Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1506-1513
DoI-10.004687/1000-9035.2025.195

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Pharmaceutical Cocrystals: A Novel Strategy for Solubility Enhancement

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Article Information
Received: 18-10-2025
Revised: 12-11-2025
Accepted: 27-11-2025
Published: 26-12-2025

Keywords
solid-state synthesis, bioavailability, pharmaceutical cocrystals, solubility improvement, sustainable drug development, and coformers

ABSTRACT
Pharmaceutical cocrystals are crystalline single-phase materials made up of a pharmaceutically approved coformer and an active pharmaceutical ingredient (API) bound together by non-covalent interactions. They offer an uncommon chance to increase medication solubility, dissolving rate, effectiveness, and stability without changing the basic pharmacological characteristics of the API. With a focus on their function in enhancing oral medication absorption, this article offers a thorough overview of the crystal design, synthesis, characterisation, and assessment. The benefits and drawbacks of various preparation procedures are covered, including solid-state processes like grinding and melted crystallization as well as solution-based methods like solvent evacuation and antisolvent crystallization. For evaluating intermolecular interactions and physicochemical features, characterization techniques including FTIR, DSC, TGA, PXRD, and terahertz research are emphasized. As part of healthy pharmaceutical development, the ecological advantages of cocrystallization are highlighted, including less solvent usage, lower use of energy, and avoidance of harmful chemicals. Applications in improving the absorption and absorption of weakly water-soluble medicines are highlighted with case studies. This study highlights cocrystals as an environmentally friendly and adaptable platform for improving medication delivery and effectiveness in therapy by aggregating existing knowledge and highlighting upcoming difficulties

1. INTRODUCTION:

The US Food and Drug Administration describe cocrystals as "crystalline materials composed of more than one molecule along the same crystal lattice". [1] At an Indo-US meeting in 2011, 46 scientists presented a generally accepted description of cocrystals, which are crystalline single-phase materials formed by two or more distinct molecular and/or ionic compounds in a stoichiometric ratio that are neither solvates nor simple salts. [2] Pharmaceutical cocrystals have at least one API and another pharmaceutically approved coformer. [3,4] Pharmaceutical cocrystals are created primarily by non-covalent interactions such as hydrogen bonding, coordinate attachment, van der Waal forces, or p-p stacking interactions involving multiple crystallized substances in certain stoichiometric ratios. [5]

Co-crystals were first discovered in 1844, but their structure was not completely understood until 1958. Etter was the first to use the word "cocrystal" and define the design principles for hydrogen bonding in an organic cocrystal. [6,7] The term "cocrystal" did not appear until 1967, when it was coined to describe a complex of hydrogen bonds formed by 9-methyl adenine and 1-methyl thymine. Desiraju, the very first researcher to establish the supramolecular synthon concept of hydrogen bond production in crystal structures, popularized the term in the 1990s. [8]

The discovery and history of organic components were examined in Stahly's study on the existence of cocrystals prior to 2000, along with examples to demonstrate the principles of cocrystal chemistry. [] The debate around cocrystals begun in 2003, with

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Desiraju posted a contentious letter explaining his use of the phrase "a multi-component system held together by non-covalent interactions." Dunitz commented, noting that the term encompasses solid solutions, encapsulated compounds, and amorphous solids. [10]

The physicochemical characteristics of active pharmaceutical ingredients (APIs), including their stability, particle size, powder flowability, taste, hygroscopicity, solubility, and compatibility, are important factors that affect both the production cost and therapeutic efficacy of solid dosage forms. [11] In oral drug administration systems, drug dissolution and solubility both have a substantial impact on gastrointestinal absorption. However, at present, roughly 90% of novel chemical entities and 40% of presently marketed medications fall inside the Biopharmaceutical Classification System II and IV classes, especially struggle with the challenges of low water solubility and low bioavailability. [12] As a result, medication absorption in the gastrointestinal system is reduced, which impedes drug therapeutic uses. Obviously, pharmaceutical solids' physicochemical qualities have a significant impact on therapeutic product performance.

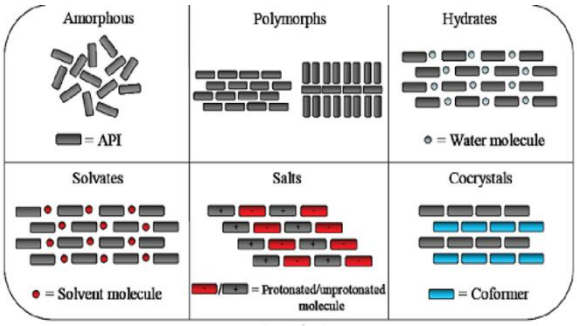

Figure 1. Types of API [13]

It is generally understood that particle packing in the combination of the cell the crystal lattice has a direct impact on the characteristics of a crystalline material. As a result, altering the crystal packing patterns can change the physicochemical characteristics of solid drug forms. [14, 15] To date, numerous solid-state techniques have been used to adjust the characteristics of APIs, such as salts [16], polymorphs [17], hydrates [18], solvates [19], and cocrystals [20,21] (Figure 1). Researchers have developed a variety of strategies to increase a drug's solubility and bioavailability. Some approaches are used to enhance the solubility of poorly water-soluble medicines. Each approach has benefits and disadvantages, so before choosing a technique, it is crucial to examine aspects such as the quality of the active pharmaceutical ingredient, the characteristics of the chosen excipients, the development process, and the nature of the dosage form. [22] The co-crystal approach is unique among these techniques in that it does not modify the drug's pharmacological characteristics, making it an environmentally friendly method of improving the drug's bioavailability and a number of physicochemical characteristics, such as solubility, penetration, bioavailability, stability, melt point, alongside tabletability (Figure 2). Without any type of chemical alterations, a drug could improve its physical and chemical attributes, which reveals the approach known like an environmental pathway [23].

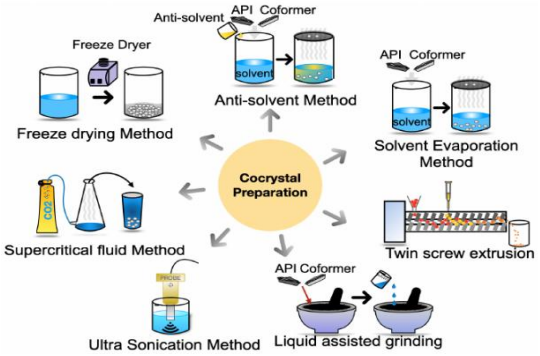

Figure 2. Shows co-crystal synthesis and application [24]

This review provides a complete analysis of medicinal co-crystals, encompassing design, synthesis, characterisation, and assessment with respect to its solubility. One of among the most essential aspects of oral medication absorption is solubility. When dissolution limits the medication absorption process, improving solubility can enhance the rate of drug dissolution and bioavailability. [25,26] Cocrystal formation has been found to boost the solubility of drugs by orders of magnitude. [27,28] Nevertheless, this cocrystal stability superiority over drug (SA=Scocrystal/Sdrug) offers a danger for precipitation resulting in less soluble forms of the drug.

1.2. Co-Crystal Preparation:

Solid-state grinding, solution reacting crystallization, solvent extraction, slurry conversion, and hot melt extrusion are some of the most common processes used for cocrystal formation. However, the picking of an appropriate cocrystallization process remains empirical. The most popular techniques for cocrystal formation may be divided into two categories: solid-based and solution-based. (Figure 3) [13].

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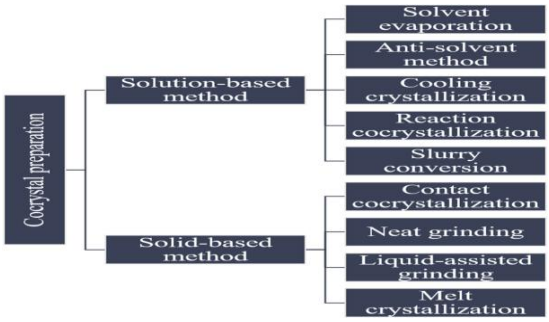

Figure 3. Methods of cocrystal preparation [13]

1.2.1. Solution based methods

The ideal state for these techniques is that the cocrystal becomes supersaturated while the molecules that react (API and coformer) are either saturated or insufficiently saturated depending the experimental circumstances. The solution contains ternary phases (API, coformer, and solvent). Therefore, the crucial factor for cocrystallization is a level of supersaturation with regard to cocrystal in solution, which may be modified by the quantities of API and coformer. [29] To direct the course of cocrystal synthesis, a phase diagram that explains the parameters for its thermodynamic stability is required constructed, which will assure that the its cocrystal stays inside of the thermodynamically stable zone and preclude the crystallization of only chemical reactants. The placement of thermally resistant cocrystal phase zones is mostly governed by the dissolved state of the reactants involved. [30]

A) Solvent evaporation method

Solvent evaporation is the predominant technique for cocrystal preparation and is often employed to synthesize high-quality single-crystal cocrystals suitable for structural investigation using single-crystal X-ray diffraction. This method involves the full dissolution of cocrystal components in an appropriate solvent at a certain stoichiometric ratio, followed by solvent evaporation to yield the cocrystal. [31] The choice of solvent affects cocrystallization, which may alter the dissolution of the reactants. The components of the cocrystal must be uniformly soluble in the specified solvent. When cocrystallization transpires among two incongruently soluble constituents, the less soluble portion preferentially precipitates, resulting in a solid combination of cocrystal and its components, or a failure to form cocrystals. [31, 32, 33] For instance, gradual evaporate of acetonitrile at ambient temperature for 3-5 days resulted in a block-shaped small crystal of a 1:1 febuxostat-piroxicam cocrystal that interacted through a carboxylic acid-azole synthon. Compared to the comparable components, the resultant cocrystal showed improved tabletability and increased solubility. [34]

B) Anti-solvent method

Antisolvent crystallization, which is carried via continuous production processes, has been regarded as an efficient method for controlling the quality, particle size, and characteristics of cocrystals. [35, 36, 37, 38, 39] For instance, Chun et al. [39] generated the indomethacin–saccharin cocrystals by anti-solvent method. As seen in Fig. 4, 150 mL of methanol was combined with a mixture of 0.034 mol/L indomethacin was used and 0.05 mol/L saccharin.

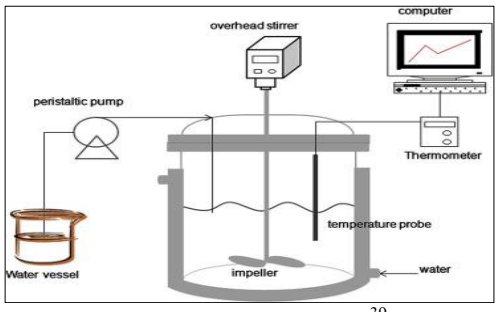

Figure 4. Apparatus for antisolvent method [39]

The solution vessel was then filled with 75 mL of water (antisolvent) using a peristaltic pump that stirred at 300 rpm for one hour at 25 °C. Better dissolving rates were attained using rod-like or columnar cocrystals. In order to achieve supersaturation during the stage of crystallization, an antisolvent is added, which reduces cocrystal solubility and causes cocrystals to precipitate. Because the cocrystal is poorly soluble in the weak solvent, it is crucial to select the right miscible solvent combination. Because the solvent's composition may affect the cocrystal's and its constituent parts' solubility, the cosolvent ratio can have a substantial impact on the cocrystal yield. The yield if carbamazepine–saccharin (CBZ–SAC) cocrystals came to the greatest value when the volume content of methanol to water was 1:2; however, CBZ hydrates would form below that ratio.[36]

There are many other Solution based methods like slurry conversion, reaction cocrystallization.

1.2.2. Solid based methods

Solid-state crystallization technologies are successful and ecologically friendly in cocrystal creation since they use less solvent; their cocrystal develops spontaneously by being in contact with increased energy inputs. They are sensible substitutes for solution-based cocrystallization techniques, which may pose environmental risks because of their high solvent usage. Numerous medicinal cocrystals have been manufactured via solid-based techniques. [40, 41, 42, 43]

A) Contact Cocrystallization

It was discovered that following "soft" mixing of the raw components, connections between the API

with coformer might happen on their own.[44, 45, 46] The two solids' vapor diffusion, moisture sorption, amorphous phase formation, amorphization, and long-range symmetric molecular migration61 have all been suggested as potential explanations for spontaneous crystallization by contact. Higher humidity, higher temperatures and smaller size fractions of input materials could promote cocrystal formation. [47] MacFhionnghaile et al. observed demonstrated caffeine–urea crystalline particles were formed over three working days by mixing separated premixing raw materials at a normal temperature and 30% moisture content. [48] The primary element influencing the development of caffeine-urea cocrystals, according to the scientists, was the interface surface contact with the solids.[49]

B) Melting crystallization

It is a different green way for preparing pharmacological cocrystals.[35] Whilst solvents aren't utilized in this technique, the thermal endurance of medication and coformer has to be carefully examined in advance.[50] Melatonin-pimelic acid cocrystal was created by Yan et al. via melt crystallization. Melatonin-pimelic acid cocrystals were created when the molten fluid was between 50 and 70 degrees Celsius. [50] The carbamazepine–nicotinamide cluster was created by melting the physical combination of drug and co forms at 160 °C and then cooling the melt to the outside temperature for crystal growth. [51]

There are many others methos includes solid state grinding, neat grinding etc.

1.3. Evaluation:

FTIR spectroscopy is employed to forecast the intermolecular medication interactions and compatibility research and co-performers. This method is frequently employed to forecast a compound's chemical configuration. To differentiate the cocrystals, Aakeroy et al. employed FTIR from salts by assessing the carboxylic acid participation in the creation of hydrogen bonds. [52] FTIR is used to analyze pure drugs, coformers, physical mixtures, and cocrystals within the 400-4000 cm-1 range. FTIR study is also employed combined with other methods. [53, 54, 55]

Cocrystal formation has been screened using DSC. Screening of cocrystals development may be determined by the existence of exothermic peak immediately by endothermic signal in DSC spectra. The existence of these lines in the physical combination of components indicates the likelihood of creation of cocrystals. Pure drug, coformer physical mixing and cocrystals were weighing out (1.5-2.5 mg) in steel pans and analysed with scorching rates of 5-30° using comparable empty pan as a reference. The nitrogen gas at flow rate 50 ml/min kept the inert environment. Melting point, glass transitions temperature, polymorphic structure, heat of fusion, ending or exothermic behaviour may be determined by utilizing DSC.[56, 57, 58]

Physical and chemical characteristics of solids are chosen by utilizing thermal testing as a function of rising temperature (through a constant heating rate) or is a function for time (with constant pressure and/or constant mass loss). TGA is an appropriate technique for determining the hydrate/solvate forms of cocrystals, the presence of volatile components, and the temperature at which breakdown or sublimation occurs. Thermal stability, interoperability and quality of cocrystals cannot be predicted by TGA study. The weight degradation of sample mass through the TGA testing is the sign of loss of volatile material or breakdown of cocrystal. [59, 60]

Terahertz time-domain-spectroscopy is an equivalent method to PXRD for the characterization of cocrystals. Chiral and dynamic molecular and supramolecular structures may be identified by terahertz spectroscopy. [61] Terahertz spectroscopy was utilized to differentiate between theophylline cocrystals with the same chemical structure and several coformers, including tartaric acid and malic acid, which were found in both racemic and chiral forms.[62]

Solubility studies may be assessed via Higuchi and Connors technique for solubility determination. The solubility of pure medication, physical combination and cocrystals can be tested in water or a suitable environment given in the cited pharmacopoeia. Drug sample and a conical flask should be filled with medium, and should shaking for 24 h at the ambient level on rotary flask shaker. The full samples should be kept against light by covering the flask by foil made of aluminum if the medication is sensitive to daylight. After 24 h specimens undergo filters using Whatman filter paper, and aliquots are appropriately diluted and tested by HPLC | UV at appropriate wavelength [63, 64.]

1.4. Co-crystallization as a sustainable route to enhance drug Solubiltity and development:

Initially, reduced solvents usage: Co-crystallization often uses less solvents compared with classic chemical production methods. As a consequence, there is less solvent waste, which minimizes the negative effects of solvent disposal on the environment and lowers the possibility of health risks linked to solvents which makes it a better fit considering for solubility of drug and its

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components.

Additionally, the use of energy: Co-crystallization techniques frequently function at gentler conditions for reaction, which may translate to cheaper energy consumption comparison with more resource-intensive reactions that involve chemicals. Reduced energy needs support overall environmental sustainability and lower carbon emissions.

Also, better medicinal qualities: Co-crystallization can be utilized to increase the properties of pharmaceuticals, such as solubility, permanence, and tolerability.

Drug makers can alter the drug compound's crystalline structure by choosing the right coformers, which enhances medication performance without requiring significant chemical changes.

Retaining the potency of the medicine: Conventional chemical adjustments of drug combinations can occasionally result in undesirable side effects or alterations in the potency of the drug. When done properly, co-crystallization can achieve the needed property enhancements while preserving the drug's medicinal usefulness.

Elimination of dangerous reagents: Many chemical processes entail the usage of hazardous agents or the formation of poisonous by-products. Co-crystallization may frequently be conducted utilizing benign precursors and solvents, lowering the possibility for dangerous waste products and increasing the total security profile of the drug during development. [65]

Regulatory along with quality improvements: Co-crystallization might give benefit in terms of approval by regulators and quality management. As long as the resultant co-crystal retains the same API, it enables pharmaceutical companies to modify already-approved medications without demanding extensive retesting or reapproval. Seventh, scalability: Co-crystallization methods may frequently be readily scaled up for industrial reasons, making it a realistic and sustainable choice for large-scale medication production.

While co-crystallization offers several ecological benefits, it is vital to assess the individual requirements and obstacles of each pharmaceutical development project. The selection of the right coformers and adjustment of crystallization settings are essential aspects in the effective utilization of co-crystallization as an ecological strategy for increasing medicinal characteristics. [65]

Solubility: One important feature of API is its solubility. In addition to other techniques including salt formation, solid dispersion, size optimization[66,] co-crystallization has been used in several studies [67, 68] to improve the solubility of medicines. The antifungal API ketoconazole's solubility was increased 53 and 100 times, respectively, by creating salts and co-crystals. As a consequence, co-crystals created a medicine that was harder to dissolve than the formation of salt [69.] When relative with the pure medication, apixaban co-crystals demonstrated a two-times higher solubility and a quicker rate of disintegration [67]

The solubility of pterostilbene-piperazine co-crystals was raised sixfold, but the drug precipitated fast for pterostilbene-glutaric acid joint crystals due to glutaric acid's high solubility [70]. 6-Mercaptopurine together with nicotinamide demonstrated a two-fold higher rate of solubility than the drug alone [71]. Theoretically, this technique is used for assessing the solubility and co-crystals in a solvent that is 100% pure, this is also an invaluable tool for compound selection and design [72]. Keq was characterized utilizing a collection with more than 40 distinct co-crystal and solvent ratios [73.]

When dissolution limits the drug absorption process, improving solubility can increase the rate of drug dissolution and bioavailability. [70, 74]

The rate and amount of a drug that reaches the systemic circulation is referred to as bioavailability. [75] Developing novel formulations of pharmaceuticals poses a huge hurdle when they pertain to their limited oral bioavailability. Crystal development plays a significant role in creating and producing pharmaceutical components that offer better bioavailability when eaten and aqueous solubility. [76]

1.5. Applications

Co-crystallization can enhance the physicochemical properties of drugs without changing their molecular structure. The API and customized project will decide whether co-crystals or chloride will have the needed qualities. In certain circumstances, salts provide superior physicochemical features than co-crystals, among them salts being a higher intrinsic solubility in water. When dissolved, salt will form ionized API, this is more soluble in water, but co-crystals have negative value of pKa will yield non-ionized medicines. When dissolving rate rather than solution solubility should be taken into account, co-crystals may be a better option than salt versions of medications. Co-crystallization is another technique for improving the solubility &

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bioavailability of medicines, especially those that are neutral, weakly ion in nature[77, 78.]

All things considered, pharmaceutical cocrystals provide new possibilities for medication development and patient-centered formulations by providing a durable and adaptable solution to problems with solubility and bioavailability.

CONCLUSION:

Pharmaceutical cocrystals have emerged as a versatile and sustainable strategy to overcome long-standing challenges of poor solubility and limited bioavailability in oral drug delivery. By enhancing dissolution, stability, and mechanical properties without altering the pharmacological identity of APIs, they offer a unique balance between innovation and practicality. The diverse preparation methods and advanced characterization techniques discussed in this review highlight both the adaptability and the scientific rigor behind cocrystal development. Yet, the path forward requires more than technical refinement—it calls for predictive design tools, greener synthesis approaches, and stronger regulatory clarity to translate laboratory success into clinical reality. Ultimately, cocrystals represent not just an incremental improvement, but a paradigm shift in pharmaceutical development, bridging scientific ingenuity with patient-centered outcomes.

Future perspectives:

Pharmaceutical cocrystals have shown definite benefits in improving solubility, dissolution, overall bioavailability, although there are still a number of unexplored areas. Future studies ought to concentrate on:

Predictive design tools: Designing computational algorithms and AI-based screening to objectively pick coformers and forecast physicochemical results.

Green synthesis methods: Expanding solvent-free and green processes such as mechanic chemistry and melts crystallization to match with sustainability aims. Clinical translation involves carrying out thorough in vivo studies in order to confirm the safety profiles and therapeutic advantages of cocrystal compositions.

Regulatory pathways: Establishing clearer rules for categorization, acceptance and quality supervision to speed industrial adoption.

Patient-centric formulations: To increase accessibility and compliance, cocrystals are being investigated in innovative dosage forms (fast-dissolving tablets, pediatric formulations, fixed-dose combos).

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