**Co-crystals in Pharmaceutics: Enhancing Solubility and Stability**

Ankita Punjaji Jatale1, Dikshita B Patil2, Mrs.Esther Swapnil Chopade3,

Mr. Swapnil Sanjay Chopade4, Ms. Sayali Diplip Powar5

PECT’s School Of Pharmacy, Pimpri Chinchwad University Pune1,2,

Tatyasaheb kore college of pharmacy Warananagar3,4,5

**Abstract**
Pharmaceutical cocrystals are multicomponent crystalline systems in which at least one component is an active pharmaceutical ingredient (API), and the others are pharmaceutically acceptable coformers. Cocrystallization of an API with a coformer is an innovative and promising strategy for enhancing the performance of pharmaceutical formulations, particularly in terms of solubility, dissolution rate, pharmacokinetics, and stability. This review provides a comprehensive overview of pharmaceutical cocrystals, including various preparation techniques, their physicochemical properties, and practical applications. Additionally, it highlights several examples of drug cocrystals to demonstrate how crystal structures can influence key aspects of active pharmaceutical ingredients, such as physical and chemical stability, mechanical properties, optical characteristics, bioavailability, sustained release, and overall therapeutic effect. This review aims to offer valuable insights for the efficient design and development of pharmaceutical cocrystals with tailored physicochemical properties and applications.

**Keywords**
Pharmaceutical cocrystals, Cocrystal engineering, Physicochemical properties, Solid dosage forms, Crystallization techniques, Drug formulation.

### 1. **Introduction**

The physicochemical properties of active pharmaceutical ingredients (APIs)—such as stability, particle size, powder flowability, taste, hygroscopicity, solubility, and compatibility—play a critical role in the therapeutic effectiveness and manufacturing cost of solid dosage forms. In oral drug delivery systems, the gastrointestinal absorption of drugs is significantly influenced by their solubility and dissolution rate. However, approximately 90% of new chemical entities and 40% of currently marketed drugs fall under the Biopharmaceutical Classification System (BCS) Classes II and IV, which are characterized by poor water solubility and low bioavailability. As a result, the absorption of these drugs in the gastrointestinal tract is limited, impeding their clinical applications. Clearly, the physicochemical properties of pharmaceutical solids have a considerable impact on drug performance.

It is well understood that the atomic packing within the unit cell and the crystal lattice structure directly influence the properties of crystalline materials. Therefore, modifying the physicochemical properties of solid drug forms can be achieved by tailoring the crystal packing arrangements. Over the years, several solid-state strategies have been employed to improve the properties of APIs, including salt formation, polymorphism, hydrates, solvates, and cocrystals. However, each approach has its limitations. For instance, salt formation is only applicable to molecules with suitable ionizable groups, and hydrates and solvates are often unstable due to the loss of water or solvent molecules over time. In contrast, any API—whether acidic, basic, or non-ionized—has the potential to form cocrystals with an appropriate coformer.

Over the past two decades, pharmaceutical cocrystals have garnered significant interest from both academia and the pharmaceutical industry for their ability to enhance the physicochemical properties of APIs by modifying the crystal structure without altering the pharmacological nature of the drug. As the field of cocrystallization has advanced, several pharmaceutical cocrystals have been successfully developed and approved, such as Steglatro® and Entresto®, with more currently in clinical trials.



 Figure 1. Different solid forms of active pharmaceutical ingredients.

**Pharmaceutical cocrystals** are defined as crystalline materials composed of two or more discrete neutral molecules in a stoichiometric ratio, bonded together through noncovalent interactions, such as hydrogen bonding, van der Waals forces, and π-π stacking. At least one of the components must be an active pharmaceutical ingredient (API), while the others are pharmaceutically acceptable excipients. Since the early 2000s, cocrystal engineering has been recognized as a promising approach to enhance the physicochemical properties of pharmaceuticals. This realization was greatly advanced by key publications between 2003 and 2004, which highlighted the importance of crystal engineering and supramolecular synthons in pharmaceutical cocrystal design, spurring the development of this strategy to improve drug performance. Several robust supramolecular synthons have been identified, which play crucial roles in cocrystal formation and drug development. These include functional groups such as carboxylic acids, amides, and alcohols, which are particularly amenable to the formation of supramolecular synthons. There are two main types of supramolecular synthons: **supramolecular homosynthons**, formed by self-complementary functional groups (e.g., carboxylic acid dimers or amide dimers), and **supramolecular heterosynthons**, formed by complementary functional groups (e.g., hydrogen bonding between carboxylic acid and pyridine, or alcohol and aromatic nitrogen).

As the development and application of pharmaceutical cocrystals have expanded, regulatory bodies have taken an increasing interest in their definition and categorization. In 2011, the U.S. Food and Drug Administration (FDA) released a draft guidance categorizing pharmaceutical cocrystals as "drug product intermediates," describing them as “dissociable API-excipient molecular complexes where both API and excipients are present in the same crystal lattice.” However, this definition was criticized by both industry and academic researchers for its simplicity and lack of clarity. In 2016, the FDA revised the guidelines, describing cocrystals as “crystalline materials composed of two or more different molecules within the same crystal lattice, associated by nonionic and noncovalent bonds.” In 2018, the FDA provided a more detailed definition, stating that pharmaceutical cocrystals are “crystalline materials composed of two or more different molecules, one of which is the API, in a defined stoichiometric ratio, within the same crystal lattice, associated by nonionic and noncovalent bonds.” Additionally, a coformer is defined as “a component that interacts nonionically with the API in the crystal lattice, is not a solvent (including water), and is typically nonvolatile.” Meanwhile, the European Medicines Agency (EMA) defines cocrystals as "homogeneous (single-phase) crystalline structures made up of two or more components in a definite stoichiometric ratio, where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)." The EMA considers cocrystals to be a viable alternative to salts of the same API, suggesting that cocrystals, while distinct in pharmacokinetic properties, are equivalent to the API in terms of their basic molecular identity.

This review will summarize the recent advances in pharmaceutical cocrystals, focusing on their preparation methods, modulation of physicochemical properties, and diverse applications. The preparation methods will include solution-based techniques (such as solvent evaporation, antisolvent methods, cooling crystallization, reaction cocrystallization, and slurry conversion) as well as solid-state methods (including neat grinding, liquid-assisted grinding, and melting crystallization). The review will then discuss how cocrystals can modulate various properties and applications, such as physical and chemical stability, mechanical and optical properties, and both in vitro and in vivo performance.

### 2. **Cocrystal Preparation**

Numerous methods have been developed for the preparation of cocrystals, including solid-state grinding, solution reaction crystallization, solvent evaporation, slurry conversion, and hot melt extrusion. However, selecting an appropriate cocrystallization method remains largely empirical. Broadly speaking, cocrystal formation methods can be classified into two main categories: **solution-based methods** and **solid-state methods**.

Solution-based methods generally require significant solvent consumption to dissolve the cocrystal constituents. The choice of solvent is crucial, as it can alter the intermolecular interactions between the API and the coformer, directly influencing the cocrystallization process and outcome. In contrast, solid-state methods offer the advantage of minimizing or eliminating solvent use, which can be beneficial in terms of cost-effectiveness and environmental impact. These methods typically require no or very little solvent, making them a more sustainable option in some cases.



Figure 2. Common methods for cocrystal preparation.

### 2.1 **Solution-based Methods**

In solution-based methods, the system involves three phases: the active pharmaceutical ingredient (API), the coformer, and the solvent. The ideal state for cocrystal formation occurs when the cocrystal is supersaturated, while the reactants (API and coformer) are either saturated or undersaturated under the experimental conditions. Therefore, the degree of supersaturation with respect to the cocrystal is a crucial parameter for successful cocrystallization. This can be controlled by adjusting the concentrations of the API and coformer.

To guide the cocrystal formation process, a phase diagram must be established to define the conditions for thermodynamic stability. This diagram ensures that the cocrystal remains in the thermodynamically stable region, thereby preventing the crystallization of pure reactants. The position of the stable cocrystal phase is primarily determined by the solubility of the reactants.

### 2.1.1 **Solvent Evaporation Method**

The solvent evaporation method is one of the most widely used techniques for preparing cocrystals and is particularly effective for synthesizing high-quality single-crystal cocrystals suitable for structural analysis through single-crystal X-ray diffraction. In this method, the cocrystal constituents are first completely dissolved in an appropriate solvent at the desired stoichiometric ratio. The solvent is then evaporated slowly, allowing the cocrystals to form.

The choice of solvent plays a crucial role in the cocrystallization process, as it can significantly affect the solubility of the reactants. For successful cocrystallization, the cocrystal components must be congruently soluble in the chosen solvent. If the components have incongruent solubility, the less soluble component may precipitate preferentially, resulting in a mixture of cocrystal and cocrystal components, or in failure to form the cocrystal altogether.

This method has been successfully applied to synthesize numerous cocrystals. For example, a block-shaped single crystal of a 1:1 febuxostat‒piroxicam cocrystal, formed through hydrogen bonding between carboxylic acid and azole functional groups, was synthesized by the slow evaporation of acetonitrile at room temperature over 3–5 days. The resulting cocrystal exhibited improved solubility and better tabletability compared to the individual components. Similarly, cocrystals of nebivolol hydrochloride‒nicotinamide, which demonstrated an enhanced dissolution rate, were also prepared using the solvent evaporation method.

### 3. **Physicochemical Properties and Applications of Cocrystals**

#### 3.1 **Physical Stability**

A physical change refers to a transformation in the state of a substance without altering its chemical composition. The physical properties of solid-state materials, including melting point, hygroscopicity, solubility, hardness, plasticity, and elasticity, are critical to the stability and performance of drug substances. Cocrystallization is an effective approach for improving the physical properties and maintaining the physical stability of drug substances, which may otherwise undergo undesired physical transformations during manufacturing and storage. In this section, we will focus on two key aspects—melting point and hygroscopicity—and discuss others in subsequent sections.

##### 3.1.1 **Melting Points**

For manufacturers, solid drug forms provide convenience in purifying, identifying, transporting, and storing drugs. For patients, solid forms are generally more convenient to carry and administer than liquid forms. However, some drugs with low melting points may remain in a liquid state at room temperature, posing challenges for formulation. Cocrystallization can alter the melting point of these liquid drugs by incorporating a suitable coformer into the crystalline lattice.

One such example is **propofol**, which is used to induce and maintain general anesthesia and sedation. Propofol has a low melting point (18°C), which results in instability, pain upon injection, and hyperlipidemia when administered. McKellar et al. demonstrated that a cocrystal of **propofol** with **isonicotinamide** could be formed, raising the melting point by approximately 50°C (Fig. 10). This increase in melting point allowed the propofol-isonicotinamide cocrystal to be stable at room temperature. Similarly, other cocrystals such as **propofol–bipyridine** and **propofol–phenazine** were shown to convert liquid propofol into a stable crystalline form.

##### 3.1.2 **Hygroscopicity**

The hygroscopicity of a drug is a critical property that can significantly affect its physicochemical stability, influencing solubility, dissolution rate, stability, bioavailability, and mechanical properties. For instance, **dasatinib anhydrate** demonstrated higher solubility than its monohydrate form. Thus, maintaining the hygroscopic stability of the anhydrate form is essential in drug development. Several strategies, including the use of excipients, packaging to reduce moisture uptake, and coating with enteric polymers, have been employed to address this challenge. Notably, cocrystal formation has been shown to enhance the hygroscopic stability of certain drugs.

In cocrystals, hydrogen bonds formed between the API and coformer can block the water molecules from interacting with the API, thus improving the compound's resistance to moisture. For example, **flavonoid-theophylline cocrystals** exhibited greater resistance to hydration compared to theophylline alone. **Caffeine**, a natural alkaloid found in coffee and tea, typically forms a nonstoichiometric hydrate under humid conditions. However, when cocrystals of caffeine with various acids (such as **oxalic acid**, **malonic acid**, **maleic acid**, and **glutaric acid**) were prepared, the **caffeine–oxalic acid cocrystal** showed significantly better hygroscopicity stability, remaining stable under humidity stress for several weeks.

Another case is **zileuton (ZIL)**, an asthma medication prone to forming a stable hydrate under moisture conditions. When ZIL was cocrystallized with **nicotinamide** and **isonicotinamide**, the resulting cocrystals exhibited better hygroscopic stability when stored at 40°C and 75% relative humidity (RH) for 4 weeks compared to the drug alone.

**Lithium chloride (LIC)**, used for treating neuropsychiatric disorders, is extremely hygroscopic and deliquescent even at very low humidity levels (11.30% RH), which limits its use in formulations. However, cocrystallization of LIC with **glucose** improved its hygroscopic stability under 40% RH, while also maintaining similar in vivo pharmacokinetics to the pure form. Similarly, the cocrystal of **metoclopramide (MCP)** with **oxalic acid** showed improved resistance to hydration, preventing the ion-exchange reactions and Maillard reactions that occur in the monohydrate form.

Finally, **oxiracetam (OX)**, a nootropic drug, is more hygroscopic in its **S-OX** form than in its racemic form **R,S-OX**. The **S-OX–gallic acid cocrystal** demonstrated significantly reduced hygroscopicity compared to the pure S-OX or the racemic parent drug, attributed to the formation of a robust hydrogen-bonded network through cocrystallization.

#### 3.2 **Chemical Stability**

Chemical degradation of drug substances is a significant challenge during the manufacturing and storage stages, often leading to the formation of undesirable degradants. Developing effective strategies to minimize or eliminate drug degradation is critical for ensuring the stability and efficacy of pharmaceutical formulations. Recently, pharmaceutical cocrystals have been explored as a promising solution to enhance the chemical stability of APIs in the solid state.

By modifying the crystal packing of an API, cocrystallization can help protect the API from degradation caused by factors such as light exposure, moisture, and temperature. This section will focus on the mechanisms by which cocrystallization improves chemical stability by altering the physical interactions and crystal structure of the drug..

### 3.3 **Mechanical Properties**

The mechanical properties of crystalline materials are crucial in the manufacturing processes of solid dosage forms, including blending, milling, granulation, tableting, and coating. For solid materials, the mechanisms of mechanical deformation include elastic, plastic, viscoelastic, and fragmentation behaviors. Materials with better plasticity tend to exhibit superior compressibility, meaning they can undergo permanent and irreversible deformation once the stress is removed. However, many organic compounds have poor mechanical properties, which can present challenges in developing tablet formulations. Cocrystallization has been shown to effectively improve the mechanical properties of drugs by altering their crystal packing.

Good tableting behavior is typically characterized by increased plastic deformation and minimal elastic recovery. Crystal structures with well-defined slip planes facilitate plastic deformation, which can improve bulk compaction behavior. Several studies have demonstrated how cocrystallization can modify the mechanical properties of drug substances, enhancing their tableting performance.

For instance, **Singaraju et al.** evaluated the compaction performance and mechanical properties of caffeine cocrystal polymorphs. Their findings indicated that **caffeine–3-nitrobenzoic acid cocrystal form I** exhibited superior plastic deformation compared to **form II** due to its 2D-layered crystal structure. Powder Brillouin light scattering spectra of form I revealed the presence of low-velocity shear modes, while energy framework calculations suggested a favorable slip system for form I. These properties contributed to its enhanced compressibility and improved tableting behavior.

**Mishra et al.** further investigated the mechanical properties of **caffeine–glutaric acid cocrystals** on different crystalline faces using nanoindentation (Fig. 15). They observed anisotropic mechanical responses, meaning the mechanical behavior varied depending on the direction of indentation. The polymorphs with a greater number of slip planes and stronger intermolecular interactions were harder, while those with fewer slip planes and weaker intermolecular forces were softer. Form I, with more facile slip planes and weaker intermolecular interactions, was identified as a potential candidate for superior tabletability compared to form II.

Another example involves the mechanical properties of **chlorzoxazone**, a first-line therapy for muscle spasms. Chlorzoxazone alone has poor compressibility, which requires wet granulation for tablet manufacture. **Roy et al.** reported that tablets made from **chlorzoxazone–picolinic acid cocrystals** exhibited significantly improved compressibility, with a tensile strength of approximately 1.6 MPa at 250 MPa compression, compared to less than 0.8 MPa for pure chlorzoxazone at 50 MPa compression. The enhanced bonding strength in the cocrystals is attributed to their denser packing compared to pure chlorzoxazone, while the slip planes in the cocrystal structure allow for better plastic deformation, further improving compressibility.

### 3.4 **Optical Properties**

The optical properties of drugs are increasingly relevant in biomedical applications. For instance, drugs exhibiting strong fluorescence can serve as biocompatible probes for bioimaging, including lipid droplet imaging in cells and tissue slices. The molecular stacking, crystal packing arrangement, and intermolecular interactions play critical roles in determining the optical properties of solid materials. Recently, cocrystal engineering has shown significant potential in modifying the optical properties of pharmaceuticals.

One example of this is the modification of the optical behavior of drugs through the introduction of coformers into the crystal lattice. **Furosemide (FS)**, a BCS IV drug used to treat edema and hypertension, is colorless in its pure form. However, when cocrystallized with **4,4′-bipyridine (4BPY)** (also colorless), the resulting polymorphic cocrystals display distinct colors. The **form I** cocrystal is pale yellow, while **form II** appears orange (Fig. 18A and B). Despite these color differences, both polymorphs share a similar sandwich centrosymmetric structure, which is formed by aromatic **π···π** stacking interactions in an "FS-4BPY-FS" arrangement (Fig. 18C).

In **form I**, the sandwich motif is stabilized by **C–H···π** interactions between the hydrogen atom of 4BPY and the π electrons of the furan, as well as **π···π** interactions between FS and 4BPY. In contrast, **form II** involves **π···π** interactions and **C=O···π** interactions that participate in the sandwich assembly. The authors suggested that the differences in **π-stacking patterns** and **hydrogen bonding interactions** between the polymorphs result in their distinct colors. Further calculations of the **HOMO (highest occupied molecular orbital)** and **LUMO (lowest unoccupied molecular orbital)** gaps via **Density Functional Theory (DFT)** simulations revealed that the band gap of form II was lower than that of form I, which accounts for the observed color differences between the two polymorphs.

### 4. **Concluding Remarks and Future Perspectives**

Over the past decade, cocrystal engineering has emerged as a promising strategy for enhancing the performance of drug substances by modifying their physicochemical properties. A large number of pharmaceutical cocrystals have been reported, with several already approved by the FDA or currently in clinical trials. However, there are still significant challenges to overcome in developing cocrystals into commercially viable drug products.

One of the most critical aspects of cocrystal design is selecting a suitable coformer. Currently, this process largely relies on trial and error, which is both time-consuming and labor-intensive. However, recent advances in computer-assisted approaches have shown promise as tools to streamline the screening process for potential cocrystals. For example, artificial neural network models have been developed to predict cocrystal formation by analyzing a network of coformers from the Cambridge Structural Database (CSD).

An enhanced understanding of the structure-property relationships is crucial for the rational design of cocrystals with targeted functions and performance characteristics. In addition, the compatibility of cocrystals with other excipients, their pharmacokinetic profiles, therapeutic efficacy, and potential toxicity must all be carefully considered when developing cocrystal formulations. Another significant challenge in commercializing cocrystals is scaling up the production of high-purity pharmaceutical cocrystals. To address this, continuous processing has emerged as a promising approach for the high-throughput manufacturing of pharmaceutical materials. Techniques like twin-screw extrusion, integrated with process analytical tools for real-time process control, have been explored to produce high-quality cocrystals.

In conclusion, this review provides a comprehensive overview of the preparation methods, physicochemical properties, and diverse applications of pharmaceutical cocrystals. As innovative technologies and more detailed regulatory guidance continue to evolve, they will play a key role in advancing the translational development of pharmaceutical cocrystals for healthcare applications. With these developments, it is anticipated that more cocrystal-based drug products will become commercially available, offering improved treatments for patients in the future.

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