

STRATEGIC FRAMEWORK: UTILISING PHARMACEUTICAL CO-CRYSTALS AS SOLUBILITY ENHANCERS

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Article Received: 04 September 2026 | Article Revised: 24 September 2026 | Article Accepted: 14 October 2026

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DOI: <https://doi.org/10.5281/zenodo.23417433>

How to cite this Article: Poonam Sonawane (2026) STRATEGIC FRAMEWORK: UTILISING PHARMACEUTICAL CO-CRYSTALS AS SOLUBILITY ENHANCERS. World Journal of Pharmaceutical Science and Research, 5(10), 718-735.



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ABSTRACT

Many active pharmaceutical ingredients (APIs) face low water solubility. In many cases, this leads to poor bioavailability, and high therapeutic effects when taken by mouth. Co-crystals of pharmaceuticals have come up as a potential solution for this problem. They are structures that are created when an API has a co-former that develops a non-covalent bonding. This process enhances some of the physicochemical properties, but does not change the drug's pharmacological activity. This work looks at the innovation and testing of pharmaceutical co-crystal structures that are used by researchers to achieve better readings. The work begins by reviewing the basic concepts of co-crystals in which are used in the selection of co-formers and common methods for the formation of co-crystals by solvent evaporation and grinding. The work explores the effects of co-crystals on solubility and dissolution of substances. Pharmaceuticals are flexible in that they can improve the efficacy of drug with low hydration properties.

KEYWORDS: co-crystals, co-former, hydrophilic drugs.

INTRODUCTION

The current process of making drugs has a big problem because most active ingredients in medicines have not enough water solubility. Some studies say that more than 40 percent of the drugs approved and almost 60 percent of new chemical compounds have solubility issue occur due to their increased complexity that raise their lipophilicity. The problem causes two inconveniences such as low oral bioavailability and vary therapeutic outcomes. Cocrystal engineering is a promising approach that helps find solutions to these issues without affecting the essential drug properties that regulate its pharmacological effect. Pharmaceutical cocrystals are solid, single (crystalline) phase materials, structures, and forms of two or more molecules, ions, or both, most often a pharmaceutical ingredient with a non-effect causing co-former, where the two compounds are arranged in a fixed molar ratio; which can unlike salts

which are formed by ionic binding or solvates where at least one component exist in a liquid form at room temperature are entirely solid at ambient conditions. They are stable due to non-covalent interactions consisting of the following elements:

- Most directional hydrogen bonding serves as the primary force of the system
- $\pi - \pi$ interactions and van der Waals bond

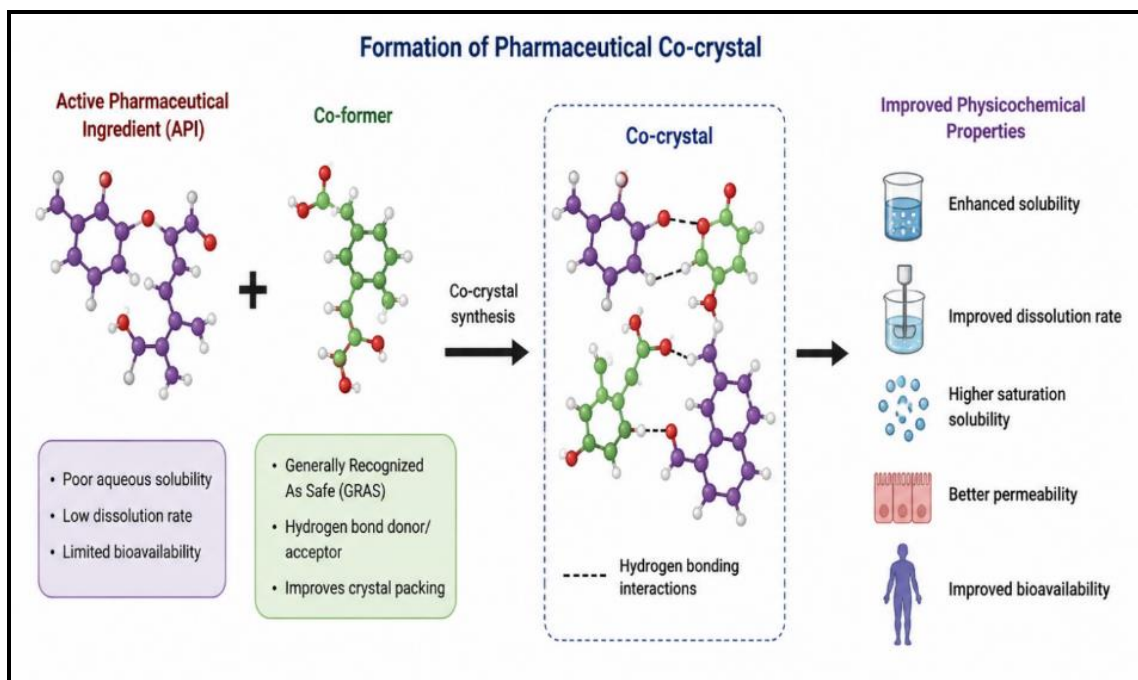


Fig. 1: Co-Crystal Overview.

Original researchers can make new forms of drugs from drugs people already take by use of their method that works for non-covalent interactions. The changes enhance how effortlessly the drug mixes with liquids, how briskly it melts, how it sticks together in a distinct way, and because of its strength but it doesn't alter in form or change its clinical effect.

Picking a good co-former is the most important part because it depends on the making of the lattice. Usually, co-formers are chosen from safe food chemicals so that they are not bad for the person taking the final product. Based on Yadav et al., the first step in making a Cocrystal is to find a functional group in the API followed by probes into Cambridge structural databases (CSD) in order to look for good matches.^[2,3]

Common strategies for co-former selection include:

ΔpK_a rule: The difference in acidity/basicity, expresses as $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$, serves as guideline:

- Values less than 0 or between 0-3 $\rightarrow$ more likely to yield co-crystals
- Values greater than 3 $\rightarrow$ generally favor salt formation

In the in-silico and computer-based methods, the use of the COSMO-RS (Conductor-like Screening Model for Real Solvents) tool aids in the calculation of excess enthalpy for drug-coformer systems which is used in virtual screening. As compared to actual experimental work, this prediction process needs less effort since the virtual screening process is simplified by using COSMO-RS for anticipatory studies.

SYNTHESIS AND CHARACTERIZATION

Several methods can be used to induce pharmaceutical cocrystals, from traditional methods such as solvent evaporation and grinding (dry or liquid assisted) to more advanced methods such as electrospray, hot melt extrusion and supercritical fluid technology. The distinctness of the cocrystal needs to be established through an exhaustive logical characterization after synthesis. The results of greasepaint X shaft Diffraction (PXRD) continue to rule the roost when it comes to attesting unique liquid arrangements, with diffraction peaks in the diffraction pattern appearing different from the parent composites. Reciprocal techniques are Differential Scanning Calorimetry (DSC) for thermal; Fourier transfigure Infrared Spectroscopy (FTIR) for probing hydrogen cling and Raman Spectroscopy for real time monitoring of structural features.

FUNDAMENTALS AND CONCEPT OF CO-CRYSTALS:

Pharmaceutical co-crystals are a novel and promising area of solid-state chemistry that could be used to improve the properties of active pharmaceutical ingredients, while preserving their original pharmacological properties. They're described as liquid excipients made up of 2 or further different neutral molecules, generally an Active Pharmaceutical Ingredient (API) and a co-former, which are bound in a specific proportion in the same crystal lattice.^[14]

Co crystallization relies on soft bonds, such as hydrogen bonding, van der Waals interactions and π stacking, instead of relying upon chemical changes. The reason for the importance of this is that it is not flexible and can be used with almost every medicine, such as a patch that is acidic, introductory, or even non ionizable. At a basic level, it's a clever approach to altering a medication's bodily action while keeping its action unchanged.

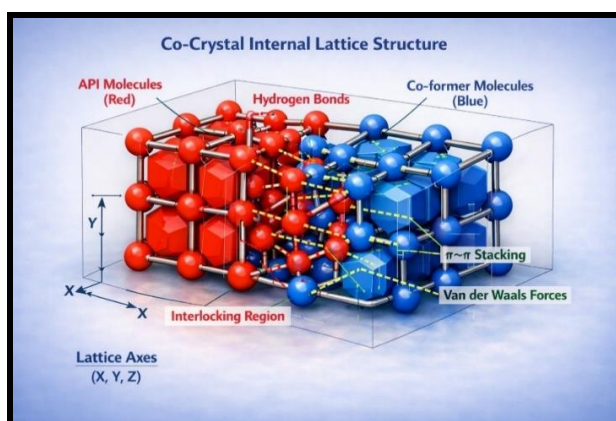


Fig. 2: co-crystal lattice structure.

DISTINGUISHING CO-CRYSTALS FROM OTHER SOLID FORMS

The co-crystal is an important form of multi-component solid form that needs to be distinguished from other forms of multi-component solids due to its difference in regulatory and physical properties.

1. Co-Crystals vs. Salts

The important difference is that of the proton. In a salt, the proton is going from the acid to the base, establishing a strong ionic bond. In a co crystal, still, no proton transfer takes place the molecules stay neutral and rather hold together through gentler forces, substantially hydrogen bonds. In a salt, the proton is transferred from the acid to the base, thus forming a strong ionic bond. In a co crystal, the molecules are still but now there is no proton transfer and they only interact through weaker forces, primarily hydrogen bond.^[14,15]

2. Co-Crystals vs. Solvates and Hydrates

They're liquid forms (solvates / Hydrates) that contain molecules of solvent, often water, in their lattice structure. They are not predictable and can later escape, and this results in a loss of stability of the solid form with time. In the case of the cocrystals, the co-former is usually a non-volatile solid under ambient conditions, typically a food additive or another drug molecule. This option increases structural stability and makes the cocrystals more stable than most solvates which can contain volatile components that tend to be lost over time.^[14,15]

3. Co-Crystals vs. Polymorphs

Polymorphism is the ability of a chemical compound to crystallize in more than one structure. A co crystal, on the other hand, is a multi-component product, composed of an API and a co former. The drug-co crystals might also be polymorphic, that is, different combinations of the same drug-co pair can be found in the crystal lattice in different arrangements.^[14,15]



Fig. 3: Various crystal forms.

THE ROLE OF HYDROGEN BONDING

In the context of pharmaceutical co crystals, hydrogen bonding is of central importance and is the most important stabilizing interaction. Experiments can be carried out with precise selection of co-formers that contain similar functional groups as amides, alcohols or carboxylic acids and lock the active pharmaceutical ingredient (API) into a new lattice structure. The reorganization of the crystal-clear structure can result in major improvements in important physicochemical properties such as solubility, dissolution rate and overall physical stability of the drug without affecting its therapeutic activity.^[15]

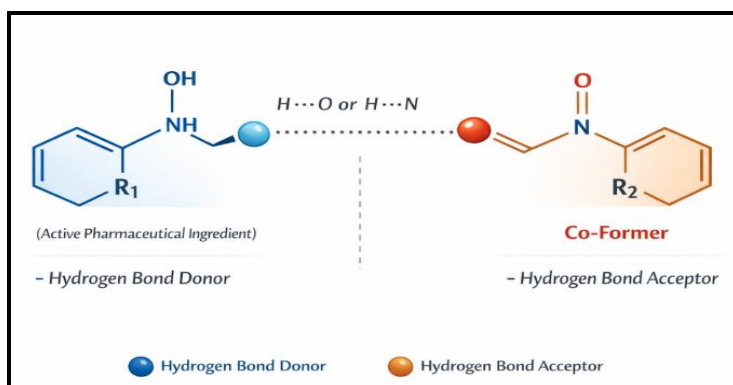


Fig. 4: Hydrogen bond interaction between api and co-former.

SOLUBILITY AND ITS SIGNIFICANCE

Solubility is the concentration of the most amount of the solute that can be dissolved into the solvent, at a certain temperature and pressure, into a stable, homogeneous molecular compound. Pharmaceutical science drug solubility is relevant to the concentration of the drug in the systemic circulation needed to evoke the pharmacological response as it directly determines the same.^[23]

There are four classes of drugs that are classified in the Biopharmaceutics Classification System (BCS) depending on their solubility and intestinal permeability.

Class I: High solubility and high permeability.

Class II: Low solubility and high permeability.

Class III: High solubility and low permeability.

Class IV: Low solubility and low permeability.

The dissolution step is the rate limiting step in the process of oral absorption for Class II & IV drugs. It is therefore critical to increase the solubility in order to increase bioavailability of these compounds, which are hydrophobic.^[23]

KEY MECHANISMS OF SOLUBILITY ENHANCEMENT

Making a drug more soluble is all about **lowering the hurdle** it has to jump to dissolve. You do this by either changing the "shape" of the drug or fixing the liquid around it so the medicine can break apart and mix in more easily.^[23]

1. Particle Size Reduction (Micronization and Nanonization)

Reducing the particle size of a drug increases its surface area which results in greater solvent contact because the drug now has more surface area. The increased surface area which results from this process leads to faster dissolution rates which improve the drug's ability to enter the body.^[25]

Micronization: Reducing the particles to the 1-1000 μ m range. This improves the **dissolution rate** but does not typically change the equilibrium solubility.

Nanonization: The process requires us to decrease the particles until they reach submicron dimensions which measure less than 1 micrometre. The Noyes-Whitney equation demonstrates that this process not only speeds up the dissolution process but also enhances saturation solubility because equilibrium solubility now depends on surface area.^[24]

Techniques: Researchers usually use techniques like **high-pressure squeezing** (homogenization), **heavy-duty grinding** (ball milling), or **specialized gas-liquid tech** (SCF) to break the drug down.^[24]

2. Solid Dispersions

A solid dispersion involves distribution of a poorly water-soluble drug within a hydrophilic, physiologically inert carrier matrix.

Molecular level dispersion prevents particle aggregation which results in maximum surface area contact between the particles and the solvent. The increased surface area leads to faster dissolution rates which results in better bioavailability.^[24]

Amorphous State Transformation The systems continuously convert their crystalline medicinal substances into an amorphous state that does not display a defined crystalline structure. The absence of ordered packing confers advanced thermodynamic energy, performing in enhanced solubility compared to their crystalline counterpart.^[25] Carriers Generally employed polymers in pharmaceutical phrasings include polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP), both of which are considerably used as carriers and stabilizers due to their favorable physicochemical properties.^[24]

3. Pharmaceutical Co-Crystals

Co-crystallization is an arising strategy that modifies the solid- state properties of a drug without changing its chemical identity.

It involves arrangement of a liquid structure between an API and a co-former (a neutral solid molecule) and are held together by non-covalent interactions like hydrogen bonding and π - π stacking.

Advantage Unlike salt formation, which requires ionizable groups, co-crystals can be designed for any molecule to fine- tune solubility, dissolution rate, and stability.

4. Micellar Solubilization and Surfactants

Surfactants are special" amphiphilic" molecules — denoting they've one end that loves water and another that hates it. When you put enough of them into a liquid, they reach a inclining point called the critical micelle concentration. At this stage, they spontaneously bunch together into bitsy clusters called micelles. The net (Micelles) Surfactants are molecules with water- loving heads and water- hating tails. At a specific concentration, they crowd into clusters called micelles. They tuck hydrophobic drugs into their unctuous centres, allowing the drug to stay dissolved in watery climates like the bloodstream.^[26] Better Mixing (Wettability) Surfactants portray like a bridge by lowering the surface tension between the drug and the liquid. This stops the medicine from aggregating or floating on top, assuring the particles get thoroughly wet and dissolve efficiently.^[24]

Table 1: Comparison of Solubility Enhancement Techniques.

Technique	Primary Mechanism	Key Advantage
Nanonization	Increased surface area	Increases saturation solubility
Solid Dispersion	Amorphous state & hydrophilic carrier	High molecular-level mixing
Co-Crystals	Supramolecular engineering	Stable, non-covalent modification
Micelles	Hydrophobic core entrapment	Prevents drug degradation

SELECTION OF CO-FORMER

Selection of co-formers is a critical decision in pharmaceutical cocrystal development that can impact the physicochemical properties and nonsupervisory acceptance of the product. Co-formers are chosen from molecules that have proven to be Generally Recognized as Safe (GRAS) and thereupon good for mortal consumption without posing toxicological concerns.^[13]

In addition to their safety, the hydrogen- bond donor/ acceptor complementarity of functional groups like carboxyl, amide, hydroxyl, amino etc is of the utmost significance since they give predictable supramolecular synthons, e.g. Acid- amide, acid- pyridine, which help to stabilize the lattice and refine reproducibility.^[1,2]

It's equivalently important to consider solubility compatibility as if solubility of API is n't compatible with co-former, it can affect in phase separation or suboptimum crystallization success, which can negatively impact product stability and scale up.^[1] Safety and toxicity should also be taken into account and the idea should be to select molecules with a pharmacologically inert or salutary effect that do not affect remedial exertion if possible.^[13] Practical factors like availableness, cost and familiarity with the nonsupervisory framework also impact co-formers choice; this is because these excipients or nutraceuticals perhaps be extensively used, which could ease the approval process and alleviate development challenges.^[3]

Incipiently, the use of advanced computational tools and crystal-clear engineering strategies is gaining further and further traction to forecast the co-former suitability and screen large libraries of implicit co-formers for favourable interaction energies and lattice stability previous to experimental trials. These criteria, when combined give a rational, clinically safe and artificial feasible approach for choosing a co-former and designing a successful co-crystal formulation that maximizes solubility, stability and bioavailability.

Table 2: Widely Used Co-Formers.

Co-former	Functional Role	Representative Notes
Nicotinamide	Hydrogen-bond donor/acceptor	Widely used; forms stable acid–amide synthons; enhances solubility (Yadav et al., 2019).
Saccharin	Acidic hydrogen donor	Safe sweetener; improves dissolution and taste masking (Sekhon, 2009).
Urea	Strong hydrogen-bond donor	Simple, inexpensive; stabilizes lattice via multiple H-bond sites (Deepthi et al., 2025).
Citric acid	Polycarboxylic donor	Provides multiple binding sites; enhances solubility and stability (Sakhiya & Borkhataria, 2024).
Succinic acid	Dicarboxylic donor	Common excipient; predictable acid–amide interactions; GRAS status (Sekhon, 2009).

METHODS OF PREPARATION

1. SOLID-STATE TECHNIQUES

This method involves in general solid phase grinding, melt extrusion and melt crystallization. It includes melting and mixing the API and co-former to form a co-crystal of a definite stoichiometric ratio. This is a good way for compounds that do not tolerate high temperatures (thermolabile), but it is a simple, scalable and continuous manufacturing process.

Dry grinding is the simplest method, where the drug and co - former are ground together in a mortar or ball mill. The principle is based on particle size reduction and intimate surface contact, which promotes hydrogen bonding and lattice rearrangement. Even though this method is eco-friendly and uses no harsh chemicals, it doesn't always work perfectly and can be hard to get the same results twice. A similar approach is neat grinding, which relies purely on "muscle"—using mechanical force to smash structures together until they form a new crystalline bond.

This method is rapid-fire and picky, but still suffers from variability in yield.^[1,2]

To overcome these downsides, liquid - assisted grinding introduces a catalytic amount of solvent, generally ethanol, methanol, or water, to enhance molecular mobility. This accelerates kinetics, improves reproducibility, and frequently yields advanced purity cocrystals nonetheless, solvent choice is critical, as inappropriate solvents may lead to unwanted phases or hydrates.^[1,2]

Eventually, hot - melt extrusion has emerged as an industrially scalable solid - state technique. In this process, the API and co - former are mixed in an extruder barrel, where controlled heat and mechanical shear forces induce co - crystallization. It's nonstop, solvent - free, and able of producing invariant cocrystals suitable for large - scale manufacturing. Its limitation lies in the thermal sensitivity of certain APIs, which may degrade under extrusion conditions.^[1]

Altogether, these solid - state methods provide a versatile toolkit for cocrystal preparation. Dry and neat grinding emphasize simplicity and sustainability, liquid - assisted grinding improves effectiveness and reproducibility, while hot - melt extrusion bridges laboratory feasibility with artificial scalability. Their selection depends on the physicochemical nature of the drug – co - former pair and the intended application, making them necessary in ultramodern cocrystal research and development.

2. SOLUTION BASED TECHNIQUES

Solution based approaches have been popular in pharmaceutical cocrystal engineering due to the principle of solubility modulation and supersaturation to encourage nucleation and growth of stable crystalline forms.

The most classical method is that of solvent evaporation, in which the API and co-former are dissolved in a common solvent and allowed to crystallize by evaporation of the solvent. The principle is to make the material supersaturated, so that cocrystals can nucleate. The method is easy and repeatable, but time consuming and it can leave a solvent residue in the product.^[3,2]

Cooling crystallization is based on solubility's dependency on temperature. A saturated solution of API and co-former is slowly cooled to decrease the solubility and produce crystals. This method can be used for controlled crystal growth and better morphology but needs careful control of cooling and is not suitable for APIs with a narrow solubility range.^[1]

The anti-solvent method is an approach that utilizes the addition of a solvent that is miscible with the solution containing the API and co-former but which causes its rapid precipitation by decreasing its solubility. It is useful because it is fast and efficient but at the same time can be subject to the formation of amorphous phases or mixed solids if not optimized carefully.^[3]

Finally, slurry conversion, a mild procedure, has been introduced in which the API and co-former are mixed in a solvent slurry. With time, the molecular reconfiguration results in the formation of cocrystals. This technique is especially advantageous for screening co-formers under mild conditions and, but has slow kinetics and is not easily scaled up.^[3,1]

These solution-based approaches allow for flexible pathways to cocrystal preparation, with a balance of simplicity, control and efficiency. Their choice relies on the physicochemical characteristics of the API–co-former combination, the desired crystal properties and practical factors like solvent selection and scale up.

3. ADVANCED TECHNIQUES

For pharmaceutical cocrystal engineering, there has been a development of new techniques to overcome the drawbacks of the conventional solid-state and solution-based methods. These strategies focus on efficiency, purity, and sustainability, and have been a growing topic of interest.

Supercritical fluid technology employs supercritical CO₂ as either a solvent or anti-solvent. Essentially, the principle is based on the fact that supercritical fluids have both gas-like diffusivity and liquid-like solvating power. This allows crystallisation without any residues and with small particles. Clean and environmentally-friendly method but high-pressure equipment is needed, and high operating expenses.^[2,3]

An advanced method is spray drying, in which a solution of API and co-former are broken up into small droplets which are rapidly dried using the evaporation of the solvent. The resultant particles can be of uniform size and appropriate for inhalation or oral administration. They offer advantages resembling as scalability and control of particle size, but can also pose difficulties in terms of the implicit presence of amorphous material and the need for considerate optimization of drying conditions.^[1,3] Finally, molecular interactions are promoted by microwave assisted synthesis, which utilizes the dielectric heating. Polar molecules are heated by microwaves due to their rapid oscillations, resulting in local heating and consequently in very short reaction times. This approach is green chemistry compliant, quick, energy efficient and uses minimal solvent. There are, however, challenges such as the limited penetration depth, degradation of thermolabile APIs, and scalability problems concerning the industrial uptake.^[2]

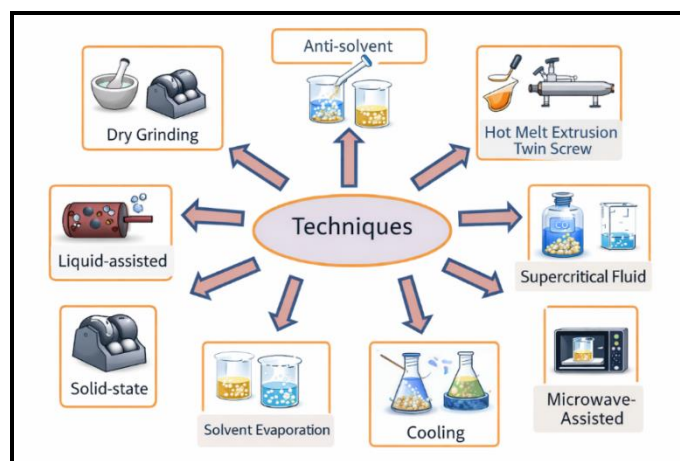


Fig. 5: Methodology used.

The combined use of these advanced methods provides a broader range of possibilities for the preparation of cocrystals and presents cleaner, faster and more controlled processes. The choice of their selection depends on the efficiency, scalability, and physicochemical compatibility of the API-co-former system and thus they are especially relevant in today's pharmaceutical development.

CHARACTERIZATION OF CO-CRYSTALS

- **Melting Point Analysis:** This test identifies the accurate temperature where a solid turns into a liquid. It's a great way to measure how tightly the molecules are "locked" together. However, it's a clear sign that you've created a brand-new crystal-clear structure rather than just a simple blend of the original ingredients, if this temperature changes. Plus, it confirms if the substance is pure and how well it stands up to heat.^[12,16]
- **FTIR Spectroscopy:** This technique uses infrared light to measure how molecules agitate. It acts like a "molecular scanner" that can spot exactly how different zone of a drug are linked. By detecting shifts in vibration frequencies, it confirms that the drug (API) and its partner molecule are actually shaking hands through hydrogen bonds, documenting they've successfully bonded into a new structure.^[12,19]

- **Differential Scanning Calorimetry (DSC):** Think of this as a "thermal profile" for your drug. It tracks how a material absorbs or releases heat as it's warmed up. By measuring these energy shifts, scientists can pinpoint the melting point and the energy needed to melt it. It's the go-to methodology for proving you've made a cocrystal; if the "heat signature" (endotherm) looks different from an introductory mix of ingredients, you know you've successfully created a new, unified structure.^[12,16]
- **Thermogravimetric analysis (TGA):** Weighs change as a function of temperature and under controlled atmosphere. Calculates lattice stability, decomposition and the possibility of the presence of a solvent molecule or water molecule in the lattice.^[16,15]
- **Powder X-ray diffraction (PXRD):** Confirmation of the formation of new crystalline phases, fingerprint pattern different from the individual components, identification of polymorphs etc.^[12,19]
- **Single crystal X-ray diffraction (SCRD):** Use single crystal to analyse diffraction of X-rays, and determine atomic arrangement. Provides definitive evidence for the formation of co-crystals (shows precise molecular geometry, hydrogen bonding and crystal packing).^[15,16]
- **Scanning electron microscopy (SEM):** Focused electron beam producing high-resolution images of surfaces. Gives morphological information, particle size and surface texture information, characterizes co-crystals from physical mixtures.^[19,15]
- **Nuclear Magnetic resonance (NMR):** Detects, magnetic properties of atomic nuclei in a magnetic field. Describes the molecular environment, intermolecular interactions and the stoichiometric composition and provides support for structure confirmation.^[15,16]

EVALUATION PARAMETERS

- **Solubility studies:** Solubility testing is one of the crucial evaluation parameters since it's the property that cocrystals end to ameliorate over the pure API. Studies generally include equilibrating fat cocrystal in water or buffer solutions, and also determining the concentration spectrophotometrically. Successful cocrystal formation is verified by enhanced solubility profiles, which can, in some cases, be pH-dependent.^[12,19]
- **Dissolution studies:** Dissolution experiments measure the rate drug is released and the amount of drug released in simulated gastrointestinal fluids. The dissolution rate is generally found to be advanced in cocrystals (which from a bioavailability point of view is also better) and is directly associated with the dissolution rate. This is an important parameter for inadequately answerable APIs for which dissolution is the rate limiting step.^[12,19]
- **Stability studies:** Stability testing under stress conditions like temperature, humidity and light exposure guarantees the long-term stability of the cocrystals. These studies have proven chemical stability, thermal stability and stability to UV degradation as well as threat of polymorphic transition or degradation.^[16,17]
- **Mechanical properties:** Tabletability, Compaction, Hardness & Friability Testing. Cocrystals can be more compressible and mechanically strong than APIs alone, which can be salutary for solid dosage form development.^[16]
- **Bioavailability studies:** The in vivo pharmacokinetic studies (bioavailability studies) have verified that cocrystals exhibit advanced peak plasma concentration (C_{max}), lesser area under the curve (AUC) and lesser bioavailability than pure drugs. It has been shown that bioavailability can be enriched in numerous cocrystal systems, similar as apixaban with baicalin.^[15]

- **Thermal analysis:** Useful approaches include DSC and TGA to understand the melting point depression and enthalpy changes, as well as decomposition patterns. The analyses differentiate between cocrystals and physical mixtures and confirm new crystalline identities.^[12,19]
- **Spectroscopic analysis FTIR:** Detection of hydrogen bonding, molecular interactions, stoichiometric composition; NMR – detection of molecular interactions. The shift of characteristic peaks, confirms the supramolecular interaction between API and co - former.^[12,19,15]
- **Structural analysis:** PXRD and SCXRD are conclusive methods for identification of new crystalline phases. PXRD gives fingerprint diffraction patterns and SCXRD gives accurate infinitesimal arrangements and hydrogen bonding networks.^[12,15]
- **Morphological studies:** SEM imaging reveals the difference in particle size, shape and surface characteristics between cocrystals and the parent components. The amended dissolution and solubility are frequently associated with morphological changes.^[19]
- **Permeability studies:** Permeability testing (e.g., Franz diffusion cells or log P measures) assesses the permeating capacity of cocrystals across natural membranes. Improved immersion and distribution as a result of an enhanced permeability.^[12]

ADVANTAGES OF PHARMACEUTICAL CO-CRYSTALS

- **Enhances solubility:** Cocrystals are well known for their ability to improve the aqueous solubility of poorly water-soluble APIs. They break down the strong lattice energies and add hydrophilic Coformers, which reduces the dissolution barrier. They include drugs such as carvedilol and ketoconazole cocrystals, in which the solubility is increased by several fold as compared to the drugs alone.^{(9,5).}
- **Increases bioavailability:** Better solubility and dissolution lead to better absorption and higher plasma levels. The oral bioavailability of Ketoconazole cocrystals was found to be up to six times higher, and anticancer drug cocrystals such as Paclitaxel had achieved substantial pharmacokinetic advantages.^(11,8)
- **Useful for non-ionizable drugs:** Salts, which need to be ionizable, can be replaced by cocrystals which do not. This makes them applicable to a wider variety of molecules such as neutral or zwitterionic drugs.^{(5,6).}
- **Improved physical and chemical stability:** Cocrystals can display better stability. They do not hydrate, photodegrade or chemically degrade during storage. Nicorandil and Ketoconazole Cocrystals have higher stability to humidity and light stress. Nicorandil and Ketoconazole Cocrystals are more stable in the presence of humidity and light.^{(6).}
- **Better manufacturability:** Cocrystals have improved mechanical properties like compressibility, flowability and tabletability. The micromeritic properties (angle of repose, Carr's index, Hausner ratio) of carvedilol cocrystals were superior than those of pure drug, which is useful in the large-scale production of the drug.^{(9).}
- **Modified release:** Cocrystals can be modified to have controlled and sustained release profiles by careful selection of co-formers. This results in consistent plasma concentrations, fewer doses and better adherence in the patient.^{(6).}
- **Organoleptic properties:** Cocrystals can be used to modify organoleptic properties, such as bitterness, for improving palatability. This is very helpful for special populations such as paediatric and geriatric preparations^{(10).}
- **Enhanced permeability:** Some cocrystals enhance the permeability of membranes, allowing for improved penetration of biological barriers by drugs. This is particularly helpful for BCS class III drugs for which the permeability is the rate limiting step.^{(16,8).}

- **Polymorphism control:** Cocrystals can prevent undesirable polymorphic transitions of APIs, which guarantees the reproducibility and regulatory compliance. This is critical for life cycle management and IP protection. ^(5,10)
- **Synergistic therapy and pill burden reduction via dual-drug delivery:** Drug–drug cocrystals are the combination of two APIs in one single lattice creating synergistic therapy and reducing pill burden. This approach has been investigated in oncology and cardiovascular diseases. ^(11,8)
- **Potential for green chemistry:** Many methods for preparation of cocrystals, including mechanochemical grinding and supercritical CO₂ methods, require limited solvents, and are consistent with the principles of green chemistry in manufacturing. ^[10,8]

LIMITATIONS AND CHALLENGES

- **Difficulties of scale up:** Lab techniques (solvent evaporation or grinding) are good for small quantities; scale up to industrial production is difficult. Many factors such as choice of solvents, crystal form reproducibility, equipment design (hot-melt extrusion vs supercritical fluid methods) make large-scale production difficult. ^[10,6]
- **Stability issues:** While cocrystals can enhance stability, they could also face the possibility of phase transitions, hydrate formation, or chemical degradation under stress. Long-term storage stability is uncertain for APIs which are thermolabile and hygroscopic. ^[11,5]
- **Toxicity of co-formers:** The coformer selected must be one that is not toxic to the animal. Not every substance used to make the drug is safe to take, and some could cause problems with the drugs' regulation. Even the GRAS listed co-formers need to be carefully assessed with regard to safety for their use over a prolonged period of time. ^[6,8]
- **Regulatory challenges:** FDA and EMA guidelines acknowledge cocrystals, but it is not always straightforward to classify them. Cocrystal identification is a critical aspect of approval; the different definitions of cocrystal found in different jurisdictions can cause delays in development. ^[5,10]
- **Patent issues:** Intellectual Property Protection is an opportunity and a challenge. Extension of product life cycles is possible but novelty and non-obviousness is hard to establish, particularly if the co-formers are well used excipients. When battling a patent dispute, it is frequently unclear whether a cocrystal is different from the previously known solid forms. ^[10,11]
- **Reproducibility:** It is hard to obtain repeatability in the batches. The solvent components, grinding process and humidity both have minor effects on polymorphic form or incomplete co-crystallization and hence on performance. ^[5,6]
- **Polymorphism and phase behaviour:** Polymorphism may occur in cocrystals, making them harder to characterise and approve. Determination and regulation of polymorphic transitions is crucial for reproducible and therapeutic consistency. ^[5,6]
- **Environmental and solvent problems:** The preparation methods need lots of organic solvents, which creates environmental and solvent problems. There are green processes such as mechanochemical grinding or using supercritical CO₂ but not always applicable for all APIs. ^[5,23]
- **Thermolabile drug incompatibility:** High temperatures used in these techniques such as hot-melt extrusion or spray drying can lead to degradation of sensitive APIs. In this way some preparation methods are restricted. ^[5,6]

- **Screening of co-formers:** To identify the suitable co-formers is time consuming and empirical. While computational methods such as COSMO-RS or Hansen solubility parameters can help to determine whether a cocrystal will form, the prediction is not certain.^[8,5]
- **Industry and clinician acceptance:** Overcoming technical challenges is not the only challenge as industry and clinicians need to be convinced of the advantages of cocrystals. There are only some commercial products available, and there is some scepticism on scalability and reproducibility.^[5,11]

REGULATORY PERSPECTIVE ON PHARMACEUTICAL CO-CRYSTALS

Regulatory views on pharmaceutical cocrystals vary extensively. The FDA first issued draft guidance in 2011, classifying cocrystals as “inseparable API – excipient molecular complexes” and treating them as drug product intermediates (DPs) rather than new active substances. This meant they were handled like polymorphs of the same API if dissociation into API and excipient was shown, no full clinical study was needed. thereafter variations (2016, 2018) defined cocrystals as liquid forms of two or further molecules in the same lattice, held by non - ionic, non - covalent interactions. FDA guidance emphasizes GMP compliance at the drug product facility level. Intellectual property filings are limited, as DPs containing cocrystals cannot be patented, though novelty and non - obviousness remain valid grounds.^[17,21]

EMA defines cocrystals as structures of two or further factors in definite stoichiometric proportions, not based on ionic bonds. Unlike the FDA, EMA views them as closer to salts than polymorphs, and they may qualify as new active substances if efficacy or safety differs from the parent API. This opens stronger patent protection and lifecycle management opportunities. Applicants can submit Active Substance Master Files, with GMP compliance anticipated at the API manufacturing level. EMA’s recognition enables use of cocrystals for exclusivity extension, API stabilization, and new dosage forms.^[11,15]

The way FDA and EMA treat cocrystals creates both hurdles and openings. The FDA’s cautious stance keeps them as intermediates, limiting submissions, while the EMA’s more flexible view allows cocrystals to be registered as new active substances when safety or efficacy differs from the parent API. This split directly shapes IP strategies: in the U.S. they can be argued as polymorphs, but in Europe as salts, enabling stronger claims. Researchers also point to the salt–cocrystal continuum, where ΔpK_a predictions alone don’t suffice and the crystal environment decides classification.^[11,15] Distinguishing between salts, solvates, hydrates, and cocrystals requires advanced tools like PXRD, DSC, Raman, and ssNMR.^[21] Supersaturation adds another wrinkle: many cocrystals show high kinetic solubility but recrystallize unless stabilizers are used.^[22] Despite these complexities, regulatory acceptance is growing, with therapies like Steglatro® and Entresto® gaining FDA/EMA approval based on proven safety and efficacy.^[15]

Table 3: Patents related to pharmaceutical co-crystals.

Drug	Co-former	Purpose	Company	Status
Ertugliflozin (Steglatro®)	L-pyroglutamic acid	Solubility & bioavailability enhancement	Merck/Pfizer	FDA & EMA approved, marketed (2017)
Sacubitril/Valsartan (Entresto®)	Drug–drug cocrystal	Synergistic therapy	Novartis	FDA & EMA approved, marketed (2015)
Celecoxib	Nicotinamide	Solubility & dissolution improvement	Pharma patents (Trask et al.)	Patented, not marketed

Carbamazepine	Saccharin, Nicotinamide	Stability & solubility enhancement	Multiple academic/industrial patents	Patented, model system
Pioglitazone	Hydroxybenzoic acid	Improved dissolution & bioavailability	Takeda (patent filings)	Patented, experimental
Dextromethorphan HBr	Tartaric acid	Solubility enhancement	University of Baghdad (Jassim et al., 2021)	Research stage, patented
Furosemide	Nicotinamide/Isonicotinamide	Solubility & stability improvement	Academic patents (Ueto et al.)	Patented, experimental
Isoniazid	Fumaric acid, Hydroxybenzoic acid	Polymorphism control & stability	Academic patents (Swapna et al.)	Patented, experimental
Indomethacin	Saccharin	Solubility & dissolution enhancement	Chun et al. (antisolvent method)	Patented, model system
Febuxostat	Piroxicam	Tabletability & solubility improvement	Academic patents (Guo et al., 2021)	Patented, experimental

NEW TRENDS

- **Nano-cocrystals:** which blend nanotechnology with supramolecular design. Nanosizing boosts dissolution, solubility, and bioavailability by increasing surface area and shortening diffusion paths. Poorly soluble drugs in nanosized cocrystals reach higher supersaturation and show better absorption than conventional forms. For example, dihydromyricetin cocrystals with caffeine or urea, stabilized by PVP K30, delivered much higher plasma exposure in vivo.^[22] This approach offers a way to tackle solubility and permeability issues in BCS Class II–IV drugs.
- **Machine learning:** It is reshaping cocrystal prediction. Tools like the Cambridge Structural Database (CSD), supramolecular synthon hierarchies, and Hansen solubility parameters are now widely used to forecast API–coformer matches. Algorithms can analyze molecular descriptors—polarity, dipole moment, hydrogen bonding tendency—to predict cocrystal formation more efficiently than trial-and-error screening.^[20,17] This reduces experimental workload and speeds up discovery. The approach aligns with pharma’s push toward in silico solid form screening, making design faster, cheaper, and more systematic.
- **Green Synthesis Approaches:** Sustainability is driving interest in green synthesis of cocrystals. Techniques like mechanochemical grinding, liquid-assisted grinding, and supercritical CO₂ use little solvent and have low environmental impact while remaining efficient. Solvent-free mechanochemistry, in particular, is reported as reliable, scalable, and eco-friendly.^[13,15] Other greener continuous processes under study include supercritical fluid technology, spray drying, and hot-melt extrusion.^[20] These approaches align with global regulatory emphasis on sustainable pharmaceutical manufacturing.
- **Co-Crystals for Nutraceuticals:** Beyond pharmaceuticals, there’s growing interest in cocrystals for nutraceuticals. Pairing APIs with GRAS co-formers have improved the bioavailability and stability of poorly soluble compounds like curcumin, flavonoids, and polyphenols.^[13,22] This opens the door to dietary supplements with stronger therapeutic effects. Safe co-formers such as amino acids, organic acids, and sugars make cocrystals especially appealing at the intersection of pharmaceutical science and functional nutrition.

FUTURE PROSPECTS

- **Industrial Potential:** Co-crystals for pharmaceutical applications are increasingly becoming mainstream. They offer good properties for improving solubility, dissolution, and stability for the drug while preserving its pharmacological activity, which makes them attractive for large-scale drug development. To address the challenges of scale up and help meet the requirements for eco-friendly production, Continuous Manufacturing (CM) technologies like hot-melt extrusion, technology Spray drying, and supercritical fluid technology are being

explored.^[15,20] The successful marketing of cocrystals such as Steglatro® and Entresto® now provides an example of how regulatory agencies are willing to consider cocrystals as drug products, and hence there is a wider opportunity to embrace cocrystals in industry.^[21,17]

- **Novel Screening Techniques:** Traditional screening of co-formers is laborious and empirical, but recent advances include the application of high throughput crystallization, slurry conversion, and in-line Raman spectroscopy to expedite discovery.^[13,15] There are several computational tools that are increasingly employed to predict successful API-coformer pairs, including supramolecular synthon analysis and Hansen solubility parameters. These are novel screening tools that not only save time and money, but also facilitate efficient and reproducible cocrystal development.^[20]
- **AI-Assisted Crystal Design:** AI and machine learning are becoming a game-changer in cocrystal design. Algorithms generated from structural database such as Cambridge Structural Database (CSD) can forecast hydrogen bond features, molecular compatibility, and lattice stability.^[17,20] With AI-based design, thousands of co-formers can be virtually screened, thus decreasing the experimental burden. The strategy is in line with the pharmaceutical industry's efforts towards in silico prediction of solid form, providing a more expedient path towards the identification of novel cocrystal candidates.
- **Increasing the role in poorly soluble drugs:** A major challenge faced by approximately 40% of marketed drugs and 60% of new chemical entities is their often-poor aqueous solubility, which is the most promising application of cocrystals.^[13,22] Cocrystals can significantly enhance dissolution and oral bioavailability by changing the lattice energy of the molecule and adding hydrophilic co-formers. Recent research on APIs like carbamazepine, indomethacin, and dextromethorphan HBr has demonstrated their efficacy in improving solubility and therapeutic efficacy.^[19,15] Cocrystals are likely to be a key technology in drug formulation with more and more molecules entering the pipelines that are lipophilic in nature.
- **Additional Prospects:** Other directions going forward include the development of drug-drug cocrystals in combination therapy, which could provide a better pill burden and improve compliance, as demonstrated by Guo et al., 2021. Nutraceutical cocrystals are used to improve the bioavailability of phytochemicals such as curcumin and flavonoids, as a link between pharmaceuticals and functional foods.^[13,22] Induction of patient-specific co-formers for personalized medicine could be applied to the optimization of pharmacokinetics and therapeutic effects⁽²¹⁾. These advances, combined, demonstrate the potential of cocrystals as a platform for next generation drug delivery.

CONCLUSION

One of the major challenges in oral drug delivery is its poor aqueous solubility, and pharmaceutical co-crystals have proven to be a reliable approach to address this problem. They form stable non-covalent interactions which enhance the solubility, dissolution, stability, and retain the pharmacological activity of the drug.

Co-crystals are a more predictable and scalable method than other traditional methods, such as micronization or solid dispersions. They are prepared using a variety of methods from simple evaporation of solvents and grinding to more sophisticated industrial processes, like hot-melt extrusion and supercritical fluid technology, which are technically feasible in the laboratory and can be scaled-up for large-scale applications.

Pharmaceutical industries have been showing great interest in it as it provides an added benefit: the improvement of the physicochemical properties and the patenting opportunities for the management of the life cycle. Co-crystals are being increasingly adopted in formulation science with regulatory approval and commercial products already demonstrating their potential.

Overall, co-crystals represent a fascinating intersection of science, industry, and medicine, with potential applications in the pharmaceutical sector that are likely to continue expanding in the years to come.

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