Review Article

Traditional, Advanced and Green preparation methods of active pharmaceutical ingredient cocrystals: A review

Puspa Dwi Pratiwi[1*], Indri Maharini[1], M. Rifqi Efendi[1], Wahyu Nidia Putri[1] and Dita Avika Musdhaliva[1]

[1] Department of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Jambi, Jambi 36122, Indonesia

* Correspondence author, E-mail: puspadwipratiwi@unja.ac.id

Health Science, Science and Technology Reviews. 2025;18(3):111-124.

Received: 5 May 2025; Revised: 26 August 2025; Accepted: 6 November 2025

Abstract

Pharmaceutical cocrystals are a type of solid-state modification for medicinal compounds, primarily used to improve solubility. Cocrystal engineering is an alternative technique for enhancing the solubility, dissolution, and bioavailability of drugs. Pharmaceutical cocrystals consist of multiple molecules bound together by non-covalent interaction such as hydrogen bonding, van der Waals forces, and π-π stacking. Traditionally, cocrystals have been developed through solvent evaporation, grinding, or slurry techniques, each with its own environmental limitations. The current trend in cocrystal manufacture uses more advanced and environmentally friendly methods that utilize high technology. This review provides a brief overview of each procedure for generating cocrystals in pharmaceutical area based on sustainability, energy efficiency, and environmental impact.

Keywords : Cocrystals, Approaches, Traditional, Advanced, Green

Introduction

Solid-state modifications are fundamental to improving chemical and physical properties of drug substances without altering their chemical identity or pharmacological activity. This allows pharmaceutical scientists to fine-tune the solubility, stability, and bioavailability of a drug, which are key factors in its therapeutic efficacy and patient compliance. The traditional solid forms, like polymorphs, salts, and solvates, have long been used to optimize drug properties. Therefore, cocrystals have attracted significant attention in pharmaceutical research and development due to their ability to modify the solid-state physicochemical properties of API (Active Pharmaceutical Ingredient) without altering their pharmacological activity [1].

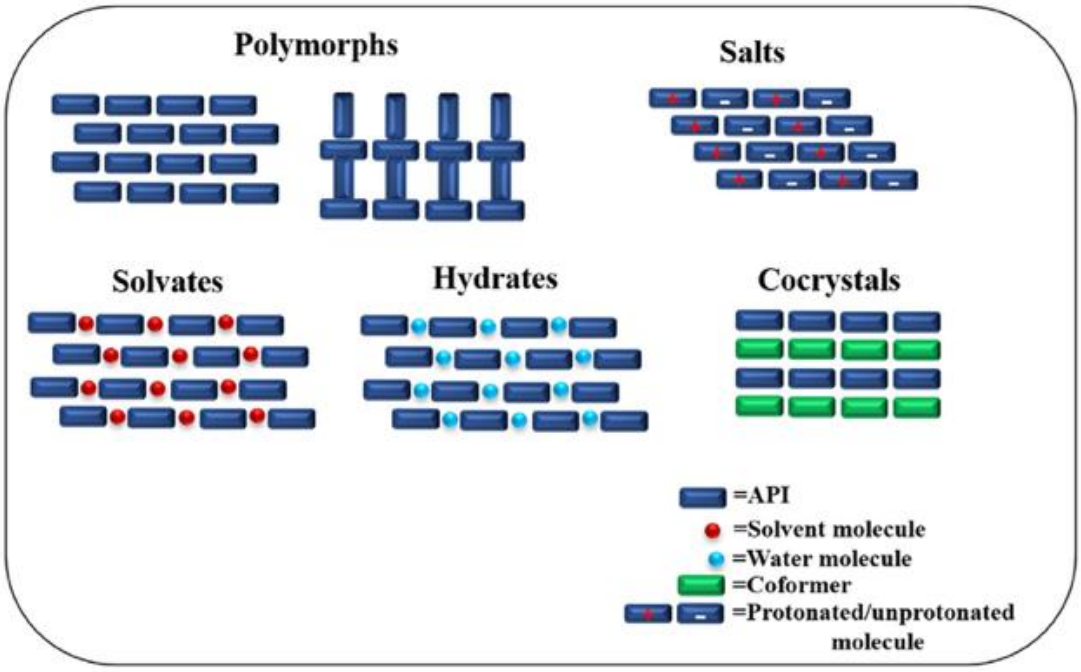

Figure 1. Different Solid Forms of Active Pharmaceutical Ingredients [2].

Cocrystal or co-crystallization, is recognised as a promising strategy in pharmaceutical development to increase the solubility and bioavailability of poorly soluble compounds. Cocrystals defined as solid crystalline substances formed by two or more combination different molecules, typically an API and a co-former. Cocrystal involves forming a solid, crystalline structure where the API interacts with one or more co-formers, typically non-toxic, small molecules. The presence of co-former molecules within the API's crystal lattice can lead to a number of advantages in the development of drug formulations. The formation of co-formers with API involves non-covalent interactions such as hydrogen bonding, van der Waals forces, and π-π stacking, which contribute to their unique structural characteristics and properties. The ability of coformers to modulate the physicochemical characteristics of an API makes them increasingly valuable in pharmaceutical science. Cocrystal is the potential approach to improve solubility, stability, and bioavailability, which are key factors in the development of effective and patient-friendly drug formulations. This is especially important for APIs that exhibit poor solubility or stability, which are common challenges in drug development [3,4].

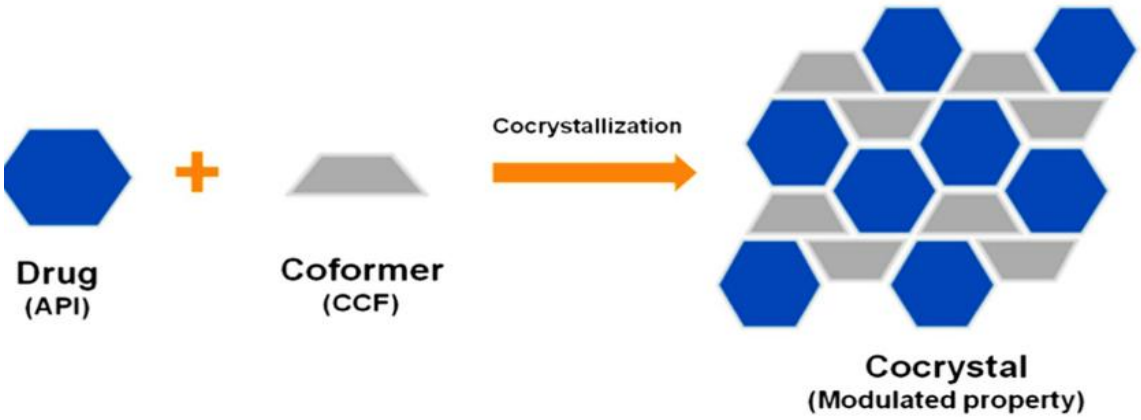

Figure 2. Formation of Cocrystal [5]

Despite this, it is remarkable that cocrystal preparation methods were essentially unknown until recently. Limited study has been dedicated explicitly at cocrystal preparation, and the majority of extant articles provide little detail on this topic. The first cocrystal-related research efforts focused on elucidating the crystal structure of cocrystals and bonding mechanisms, which necessitated high-quality single crystals from cocrystal samples. This was typically accomplished by trial and error methods based on solvent evaporation method only, which occasionally resulted in cocrystals [6].

Over the past decade, significant progress has been made in the development of cocrystal preparation methods. Today, a variety of approaches are available for synthesizing cocrystals, each with its own advantages depending on the specific API and coformer being used, as well as the desired properties of the final product. These methods offer increased reproducibility, scalability, and efficiency, making cocrystals a viable option for industrial-scale pharmaceutical production. But, the inconsistencies in the application of cocrystal preparation methods and the lack of standardized terminology create significant challenges for the field, particularly in terms of reproducibility, comparability, and accessibility for newcomers. However, as the field matures, there is a growing recognition of the need for standardized protocols and clearer reporting guidelines. By improving methodological consistency, terminological clarity, and best practice sharing, the cocrystal community can make the process more reliable and easier for both researchers and formulators to navigate, ultimately accelerating the development and application of cocrystals in pharmaceutical science [6].

As pharmaceutical science research increasingly emphasizes sustainability, green methods for cocrystal synthesis present a promising pathway for producing high-quality cocrystals with minimal environmental impact through the techniques offer a more sustainable approach to improving the solubility, bioavailability, and stability of pharmaceutical compounds. As the methods become more refined, they may become the industry standard for cocrystal development, particularly in light of growing environmental concerns. Green principles emphasize sustainability, energy efficiency, and minimizing the environmental impact of chemical processes. When it comes to the synthesis of cocrystals in pharmaceutical development, green methods aim to reduce or eliminate the use of hazardous solvents, minimize energy consumption, and utilize environmentally friendly reagents and techniques [7].

The objective of a review article on cocrystal preparation methods and applications would be to provide a comprehensive and organized summary of the current state of knowledge in this area. The review would aim to systematically present all the methodologies and developments from traditional methods to advanced and green methods related to cocrystals, with the goal of making it easier for researchers to navigate this evolving field.

Materials and Methods

This article review was written based on a literature study from electronic databases such as Pubmed, ScienceDirect, and Google Scholar, which provide information related to the topic in either Indonesian or English using one keyword or a combination, e.g., cocrystal, cocrystallization, green, methods, methodologies, techniques, and approaches. The source article is an article published in 2020-2025.

Results

The solid-state synthesis of pharmaceutical cocrystals has attracted significant interest recently due to its promising benefits over traditional solution-based crystallization methods. Several techniques have been developed to create the solid-state formation of pharmaceutical cocrystals with its own advantages and challenges. The selection of the appropriate cocrystallization technique is critical point for ensuring the cocrystal exhibits the desired properties, and its final performance in pharmaceutical applications.

Cocrystal methods are broadly divided into two types, The first is determined by the driving force (thermodynamic or kinetic, i.e., grinding, spray-drying, slurry sonication, and) and solvent (solvent-based and solvent-free method) [8]. On the other hand, below we discuss the traditional and the most recent advanced developments in solid-state cocrystal synthesis and evaluate the advantages and disadvantages of each approach with minimal environmental impact.

Traditional Methods of Cocrystal

1. Solvent Evaporation

Solvent evaporation is widely used laboratory scale technique that does not require complicated tools for preparation and produces cocrystals with high quality and minimal impurity. In this method, drug and coformer in a stoichiometric ratio are dissolved in a certain solvent and stirred in a suitable solvent to facilitate molecular interactions between the drug and the coformer in solution. The solvent is then evaporate to form cocrystals. The main condition that must be considered is that both drug and coformer must have sufficient solubility in chosen solvent to ensure they are present in solution and can interact because the solubility of the drug and coformer to the selected solvent plays an important role in cocrystal formation [9,10]. If the solubility of the two materials is not the same, the material with the lower solubility will precipitate. To form cocrystals, molecules must have the ability to interact between molecules [11].

The preparation of cocrystals by this method involves three process steps: supersaturation, nucleation, and crystal growth, where the supersaturation step is supersaturation, in particular, plays a crucial role in controlling the nucleation and crystal growth steps. Once the solution reaches supersaturation, this leads to the formation of a solid state faster or slower depending on the crystallization conditions. The advantage of this method is that cocrystals made through this process are thermodynamically preferred. The disadvantages of this method are that it requires heating, is recommended only for thermostable compounds, requires a lot of solvents, and has a low success rate of cocrystal growth to make large-scale cocrystals [12].

2. Slurry Method

The slurry method, a simple process, involves adding a small amount of solvent to the drug-coformer mixture, and later a muddy/suspension will be formed and then stirred until the cocrystallization process is complete, the solvent is then evaporated at room temperature to obtain cocrystals. The solvent must provide adequate solubility for both the API and the coformer, ensuring that they can reach the right level of supersaturation without precipitating prematurely [13]. Slurry techniques have become a popular and effective approach for cocrystallization in pharmaceutical applications, due to their simplicity, versatility, and ability to yield high-purity and thermodynamically stable products. The technique is also scalable, making it suitable for both laboratory-scale screening and industrial-scale production [14].

Slurrying accordingly performed better than mechanochemistry, which produces small amounts of unreacted coformer(s) as byproducts, and solution crystallisation, which frequently yields crystals of the least soluble coformer due to the difficulty of controlling the saturation of three or more solids. Perhaps the most interesting and surprising finding from previous research was that water slurrying was extremely effective, even for low-solubility coformers. water slurry has been successfully used as a method of forming 21 of the 25 cocrystals examined [14].

3. Grinding or Mechanochemical Method

Mechanochemical method, or grinding (both neat and liwuid-assisted grinding) are often more efficient for cocrystal formation compared to solvent evaporation metods [15]**.** In neat or dry grinding method, the drug and coformer are mixed and crushed using a mortar and pestle or with a mill such as a ball mill or vibrator mill. The grinding duration ranges from 30 to 60 minutes. With this method, there may be a possibility of failure in the formation of cocrystals due to the inability to form crystal structures with poor grinding. The stability of the material can be affected by the heat generated during the grinding process [9].

Liquid Assisted Grinding (LAG), or solvent-drop grinding, is another solvent method. In addition to providing a faster rate of cocrystal formation than dry grinding, this method is also more reliable and suitable. LAG is an extension of the traditional solvent-free mechanochemical techniques, with the key distinction being the introduction of a small amount of liquid to enhance or control the reactivity during the grinding process. By adding a tiny volume of liquid, LAG effectively modifies the mechanical environment to improve the efficiency an selectivity of the cocrystallization process, especially for systems that might be difficult to work with under neat grinding conditions. This method is known to be an environmentally friendly method for industrial production because of the less amount of solvent used. This process is also temperature independent, and more importantly, it reduces the possibility of unwanted solvate formation. This method can also be an alternative for compounds with very high melting points, such as theobromine (>400°C). However, the disadvantage is that if the addition of the solvent used is not appropriate, the cocrystal will not form but only produce a solution [16,17]. Table 1 shows a list of cocrystals that were successfully created utilising the solvent evaporation, slurry, and grinding methods.

Table 1. Examples of Cocrystal Manufacturing Using Traditional Approaches.

Drug	Co-former	Method	Results
Efavirenz [18]	DL-alanine, oxalic acid, maleic acid, and nicotinamide	Solvent evaporation	Cocrystals have been successfully prepared but the dissolution profile was increased seen only for efavirenz with DL-alanine and oxalic acid as coformer, whereas maleic acid and nicotinamide as coformer with efavirenz had a lower dissolution rate than pure efavirenz.
Ketoprofen [19]	Urea	Solvent evaporation	The results showed that the ketoprofen-urea-NaCl cocrystal solid had a higher dissolution and solubility rate than the ketoprofen-urea and ketoprofen cocrystal solids.
Cipfloxacin [6]	Isonicotinic acid	Grinding method	The cocrystal was successfully formed with Dry grinding, ball milling, and hot-melt extrusion method. The results showed these method increased the dissolution rate of the ciprofloxacin-isonicotinic acid cocrystal compared to pure ciprofloxacin.
Lamotrigine [20]	L-proline	Grinding method	Cocrystal of lamotrigine with L-Proline using liquid assisted grinding method was employed to improve the percentage dissolution efficiency of lamotrigine. The 1:4 molar ratio of malotrigine to L-proline showed significantly higer dissolution rate (dissolusion efficiency = 80.57%) compare to lamotrigine alone. Tablets formulated with this 1:4 molar ratio exhibited faster disintegration time and rapid dissolution rate compared to control tablets (containing pure lamotrigine)
Gliclazide [21]	3,5- Dinitrosalicylic acid	Grinding method	The cocrystal showed good results with high solubility (6.3 times), dissolution rate (1.5 times), and relative bioavailability (1.8 times) than pure glinclazide.
Cefixime [22]	Nicotinamide	Grinding method	Cocrystal of cefixime-nicotinamide have been successfully prepared using liquid assisted and dry grinding (LAG and DG) method based DSC (Differential Scanning Calorimetry), FTIR (Fourier Transform Infrared), SEM (Scanning Electron Microscope) and XRD (X-Ray Diffraction) characterization. Both method can increase the solubility, dissolution and permeability of cocrystal than cefixime. But LAG method showed higher result than DG method.

Advanced Methods

1. High Shear Granulation

High-shear granulation has emerged as a viable and effective synthetic method for producing co-crystal granules in pharmaceutical industry. This process agglomerates tiny particles using a granulation liquid. The primary objectives are to enhance flowability, improve uniformity in drug distribution, prevent segregation, and reduce the amount of dust release. The method is separated into three parts. The material are combined first, and then the granulation liquid is added. The moist material is next wet-massed, and finally dried. Process-induced solid-state changes can occur at any phase and can be investigated using XRPD, near infrared, and spectroscopy. These process-induced changes can be caused by water exposure, heat stress, or mechanical stress. They are usually undesirable since they are difficult to manage and can change the physicochemical properties of the API [23,24].

2. Spray drying

Spray drying is a single-step, continuously scalable technique. Using spray dryer equipment, this technique converts liquids such as solution and suspension into solid powder. Spray drying is often employed to make amorphous solid dispersions. however, it can also result in the synthesis of crystalline materials.This technique has been demonstrated to be a practical and scalable method for producing pure cocrystals from both congruent and incongruently saturated fluids.

In the spray drying approach, both the active pharmaceutical ingredient and the coformer are dissolved in a solvent and sprayed at a specific atomisation pressure using a continual vacuum application .The spray dried product is recovered using a cyclone collector and kept at ambient temperature. However, spray drying involves expensive equipment that must be well-maintained in order to function properly, as well as a skilled operator. The process is utilised for creating amorphous solids. It can be challenging to create crystalline phases from cocrystal components [25].

3. Microwave assisted synthesis

The microwave-assisted cocrystal process is clean, inexpensive, quick, and scalable. This can result in improved yields by using a shorter reaction time compared to the traditional heating process. The use of a microwave as a heating source accelerates the development of cocrystals when compared to conventional heating. Cocrystal components and solvents are placed in a microwave radiation reactor at appropriate temperatures and pressure for a set duration to create the required cocrystal product. In microwave assisted synthesis, drug substance (API) and coformer are mixed in equimolar ratios and microwave-irradiated in a microwave reactor, with or without solvent. The goal time and temperature are set by the microwave heating profiles of the drug and coformer, which are kept constant during the experiment [26]

Dipali Ahuja et al. used microwave-aided cocrystal to create sulfamethazine cocrystals. This study reveals that using a microwave as a heating source speeds up the creation of cocrystals as compared to the regular heating process. The study shows that microwave-assisted co-crystallization has the ability to increase production capacity from 0.2 to 20 g while maintaining product quality. These advantages can be used in companies to speed up formulation and produce high-quality products [27].

4. Ultrasound assisted solution cocrystallization

Ultrasound-assisted solution crystallization is a technique that utilizes the physical effects of ultrasound waves to promote the formation of drug cocrystals during the crystallization process. Ultrasound waves generate air bubbles or microbubbles within the solution. As the ultrasound waves pass through the liquid, they create alternating high- and low-pressure cycles. The low-pressure cycle causes the formation of bubbles, while the high-pressure cycle compresses and causes these bubbles to collapse. During the compression phase, the bubbles violently collapse, releasing a significant amount of energy. This sudden collapse generates localized high temperatures and pressures at the site of bubble implosion. The release of energy during bubble collapse raises the temperature and alters the pressure locally within the solution. This sudden change can promote the nucleation process—the formation of tiny solid particles or "nuclei"—which are the starting points for crystal growth. In the case of cocrystal, the energy from the collapsing bubbles induces interactions between the API and a co-former molecule, leading to the formation of cocrystals (26).

5. Supercritical fluid (SCF) technology

This approach combines several advanced concepts in crystallization. The API and the co-former (usually another drug or excipient) are carefully mixed together. This can be done by magnetic stirring in a suitable solvent, ensuring that both the API and the coformer are dissolved or sufficiently mixed in the solution. The solution containing the API and co-former is then placed in a high-pressure vessel**.** Supercritical CO_2 is introduced into the vessel. CO_2 becomes supercritical when it is at high pressure and temperature, above its critical point. Pressurized supercritical CO_2 acts as an anti-solvent, which induces the prepitation of cocrystals. The primary advantages of adopting SCF technology for cocrystallization are: high purity of cocrystals, one-step procedure, crystalline polymorphism control, processing of termolabile molecules, reduced usage of organic solvents, and environmentally acceptable technology [28]. Table 2 shows a list of cocrystals that were successfully created by the advanced approches.

Table 2. Examples Of Cocrystal Manufacturing Using Advanced Approaches.

Drug	**Co-former**	**Method**	**Results**
Cilostazol [29]	Hydroxybenzoic Acid	Spray Drying	The results showed that spray drying enhanced the dissolution of Cilostazol-Hydroxybenzoic Acid cocrystals. This indicates that water-insoluble drug cocrystals can be prepared by spray drying method.
Salicylic Acid [30]	Caffeine	Spray Drying	Cocrystals of salicylic acid and caffeine have been prepared via a series of spray drying methods (two fluid and three fluid). Salicylic Acid- Caffeine was successfully prepared regardless of solvent proportions, feedstock concentration or nozzle type although all spray drying methods showed the difference of characteristic of cocrystal.

Drug	Co-former	Method	Results
Diclofenac acid [31]	L-proline	Spray Drying	Forming a cocrystal with L-proline, a naturally occurring amino acid, is a well established technique to modify the physicochemical properties of drug. There is an increase in the physical stability of Diclofenac acid cocrystal with L-proline as coformer in crystalline solid dispersions due to efficient mixing of the polymer and cocrystals at the molecular level mixing achieved by spray drying within an in situ gelling of polymer matrix.
Acyclovir [32]	Tartaric Acid	Microwave-assisted Synthesized	In this study, acyclovir-tartaric acid cocrystals were successfully prepared using the help of a microwave – assisted solvent evaporation method. The solubility of acyclovir is greatly increased when tartaric acid is used as a coformant of acyclovir.
Telmisartan [33]	Oxalic Acid	Ultrasound assisted cocrystal	The dissolution profile of telmisartan-oxalic acid cocrystals can improve the dissolution rate of Telmisartan. Then also telmisartan-oxalic acid co-crystals prepared by ultrasound-assisted cocrystal method has improved the mechanical properties of telmisartan tablets.
Norfloxacin [34]	Urea	Ultrasound assisted solution cocrystal	Norfloxacin-urea cocrystals were successfully prepared by ultrasound-assisted slurry cocrystalmethod. The formation of norfloxacin-urea cocrystals can increase the solubility of norfloxacin in water.
Dexibuprofen [35]	Caffeine	Ultrasound assisted solution cocrystal	Improvement of the mechanical properties of dexibuprofen has been successful by ultrasound assisted solution cocrystaln method using chloroform solvent. The dexibuprofen - caffeine cocrystals showed better mechanical properties, such as flowability (compressibility index) and tabletability (tensile strength and elastic recovery) than dexibuprofen..

Drug	Co-former	Method	Results
Indomethacin [36]	Saccharin	High-shear wet granulation	Indomethacin are produced to cocrystal components with saccharin as coformer using ethanol as granulation fluid and polyethylene oxide as granulation agent. Coprocessing of reactants with polymers facilitates the formation of cocrystal granules in high yields (>96% w/w) even though the reactants are only slightly soluble in the granulation fluid.
p-Methoxycinnamic [37]	Succinic Acid	Microwave assisted synthesis (Microwave Irradiation)	The solubility of p-Methoxycinnamic increased solubility in cocrystals with the microwave radiation method by 1.16 times compared to p-Methoxycinnamic. The dissolution rate of cocrystals using the microwave radiation method increased 2.29 times compared to p-Methoxycinnamic.

Green Approach of Pharmaceutical Cocrystal

The primary goal of cocrystal's green approach is to reduce environmental impact by minimizing or eliminating the usage of organic solvents and greenhouse gases. However, advances in formulation processes have an indirect influence on the environment because they use electrical energy from a variety of conventional sources. It is necessary to compare and calculate the final impact of solvent-utilizing procedures and highly advanced methods. Cocrystals are formed utilizing several unique ways that demand expensive equipment and much more energy consumption for the final co-crystal product. Improving the existing technology, such as managing the solvent evaporation process at a specified temperature and pressure, may improve cocrystal formation without the use of high-end equipment [38].

Mechanochemistry is regarded as an appealing greener traditional approach to the preparation of cocrystals by using mechanical forces and has become an popular technique across various scientific diciplines (e.g., physics, chemistry, and material science) because it is an eco-friendly by eliminating or minimizing solvent use. This minimal solvent can act as a catalyst without the encironmental burden of large solvent volumes [39,40].

Other green advance approaches, such as spray drying and supercritical fluid technology, can reduce the negative impact on the environment, but it is expensive and require a large amount of electrical energy to make cocrystals. These procedures do not use organic solvents or hazardous chemicals, but they are energy intensive and require a skilled operator to produce cocrystals [38]. Furthermore, it is important to understand that spray drying has the same limitations as a conventional solvent-based method (process time and costs). In this context, Supercritical Fluid technologies represents a more sustainable approach due to the use of "green" solvents. Although it has considerable environmental benefits, such as being non-toxic and non-

flammable, it is still limited due to the poor solubility of active chemicals in supercritical CO_2, as well as the difficulty of processing feeds with high pressure gases [38].

In the case of SCF methods that use supercritical CO2 as an anti-solvent, additional limitations include the necessity to use organic solvent(s) to dissolve the medicinal compounds, and said solvent(s) must be miscible with supercritical CO2, restricting the solvent selection.As a result, it is reasonable to conclude that there is a lack of scalable technologies that combine the best of particle engineering and 'green chemistry' sectors to produce cocrystals for pharmaceutical purposes [41].

On the other research, spray congealing, gaining attention as an alternative method for drug cocrystallization. The process is simple, energy-efficient, and solvent-free, making it a strong candidate for pharmaceutical approache for cocrystal. This approach involves atomizing the liquid feed into fine droplets followed by rapid cooling and solidification via co-current cooling gas. The resulting soling particles are then effectively separated from the gas stream using cyclone before beeing collected. This technique alighns with green chemistry and sustainable pharmacy by minimizing cost and avoiding solvate formation [41].

Conclusions

Cocrystal is one of the most promising ways for improving the physicochemical properties of APIs. There are numerous alternatives for preparing cocrystals, ranging from classic to advanced methods that can be utilised from routine laboratory scale to large-scale continuous manufacturing in the pharmaceutical industry. All of the technologies presented can be considered for use based on their environmental impact by reducing or eliminating the use of organic solvents and greenhouse gases.

Acknowledgements

The present research was supported by Hibah Penelitian Dasar, a research grant scheme provided by Fakultas Kedokteran dan Ilmu Kesehatan, Universitas Jambi, 2024 number 202/UN21.11/PT.01.05/SPK/2024.

References

[1] Jayram P, Sudheer P. Pharmaceutical Co-crystals: A Systematic Review. Int J Pharm Investig. 2020;10:246–52. doi.org/10.5530/IJPI.2020.3.45.

[2] Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. Acta Pharm Sin B. 2021;11:2537–64. doi.org/10.1016/J.APSB.2021.03.030.

[3] Rathi R, Kaur S, Singh I. A Review on Co-crystals of Herbal Bioactives for Solubility Enhancement: Preparation Methods and Characterization Techniques. Cryst Growth Des 2022;22:2023–42. doi.org/10.1021/ACS.CGD.1C01408/ASSET/IMAGES/MEDIUM/CG1C01408_0009.GIF.

[4] Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. Acta Pharm Sin B. 2021;11:2537–64. doi.org/10.1016/J.APSB.2021.03.030.

[5] Mardiyanto, Untari B, Mara A, Ferdiansyah DF. Formation of Hydroxyl-Amide Solid Dispersion Involving Azithromycin and Chitosan-Alginate Biopolymer to Increase the Dissolution Rate of Azithromycin. Science and Technology Indonesia. 2023;8:647–53. doi.org/10.26554/STI.2023.8.4.647-653.

[6] Jafari MK, Ziaee A, O'Reilly E, Croker D, Walker G. Formation of Ciprofloxacin–Isonicotinic Acid Cocrystal Using Mechanochemical Synthesis Routes—An Investigation into Critical Process Parameters. Pharmaceutics. 2022;14:1–19. doi.org/10.3390/pharmaceutics14030634.

[7] Chettri A, Subba A, Singh GP, Bag PP. Pharmaceutical co-crystals: A green way to enhance drug stability and solubility for improved therapeutic efficacy. Journal of Pharmacy and Pharmacology. 2024;76:1–12. doi.org/10.1093/JPP/RGAD097.

[8] Pawar N, Saha A, Nandan N, Parambil J V. Solution Cocrystallization: A Scalable Approach for Cocrystal Production. Crystals. 2021,11(3)303. doi.org/10.3390/CRYST11030303.

[9] Baby P, Shabaraya AR, Bhavyashree T. Pharmaceutical Cocrystals: a Novel Approach for Solubility Modification. World J Pharm Res. 2021;10:1707–24. doi.org/10.20959/wjpr20214-20205.

[10] Dutt B, Choudhary M, Budhwar V. Cocrystallization: An Innovative Route toward Better Medication. Journal of Reports in Pharmaceutical Sciences. 2020;9(2):256–70. doi.org/10.4103/jrptps.JRPTPS_103_19.

[11] Ngilirabanga JB, Samsodien H. Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy. Nano Select 2021;2(3):512–26. doi.org/10.1002/nano.202000201.

[12] Baby P, Shabaraya AR. Pharmaceutical Cocrystals: A Novel Approach for Solubility Modification. World J Pharm Res 2021;10(4):1708. doi.org/10.20959/wjpr20214-20205.

[13] Nurismi E, Rosaini H, Octavia dan MD. Review: Effect of Different Methods on the Multicomponents Crystal Formation from Medicinal Natural Ingredient Compounds. IJPSM 2021;6(5):32–9. doi.org/10.47760/IJPSM.2021.V06I05.004.

[14] Haskins MM, Zaworotko MJ. Screening and Preparation of Cocrystals: A Comparative Study of Mechanochemistry vs Slurry Methods. Cryst Growth Des. 2021;21(7):4141–50. doi.org/10.1021/ACS.CGD.1C00418/ASSET/IMAGES/MEDIUM/CG1C00418_0009.GIF.

[15] Solares-Briones M, Coyote-Dotor G, Páez-Franco JC, Zermeño-Ortega MR, Contreras CM de la O, Canseco-González D, et al. Mechanochemistry: A Green Approach in the Preparation of Pharmaceutical Cocrystals. Pharmaceutics 2021;13(6):790. doi.org/10.3390/PHARMACEUTICS13060790.

[16] Gołdyn MR, Larowska D, Bartoszak-Adamska E. Novel Purine Alkaloid Cocrystals with Trimesic and Hemimellitic Acids as Coformers: Synthetic Approach and Supramolecular Analysis. Cryst Growth Des. 2021;21(1):396–413. doi.org/10.1021/ACS.CGD.0C01242/SUPPL_FILE/CG0C01242_SI_001.PDF.

[17] Ying P, Yu J, Su W. Liquid-Assisted Grinding Mechanochemistry in the Synthesis of Pharmaceuticals. Adv Synth Catal. 2021;363(5):1246–71. doi.org/10.1002/adsc.202001245.

[18] Gowda BHJ, Ahmed MG, Shankar SJ, Paul K, Chandan RS, Sanjana A, et al. Preparation and characterization of efavirenz cocrystals: An endeavor to improve the physicochemical parameters. Mater Today Proc. 2022;57(2):878–86. doi.org/10.1016/J.MATPR.2022.02.543.

[19] Laily AP, Irawan ED, Wisudyaningsih B, Barikah KZ, Wicaksono Y. Pembentukan kokristal Ketoprofen-Urea-NaCl untuk Peningkatan Sifat Kelarutan. Journal of Agropharmacy. 2024;1:26–32.

[20] Abdelrahman H, Essa E, Maghraby G El, Arafa M. L-Proline as Co-Crystal Forming Amino Acid for Enhanced Dissolution Rate of Lamotrigine : Development of Oral Dispersible Tablet. Indonesian Journal of Pharmacy. 2023;34:574–83.

[21] Eesam S, Bhandaru JS, Akkinepally RR, Bobbala RK. Cocrystallization of Gliclazide with Improved Physicochemical Properties. Futur J Pharm Sci. 2021;7:1–13. doi.org/10.1186/s43094-021-00261-z.

[22] Abdullah A, Mutmainnah, Wikantyasning ER. Cocrystals of Cefixime with Nicotinamide: Improved Solubility, Dissolution, and Permeability. Indonesian Journal of Pharmacy. 2022;33:394–400. doi.org/10.22146/ijp.2530.

[23] Dhondale MR, Thakor P, Nambiar AG, Singh M, Agrawal AK, Shastri NR, et al. Co-Crystallization Approach to Enhance the Stability of Moisture-Sensitive Drugs. Pharmaceutics. 2023;15:189. doi.org/10.3390/PHARMACEUTICS15010189/S1.

[24] Kumar Bandaru R, Rout SR, Kenguva G, Gorain B, Alhakamy NA, Kesharwani P, et al. Recent Advances in Pharmaceutical Cocrystals: From Bench to Market. Front Pharmacol. 2021;12:780582. doi.org/10.3389/FPHAR.2021.780582.

[25] Sakhiya DC, Borkhataria CH. A review on advancement of cocrystallization approach and a brief on screening, formulation and characterization of the same. Heliyon. 2024;10:e29057. doi.org/10.1016/j.heliyon.2024.e29057.

[26] Sakhiya DC, Borkhataria CH. A review on advancement of cocrystallization approach and a brief on screening, formulation and characterization of the same. Heliyon. 2024;10:e29057. doi.org/10.1016/J.HELIYON.2024.E29057.

[27] Ahuja D, Ramisetty KA, Sumanth PK, Crowley CM, Lusi M, Rasmuson AC. Microwave assisted slurry conversion crystallization for manufacturing of new co-crystals of sulfamethazine and sulfamerazine. CrystEngComm. 2020;22:1381–94. doi.org/10.1039/C9CE01886G.

[28] MacEachern L, Kermanshahi-Pour A, Mirmehrabi M. Supercritical carbon dioxide for pharmaceutical co-crystal production. Cryst Growth Des. 2020;20:6226–44. doi.org/10.1021/ACS.CGD.0C00571/ASSET/IMAGES/MEDIUM/CG0C00571_0008.GIF.

[29] Urano M, Kitahara M, Kishi K, Goto E, Tagami T, Fukami T, et al. Physical characteristics of cilostazol– hydroxybenzoic acid cocrystals prepared using a spray drying method. Crystals. (Basel) 2020;10. doi.org/10.3390/cryst10040313.

[30] Hibbard T, Shankland K, Al-Obaidi H. Evaluation of two and three fluid nozzle spray drying to prepare co-crystals of salicylic acid and caffeine with improved physicochemical properties. J Drug Deliv Sci Technol. 2023;89:105073. doi.org/10.1016/j.jddst.2023.105073.

[31] Shao SZ, Stocker MW, Zarrella S, Korter TM, Singh A, Healy AM. In Situ Cocrystallization via Spray Drying with Polymer as a Strategy to Prevent Cocrystal Dissociation. Mol Pharm. 2023;20:4770–85. doi.org/10.1021/acs.molpharmaceut.3c00564.

[32] Bandaru RK, Rout SR, Kenguva G, Gorain B, Alhakamy NA, Kesharwani P, et al. Recent Advances in Pharmaceutical Cocrystals: From Bench to Market. Front Pharmacol. 2021;12:780582. doi.org/10.3389/FPHAR.2021.780582.

[33] Ratih H, Pamudji JS, Alatas F, Soewandhi SN. Improving telmisartan mechanical properties through the formation of telmisartan and oxalic acid co-crystal by slow evaporation and ultrasound assisted co-crystallization from solution methods. Songklanakarin Journal of Science and Technology. 2020;42:188–95. doi.org/10.14456/sjst-psu.2020.25.

[34] Alatas F, Stiawan D, Al-Hakim NA. Solubility and Scale-Up Potency of Norfloxacin-Urea Co-Crystal Prepared by Ultrasound-Assisted Slurry Co-Crystallization Method. Borneo Journal of Pharmacy. 2023;6:158–67. doi.org/10.33084/bjop.v6i2.4173.

[35] Alatas F, Sutarna TH, Fakhrona Salman R, Nurono Soewandhi S. Mechanical Properties Improvement of Dexibuprofen through Dexibuprofen-Caffeine Co-crystal Formation by Ultrasound assisted Solution Co-crystallization Method. Indonesian Journal of Pharmaceutical Science and Technology. 2022;9:45. doi.org/10.24198/ijpst.v1i1.34713.

[36] Tanaka R, Duggirala NK, Hattori Y, Otsuka M, Suryanarayanan R. Formation of Indomethacin-Saccharin Cocrystals during Wet Granulation: Role of Polymeric Excipients. Mol Pharm. 2020;17:274–83. doi.org/10.1021/acs.molpharmaceut.9b01004.

[37] Sulistyowaty MI, Setyawan D, Prameswari PPM, Susilo RJK, Amrillah T, Zaini E, et al. A Comparison Study between Green Synthesis of Microwave Irradiation and Solvent Evaporation Methods in The Formation of p-Methoxycinnamic Acid-Succinic Acid Cocrystals. Science and Technology Indonesia. 2024;9:629–36. doi.org/10.26554/sti.2024.9.3.629-636.

[38] Sakhiya DC, Borkhataria CH. A review on advancement of cocrystallization approach and a brief on screening, formulation and characterization of the same. Heliyon. 2024;10:e29057. doi.org/10.1016/j.heliyon.2024.e29057.

[39] Duarte Í, Andrade R, Pinto JF, Temtem M. Green production of cocrystals using a new solvent-free approach by spray congealing. Int J Pharm. 2016;506:68–78. doi.org/10.1016/J.IJPHARM.2016.04.010.

[40] Qi L, Li C, Cheng X, Hao H, Xie C. Green Mechanochemical Preparation of Cocrystal Polymorphs: Significant Effect of Intermediates and Solvents. Cryst Growth Des. 2024;24:6196–203. doi.org/10.1021/ACS.CGD.4C00340/SUPPL_FILE/CG4C00340_SI_001.PDF.

[41] Duarte Í, Andrade R, Pinto JF, Temtem M. Green production of cocrystals using a new solvent-free approach by spray congealing. Int J Pharm. 2016;506:68–78. doi.org/10.1016/J.IJPHARM.2016.04.010.