient Purification of an Active Pharmaceutical Ingredient via Cocrystallization: From Thermodynamics to Scale-Up. *Org. Process Res. Dev.* **2013**, *17*, 505–511. [CrossRef]
10. Powell, K.A.; Bartolini, G.; Wittering, K.E.; Saleemi, A.N.; Wilson, C.C.; Rielly, C.D.; Nagy, Z.K. Toward Continuous Crystallization of Urea-Barbituric Acid: A Polymorphic Co-Crystal System. *Cryst. Growth Des.* **2015**, *15*, 4821–4836. [CrossRef]
11. Porter, W.W.; Elie, S.C.; Matzger, A.J. Polymorphism in Carbamazepine Cocrystals. *Cryst. Growth Des.* **2008**, *8*, 14–16. [CrossRef]
12. Leyssens, T.; Tumanova, N.; Robeyns, K.; Candoni, N.; Veesler, S. Solution Cocrystallization, an Effective Tool to Explore the Variety of Cocrystal Systems: Caffeine/Dicarboxylic Acid Cocrystals. *CrystEngComm* **2014**, *16*, 9603–9611. [CrossRef]
13. Kavanagh, O.N.; Croker, D.M.; Walker, G.M.; Zaworotko, M.J. Pharmaceutical Cocrystals: From Serendipity to Design to Application. *Drug Discov. Today* **2019**, *24*, 796–804. [CrossRef]
14. Shan, N.; Zaworotko, M.J. The Role of Cocrystals in Pharmaceutical Science. *Drug Discov. Today* **2008**, *13*, 440–446. [CrossRef]

15. Javoor, M.; Mondal, P.; Chopra, D. Cocrystals: A Review of Recent Trends in Pharmaceutical and Material Science Applications. *Mater. Sci. Res. India* **2017**, *14*, 09–18. [CrossRef]
16. Almarsson, Ö.; Peterson, M.L.; Zaworotko, M. The A to Z of Pharmaceutical Cocrystals: A Decade of Fast-Moving New Science and Patents. *Pharm. Pat. Anal.* **2012**, *1*, 313–327. [CrossRef]
17. Bolla, G.; Nangia, A. Pharmaceutical Cocrystals: Walking the Talk. *Chem. Commun.* **2016**, *52*, 8342–8360. [CrossRef]
18. Steed, J.W. The Role of Co-Crystals in Pharmaceutical Design. *Trends Pharmacol. Sci.* **2013**, *34*, 185–193. [CrossRef]
19. Wang, X.; Du, S.; Zhang, R.; Jia, X.; Yang, T.; Zhang, X. Drug-Drug Cocrystals: Opportunities and Challenges. *Asian J. Pharm. Sci.* 2020. [CrossRef]
20. Sekhon, B.S. Drug-Drug Co-Crystals. *DARU J. Pharm. Sci.* **2012**, *20*, 1–2. [CrossRef]
21. Grobelny, P.; Mukherjee, A.; Desiraju, G. Drug-Drug Co-Crystals: Temperature-Dependent Proton Mobility in the Molecular Complex of Isoniazid with 4-Aminosalicylic Acid. *CrystEngComm* **2011**, *13*, 4304–4306. [CrossRef]
22. Braga, D.; Grepioni, F.; Maini, L.; Capucci, D.; Nanna, S.; Wouters, J.; Aerts, L.; Quéré, L. Combining Piracetam and Lithium Salts: Ionic Co-Crystals and Co-Drugs? *Chem. Commun.* **2012**, *48*, 8219–8221. [CrossRef]
23. Bianchi, F.; Fornari, F.; Riboni, N.; Spadini, C.; Cabassi, C.S.; Iannarelli, M.; Carraro, C.; Mazzeo, P.P.; Bacchi, A.; Orlandini, S.; et al. Development of Novel Cocrystal-Based Active Food Packaging by a Quality by Design Approach. *Food Chem.* **2021**, *347*, 1–9. [CrossRef]
24. Zhu, S.; Zhang, S.; Gou, R.; Wu, C.; Han, G.; Jia, H. Understanding the Effect of Solvent on the Growth and Crystal Morphology of MTNP/CL-20 Cocrystal Explosive: Experimental and Theoretical Studies. *Cryst. Res. Technol.* **2018**, *53*, 1700299. [CrossRef]
25. Holaň, J.; Štěpánek, F.; Billot, P.; Ridvan, L. The Construction, Prediction and Measurement of Co-Crystal Ternary Phase Diagrams as a Tool for Solvent Selection. *Eur. J. Pharm. Sci.* **2014**, *63*, 124–131. [CrossRef]
26. Leyssens, T.; Springuel, G.; Montis, R.; Candoni, N.; Veesler, S. Importance of Solvent Selection for Stoichiometrically Diverse Cocrystal Systems: Caffeine/Maleic Acid 1:1 and 2:1 Cocrystals. *Cryst. Growth Des.* **2012**, *12*, 1520–1530. [CrossRef]
27. Yu, Q.; Jia, W.; Pu, J.; Wang, Y.; Yang, H. Cocrystallization of Urea and Succinic Acid in "Nano-Crystallizer". *Chem. Eng. Sci.* **2021**, *229*, 116082. [CrossRef]
28. Huang, Y.; Zhou, L.; Yang, W.; Li, Y.; Yang, Y.; Zhang, Z.; Wang, C.; Zhang, X.; Yin, Q. Preparation of Theophylline-Benzoic Acid Cocrystal and On-Line Monitoring of Cocrystallization Process in Solution by Raman Spectroscopy. *Crystals* **2019**, *9*, 329. [CrossRef]
29. Thakor, P.; Yadav, B.; Modani, S.; Shastri, N.R. Preparation and Optimization of Nano-Sized Cocrystals Using a Quality by Design Approach. *CrystEngComm* **2020**, *22*, 2304–2314. [CrossRef]
30. Yang, Z.; Wang, H.; Zhang, J.; Ma, Y.; Tan, Y.; Nie, F.; Zhang, J.; Li, H. Rapid Cocrystallization by Exploiting Differential Solubility: An Efficient and Scalable Process toward Easily Fabricating Energetic Cocrystals. *Cryst. Growth Des.* **2020**, *20*, 2129–2134. [CrossRef]
31. Guo, C.; Zhang, Q.; Zhu, B.; Zhang, Z.; Bao, J.; Ding, Q.; Ren, G.; Mei, X. Pharmaceutical Cocrystals of Nicorandil with Enhanced Chemical Stability and Sustained Release. *Cryst. Growth Des.* **2020**, *20*, 6995–7005. [CrossRef]
32. Wu, N.; Zhang, Y.; Ren, J.; Zeng, A.; Liu, J. Preparation of Quercetin–Nicotinamide Cocrystals and Their Evaluation under in Vivo and in Vitro Conditions. *RSC Adv.* **2020**, *10*, 21852–21859. [CrossRef]
33. Luo, C.; Liang, W.; Chen, X.; Wang, J.; Deng, Z.; Zhang, H. Pharmaceutical Cocrystals of Naringenin with Improved Dissolution Performance. *CrystEngComm* **2018**, *20*, 3025–3033. [CrossRef]
34. Inam, M.; Wu, J.; Shen, J.; Phan, C.; Tang, G.; Hu, X. Preparation and Characterization of Novel Pharmaceutical Co-Crystals: Ticagrelor with Nicotinamide. *Crystals* **2018**, *8*, 336. [CrossRef]
35. Cuadra, I.A.; Cabañas, A.; Cheda, J.A.R.; Pando, C. Polymorphism in the Co-Crystallization of the Anticonvulsant Drug Carbamazepine and Saccharin Using Supercritical CO2 as an Anti-Solvent. *J. Supercrit. Fluids* **2018**, *136*, 60–69. [CrossRef]
36. Apshingekar, P.P.; Aher, S.; Kelly, A.L.; Brown, E.C.; Paradkar, A. Synthesis of Caffeine/Maleic Acid Co-Crystal by Ultrasound-Assisted Slurry Co-Crystallization. *J. Pharm. Sci.* **2017**, *106*, 66–70. [CrossRef]
37. Liu, M.; Hong, C.; Yao, Y.; Shen, H.; Ji, G.; Li, G.; Xie, Y. Development of a Pharmaceutical Cocrystal with Solution Crystallization Technology: Preparation, Characterization, and Evaluation of Myricetin-Proline Cocrystals. *Eur. J. Pharm. Biopharm.* **2016**, *107*, 151–159. [CrossRef]
38. Pantwalawalkar, J.; More, H.; Bhange, D.; Patil, U.; Jadhav, N. Novel Curcumin Ascorbic Acid Cocrystal for Improved Solubility. *J. Drug Deliv. Sci. Technol.* **2021**, *61*, 102233. [CrossRef]
39. Li, Z.; Matzger, A.J. Influence of Coformer Stoichiometric Ratio on Pharmaceutical Cocrystal Dissolution: Three Cocrystals of Carbamazepine/4-Aminobenzoic Acid. *Mol. Pharm.* **2016**, *13*, 990–995. [CrossRef]
40. Chow, S.F.; Shi, L.; Ng, W.W.; Leung, K.H.Y.; Nagapudi, K.; Sun, C.C.; Chow, A.H.L. Kinetic Entrapment of a Hidden Curcumin Cocrystal with Phloroglucinol. *Cryst. Growth Des.* **2014**, *14*, 5079–5089. [CrossRef]
41. Desai, H.; Rao, L.; Amin, P. Carbamazepine Cocrystals by Solvent Evaporation Technique: Formulation and Characterization Studies. *Am. J. PharmTech Res.* **2014**, *4*, 479–493.
42. Winantari, A.N.; Setyawan, D.; Siswodihardjo, S.; Soewandhi, S.N. Cocrystallization Acyclovir-Succinic Acid Using Solvent Evaporation Methods. *Asian J. Pharm. Clin. Res.* **2017**, *10*, 91. [CrossRef]
43. Sarkar, A.; Rohani, S. Cocrystals of Acyclovir with Promising Physicochemical Properties. *J. Pharm. Sci.* **2015**, *104*, 98–105. [CrossRef]

44. Pan, X.; Zheng, Y.; Chen, R.; Qiu, S.; Chen, Z.; Rao, W.; Chen, S.; You, Y.; Lü, J.; Xu, L.; et al. Cocrystal of Sulfamethazine and P-Aminobenzoic Acid: Structural Establishment and Enhanced Antibacterial Properties. *Cryst. Growth Des.* **2019**, *19*, 2455–2460. [CrossRef]
45. Nechipadappu, S.K.; Trivedi, D.R. Cocrystal of Nutraceutical Sinapic Acid with Active Pharmaceutical Ingredients Ethenzamide and 2-Chloro-4-Nitrobenzoic Acid: Equilibrium Solubility and Stability Study. *J. Mol. Struct.* **2018**, *1171*, 898–905. [CrossRef]
46. Xuan, B.; Wong, S.N.; Zhang, Y.; Weng, J.; Tong, H.H.Y.; Wang, C.; Sun, C.C.; Chow, S.F. Extended Release of Highly Water Soluble Isoniazid Attained through Cocrystallization with Curcumin. *Cryst. Growth Des.* **2020**, *20*, 1951–1960. [CrossRef]
47. Darwish, S.; Zeglinski, J.; Krishna, G.R.; Shaikh, R.; Khraisheh, M.; Walker, G.M.; Croker, D.M. A New 1:1 Drug-Drug Cocrystal of Theophylline and Aspirin: Discovery, Characterization, and Construction of Ternary Phase Diagrams. *Cryst. Growth Des.* **2018**, *18*, 7526–7532. [CrossRef]
48. do Amaral, L.H.; do Carmo, F.A.; Amaro, M.I.; de Sousa, V.P.; da Silva, L.C.R.P.; de Almeida, G.S.; Rodrigues, C.R.; Healy, A.M.; Cabral, L.M. Development and Characterization of Dapsone Cocrystal Prepared by Scalable Production Methods. *AAPS PharmSciTech* **2018**, *19*, 2687–2699. [CrossRef]
49. Bag, P.P.; Patni, M.; Malla Reddy, C. A Kinetically Controlled Crystallization Process for Identifying New Co-Crystal Forms: Fast Evaporation of Solvent from Solutions to Dryness. *CrystEngComm* **2011**, *13*, 5650–5652. [CrossRef]
50. Wood, B.; Girard, K.P.; Polster, C.S.; Croker, D.M. Progress to Date in the Design and Operation of Continuous Crystallization Processes for Pharmaceutical Applications. *Org. Process Res. Dev.* **2019**, *23*, 122–144. [CrossRef]
51. Gao, Z.; Rohani, S.; Gong, J.; Wang, J. Recent Developments in the Crystallization Process: Toward the Pharmaceutical Industry. *Engineering* **2017**, *3*, 343–353. [CrossRef]
52. Trampuž, M.; Teslić, D.; Likozar, B. Crystal-Size Distribution-Based Dynamic Process Modelling, Optimization, and Scaling for Seeded Batch Cooling Crystallization of Active Pharmaceutical Ingredients (API). *Chem. Eng. Res. Des.* **2021**, *165*, 254–269. [CrossRef]
53. Yu, Z.Q.; Chow, P.S.; Tan, R.B.H. Operating Regions in Cooling Cocrystallization of Caffeine and Glutaric Acid in Acetonitrile. *Cryst. Growth Des.* **2010**, *10*, 2382–2387. [CrossRef]
54. He, G.; Chow, P.S.; Tan, R.B.H. Investigating the Intermolecular Interactions in Concentration-Dependent Solution Cocrystallization of Caffeine and p -Hydroxybenzoic Acid. *Cryst. Growth Des.* **2010**, *10*, 3763–3769. [CrossRef]
55. Sathisaran, I.; Dalvi, S.V. Investigating Cocrystallization of Carbamazepine with Structurally Compatible Coformers: New Cocrystal and Eutectic Phases with Enhanced Dissolution. *AAPS PharmSciTech* **2021**, *22*, 29. [CrossRef]
56. Engku Mat Nasir, E.N.; Rahman, F.A.; Abd Rahim, S.; Edros, R.Z.; Anuar, N. Crystallisation Parameters Effect on the Particle Size Distribution (PSD) of Carbamazepine-Saccharin (CBZ-SAC) Co-Crystals in Batch Cooling Crystallisation. In *IOP Conference Series: Materials Science and Engineering*; IOP Publishing: Bristol, UK, 2020; Volume 736, p. 022109. [CrossRef]
57. Kitamura, M. Controlling Factor of Polymorphism in Crystallization Process. *J. Cryst. Growth* **2002**, *237–239*, 2205–2214. [CrossRef]
58. Parambil, J.V.; Schaepertoens, M.; Williams, D.R.; Heng, J.Y.Y. Effects of Oscillatory Flow on the Nucleation and Crystallization of Insulin. *Cryst. Growth Des.* **2011**, *11*, 4353–4359. [CrossRef]
59. Li, Z.H.; Yu, T.; Lee, T.; Kim, W.S. Cocrystallization of Caffeine-Maleic Acid in a Batchelor Vortex Flow. *Cryst. Growth Des.* **2020**, *20*, 1618–1627. [CrossRef]
60. Chen, T.H.; Yeh, K.L.; Chen, C.W.; Lee, H.L.; Hsu, Y.C.; Lee, T. Mixing Effect on Stoichiometric Diversity in Benzoic Acid-Sodium Benzoate Cocrystals. *Cryst. Growth Des.* **2019**, *19*, 1576–1583. [CrossRef]
61. Hickey, M.B.; Peterson, M.L.; Scoppettuolo, L.A.; Morrisette, S.L.; Vetter, A.; Guzmán, H.; Remenar, J.F.; Zhang, Z.; Tawa, M.D.; Haley, S. Performance Comparison of a Co-Crystal of Carbamazepine with Marketed Product. *Eur. J. Pharm. Biopharm.* **2007**, *67*, 112–119. [CrossRef]
62. Kim, K.-J. Industrial Crystallization. *Chem. Eng. Technol.* **2016**, *39*, 1212. [CrossRef]
63. Kudo, S.; Takiyama, H. Solubility Determination for Carbamazepine and Saccharin in Methanol/Water Mixed Solvent: Basic Data for Design of Cocrystal Production by Antisolvent Crystallization. *J. Chem. Eng. Data* **2018**, *63*, 451–458. [CrossRef]
64. Lange, L.; Heisel, S.; Sadowski, G. Predicting the Solubility of Pharmaceutical Cocrystals in Solvent/Anti-Solvent Mixtures. *Molecules* **2016**, *21*, 593. [CrossRef]
65. Veith, H.; Schleinitz, M.; Schauerte, C.; Sadowski, G. Thermodynamic Approach for Co-Crystal Screening. *Cryst. Growth Des.* **2019**, *19*, 3253–3264. [CrossRef]
66. Loschen, C.; Klamt, A. Cocrystal Ternary Phase Diagrams from Density Functional Theory and Solvation Thermodynamics. *Cryst. Growth Des.* **2018**, *18*, 5600–5608. [CrossRef]
67. Wang, I.-C.; Lee, M.-J.; Sim, S.-J.; Kim, W.-S.; Chun, N.-H.; Choi, G.J. Anti-Solvent Co-Crystallization of Carbamazepine and Saccharin. *Int. J. Pharm.* **2013**, *450*, 311–322. [CrossRef] [PubMed]
68. Lee, M.-J.; Wang, I.-C.; Kim, M.-J.; Kim, P.; Song, K.-H.; Chun, N.-H.; Park, H.-G.; Choi, G.J. Controlling the Polymorphism of Carbamazepine-Saccharin Cocrystals Formed during Antisolvent Cocrystallization Using Kinetic Parameters. *Korean J. Chem. Eng.* **2015**, *32*, 1910–1917. [CrossRef]
69. Leung, D.H.; Lohani, S.; Ball, R.G.; Canfield, N.; Wang, Y.; Rhodes, T.; Bak, A. Two Novel Pharmaceutical Cocrystals of a Development Compound—Screening, Scale-up, and Characterization. *Cryst. Growth Des.* **2012**, *12*, 1254–1262. [CrossRef]
70. Chun, N.H.; Lee, M.J.; Song, G.H.; Chang, K.Y.; Kim, C.S.; Choi, G.J. Combined Anti-Solvent and Cooling Method of Manufacturing Indomethacin-Saccharin (IMC-SAC) Co-Crystal Powders. *J. Cryst. Growth* **2014**, *408*, 112–118. [CrossRef]

71. Fontana, F.; Figueiredo, P.; Zhang, P.; Hirvonen, J.T.; Liu, D.; Santos, H.A. Production of Pure Drug Nanocrystals and Nano Co-Crystals by Confinement Methods. *Adv. Drug Deliv. Rev.* **2018**, *131*, 3–21. [CrossRef]
72. Zhang, G.G.Z.; Henry, R.F.; Borchardt, T.B.; Lou, X. Efficient Co-Crystal Screening Using Solution-Mediated Phase Transformation. *J. Pharm. Sci.* **2007**, *96*, 990–995. [CrossRef]
73. Aitipamula, S.; Wong, A.B.H.; Chow, P.S.; Tan, R.B.H. Cocrystallization with Flufenamic Acid: Comparison of Physicochemical Properties of Two Pharmaceutical Cocrystals. *CrystEngComm* **2014**, *16*, 5793–5801. [CrossRef]
74. Hong, C.; Xie, Y.; Yao, Y.; Li, G.; Yuan, X.; Shen, H. A Novel Strategy for Pharmaceutical Cocrystal Generation without Knowledge of Stoichiometric Ratio: Myricetin Cocrystals and a Ternary Phase Diagram. *Pharm. Res.* **2015**, *32*, 47–60. [CrossRef]
75. Ahuja, D.; Ramisetty, K.A.; Sumanth, P.K.; Crowley, C.M.; Lusi, M.; Rasmuson, Å.C. Microwave Assisted Slurry Conversion Crystallization for Manufacturing of New Co-Crystals of Sulfamethazine and Sulfamerazine. *CrystEngComm* **2020**, *22*, 1381–1394. [CrossRef]
76. Aher, S.; Dhumal, R.; Mahadik, K.; Paradkar, A.; York, P. Ultrasound Assisted Cocrystallization from Solution (USSC) Containing a Non-Congruently Soluble Cocrystal Component Pair: Caffeine/Maleic Acid. *Eur. J. Pharm. Sci.* **2010**, *41*, 597–602. [CrossRef]
77. Soares, F.L.F.; Carneiro, R.L. In-Line Monitoring of Cocrystallization Process and Quantification of Carbamazepine-Nicotinamide Cocrystal Using Raman Spectroscopy and Chemometric Tools. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **2017**, *180*, 1–8. [CrossRef]
78. Qu, H.; Jin, S.; Gong, J.; Du, S.; Jia, L.; Wu, S. Enhancing Stability and Formulation Capability of Fungicides by Cocrystallization through a Novel Multistep Slurry Conversion Process. *Cryst. Growth Des.* **2020**, *20*, 7356–7367. [CrossRef]
79. Pawar, N.; Agrawal, S.; Methekar, R. Modeling, Simulation, and Influence of Operational Parameters on Crystal Size and Morphology in Semibatch Antisolvent Crystallization of α-Lactose Monohydrate. *Cryst. Growth Des.* **2018**, *18*, 4511–4521. [CrossRef]
80. Rodrigues, M.; Lopes, J.; Guedes, A.; Sarraguça, J.; Sarraguça, M. Considerations on High-Throughput Cocrystals Screening by Ultrasound Assisted Cocrystallization and Vibrational Spectroscopy. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **2020**, *229*, 117876. [CrossRef] [PubMed]
81. Ober, C.A.; Montgomery, S.E.; Gupta, R.B. Formation of Itraconazole/L-Malic Acid Cocrystals by Gas Antisolvent Cocrystallization. *Powder Technol.* **2013**, *236*, 122–131. [CrossRef]
82. Wichianphong, N.; Charoenchaitrakool, M. Statistical Optimization for Production of Mefenamic Acid–Nicotinamide Cocrystals Using Gas Anti-Solvent (GAS) Process. *J. Ind. Eng. Chem.* **2018**, *62*, 375–382. [CrossRef]
83. Pessoa, A.S.; Aguiar, G.P.S.; Vladimir Oliveira, J.; Bortoluzzi, A.J.; Paulino, A.; Lanza, M. Precipitation of Resveratrol-Isoniazid and Resveratrol-Nicotinamide Cocrystals by Gas Antisolvent. *J. Supercrit. Fluids* **2019**, *145*, 93–102. [CrossRef]
84. Ribas, M.M.; Aguiar, G.P.S.; Muller, L.G.; Siebel, A.M.; Lanza, M.; Oliveira, J.V. Curcumin-Nicotinamide Cocrystallization with Supercritical Solvent (CSS): Synthesis, Characterization and in Vivo Antinociceptive and Anti-Inflammatory Activities. *Ind. Crops Prod.* **2019**, *139*, 111537. [CrossRef]
85. Padrela, L.; Rodrigues, M.A.; Tiago, J.; Velaga, S.P.; Matos, H.A.; de Azevedo, E.G. Insight into the Mechanisms of Cocrystallization of Pharmaceuticals in Supercritical Solvents. *Cryst. Growth Des.* **2015**, *15*, 3175–3181. [CrossRef]
86. Pando, C.; Cabañas, A.; Cuadra, I.A. Preparation of Pharmaceutical Co-Crystals through Sustainable Processes Using Supercritical Carbon Dioxide: A Review. *RSC Adv.* **2016**, *6*, 71134–71150. [CrossRef]
87. MacEachern, L.; Kermanshahi-pour, A.; Mirmehrabi, M. Supercritical Carbon Dioxide for Pharmaceutical Co-Crystal Production. *Cryst. Growth Des.* **2020**, *20*, 6226–6244. [CrossRef]
88. Long, B.; Ryan, K.M.; Padrela, L. From Batch to Continuous—New Opportunities for Supercritical CO2 Technology in Pharmaceutical Manufacturing. *Eur. J. Pharm. Sci.* **2019**, *137*, 104971. [CrossRef]
89. Sun, S.; Zhang, H.; Xu, J.; Wang, S.; Wang, H.; Yu, Z.; Zhao, L.; Zhu, C.; Sun, J. The Competition between Cocrystallization and Separated Crystallization Based on Crystallization from Solution. *J. Appl. Crystallogr.* **2019**, *52*, 769–776. [CrossRef]
90. De Maere D'Aertrycke, J.B.; Payen, R.; Collard, L.; Robeyns, K.; Croker, D.; Leyssens, T. Enabling Cocrystallization of Challenging Systems: Passing through a Stable Cocrystal Solvate as a Pathway to Strenuous Cocrystal Forms. *Cryst. Growth Des.* **2020**, *20*, 2035–2043. [CrossRef]
91. Mohammad, K.A.; Abd Rahim, S.; Abu Bakar, M.R. Kinetics and Nucleation Mechanism of Carbamazepine–Saccharin Co-Crystals in Ethanol Solution. *J. Therm. Anal. Calorim.* **2017**, *130*, 1663–1669. [CrossRef]
92. Croker, D.M.; Davey, R.J.; Rasmuson, Å.C.; Seaton, C.C. Nucleation in the p -Toluenesulfonamide/Triphenylphosphine Oxide Co-Crystal System. *Cryst. Growth Des.* **2013**, *13*, 3754–3762. [CrossRef]
93. Sheikh, A.Y.; Rahim, S.A.; Hammond, R.B.; Roberts, K.J. Scalable Solution Cocrystallization: Case of Carbamazepine-Nicotinamide I. *CrystEngComm* **2009**, *11*, 501–509. [CrossRef]
94. Yu, Z.Q.; Chow, P.S.; Tan, R.B.H. Design Space for Polymorphic Co-Crystallization: Incorporating Process Model Uncertainty and Operational Variability. *Cryst. Growth Des.* **2014**, *14*, 3949–3957. [CrossRef]
95. Weng, J.; Wong, S.N.; Xu, X.; Xuan, B.; Wang, C.; Chen, R.; Sun, C.C.; Lakerveld, R.; Kwok, P.C.L.; Chow, S.F. Cocrystal Engineering of Itraconazole with Suberic Acid via Rotary Evaporation and Spray Drying. *Cryst. Growth Des.* **2019**, *19*, 2736–2745. [CrossRef]
96. MacEachern, L.A.; Walwyn-Venugopal, R.; Kermanshahi-pour, A.; Mirmehrabi, M. Ternary Phase Diagram Development and Production of Niclosamide-Urea Co-Crystal by Spray Drying. *J. Pharm. Sci.* **2020**. [CrossRef]

97. Walsh, D.; Serrano, D.R.; Worku, Z.A.; Norris, B.A.; Healy, A.M. Production of Cocrystals in an Excipient Matrix by Spray Drying. *Int. J. Pharm.* **2018**, *536*, 467–477. [CrossRef]
98. Pawar, N.; Agrawal, S.; Methekar, R. Continuous Antisolvent Crystallization of α-Lactose Monohydrate: Impact of Process Parameters, Kinetic Estimation, and Dynamic Analysis. *Org. Process Res. Dev.* **2019**, *23*, 2394–2404. [CrossRef]
99. Darmali, C.; Mansouri, S.; Yazdanpanah, N.; Woo, M.W. Mechanisms and Control of Impurities in Continuous Crystallization: A Review. *Ind. Eng. Chem. Res.* **2019**, *58*, 1463–1479. [CrossRef]
100. Pu, S.; Hadinoto, K. Continuous Crystallization as a Downstream Processing Step of Pharmaceutical Proteins: A Review. *Chem. Eng. Res. Des.* **2020**, *160*, 89–104. [CrossRef]
101. Orehek, J.; Teslić, D.; Likozar, B. Continuous Crystallization Processes in Pharmaceutical Manufacturing: A Review. *Org. Process Res. Dev.* **2021**, *25*, 16–42. [CrossRef]
102. Kelly, A.L.; Gough, T.; Dhumal, R.S.; Halsey, S.A.; Paradkar, A. Monitoring Ibuprofen-Nicotinamide Cocrystal Formation during Solvent Free Continuous Cocrystallization (SFCC) Using near Infrared Spectroscopy as a PAT Tool. *Int. J. Pharm.* **2012**, *426*, 15–20. [CrossRef] [PubMed]
103. Moradiya, H.G.; Islam, M.T.; Halsey, S.; Maniruzzaman, M.; Chowdhry, B.Z.; Snowden, M.J.; Douroumis, D. Continuous Cocrystallisation of Carbamazepine and Trans-Cinnamic Acid via Melt Extrusion Processing. *CrystEngComm* **2014**, *16*, 3573–3583. [CrossRef]
104. Chabalenge, B.; Korde, S.; Kelly, A.L.; Neagu, D.; Paradkar, A. Understanding Matrix-Assisted Continuous Co-Crystallization Using a Data Mining Approach in Quality by Design (QbD). *Cryst. Growth Des.* **2020**, *20*, 4540–4549. [CrossRef]
105. Shaikh, R.; Walker, G.M.; Croker, D.M. Continuous, Simultaneous Cocrystallization and Formulation of Theophylline and 4-Aminobenzoic Acid Pharmaceutical Cocrystals Using Twin Screw Melt Granulation. *Eur. J. Pharm. Sci.* **2019**, *137*, 104981. [CrossRef]
106. Lee, T.; Chen, H.R.; Lin, H.Y.; Lee, H.L. Continuous Co-Crystallization As a Separation Technology: The Study of 1:2 Co-Crystals of Phenazine–Vanillin. *Cryst. Growth Des.* **2012**, *12*, 5897–5907. [CrossRef]
107. McGlone, T.; Briggs, N.E.B.; Clark, C.A.; Brown, C.J.; Sefcik, J.; Florence, A.J. Oscillatory Flow Reactors (OFRs) for Continuous Manufacturing and Crystallization. *Org. Process Res. Dev.* **2015**, *19*, 1186–1202. [CrossRef]
108. Zhao, L.; Raval, V.; Briggs, N.E.B.; Bhardwaj, R.M.; McGlone, T.; Oswald, I.D.H.; Florence, A.J. From Discovery to Scale-up: α-Lipoic Acid: Nicotinamide Co-Crystals in a Continuous Oscillatory Baffled Crystalliser. *CrystEngComm* **2014**, *16*, 5769–5780. [CrossRef]
109. Nishimaru, M.; Nakasa, M.; Kudo, S.; Takiyama, H. Operation Condition for Continuous Anti-Solvent Crystallization of CBZ-SAC Cocrystal Considering Deposition Risk of Undesired Crystals. *J. Cryst. Growth* **2017**, *470*, 89–93. [CrossRef]
110. Svoboda, V.; Macfhionnghaile, P.; McGinty, J.; Connor, L.E.; Oswald, I.D.H.; Sefcik, J. Continuous Cocrystallization of Benzoic Acid and Isonicotinamide by Mixing-Induced Supersaturation: Exploring Opportunities between Reactive and Antisolvent Crystallization Concepts. *Cryst. Growth Des.* **2017**, *17*, 1902–1909. [CrossRef]
111. Holaň, J.; Ridvan, L.; Billot, P.; Štěpánek, F. Design of Co-Crystallization Processes with Regard to Particle Size Distribution. *Chem. Eng. Sci.* **2015**, *128*, 36–43. [CrossRef]
112. Erriguible, A.; Neurohr, C.; Revelli, A.L.; Laugier, S.; Fevotte, G.; Subra-Paternault, P. Cocrystallization Induced by Compressed CO2 as Antisolvent: Simulation of a Batch Process for the Estimation of Nucleation and Growth Parameters. *J. Supercrit. Fluids* **2015**, *98*, 194–203. [CrossRef]
113. Neurohr, C.; Erriguible, A.; Laugier, S.; Subra-Paternault, P. Challenge of the Supercritical Antisolvent Technique SAS to Prepare Cocrystal-Pure Powders of Naproxen-Nicotinamide. *Chem. Eng. J.* **2016**, *303*, 238–251. [CrossRef]
114. Mishra, V.; Thakur, S.; Patil, A.; Shukla, A. Quality by Design (QbD) Approaches in Current Pharmaceutical Set-Up. *Expert Opin. Drug Deliv.* **2018**, *15*, 737–758. [CrossRef] [PubMed]
115. Simon, L.L.; Pataki, H.; Marosi, G.; Meemken, F.; Hungerbühler, K.; Baiker, A.; Tummala, S.; Glennon, B.; Kuentz, M.; Steele, G.; et al. Assessment of Recent Process Analytical Technology (PAT) Trends: A Multiauthor Review. *Org. Process Res. Dev.* **2015**, *19*, 3–62. [CrossRef]
116. Powell, K.A.; Croker, D.M.; Rielly, C.D.; Nagy, Z.K. PAT-Based Design of Agrochemical Co-Crystallization Processes: A Case-Study for the Selective Crystallization of 1:1 and 3:2 Co-Crystals of p-Toluenesulfonamide/Triphenylphosphine Oxide. *Chem. Eng. Sci.* **2016**, *152*, 95–108. [CrossRef]
117. Chavan, R.B.; Thipparaboina, R.; Yadav, B.; Shastri, N.R. Continuous Manufacturing of Co-Crystals: Challenges and Prospects. *Drug Deliv. Transl. Res.* **2018**, *8*, 1726–1739. [CrossRef] [PubMed]
118. Su, Q.; Ganesh, S.; Moreno, M.; Bommireddy, Y.; Gonzalez, M.; Reklaitis, G.V.; Nagy, Z.K. A Perspective on Quality-by-Control (QbC) in Pharmaceutical Continuous Manufacturing. *Comput. Chem. Eng.* **2019**, *125*, 216–231. [CrossRef]