WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 20, 750-769. Research Article ISSN 2277–7105

COCRYSTAL TECHNIQUE FOR THE IMPROVEMENT OF SOLUBILITY

Deepayan Kar[1]*, Mousumi Das[1], Susmita Maiti[1], Nilanjan Adhikari[2], Biplab Kumar Chakra[2]

[1]*Department of Pharmaceutics, P.G. Institute of Medical Sciences, Chandrakona Town, Paschim Medinipur, West Bengal, India, Pin – 721201.

[2]Department of Pharmacology, P.G. Institute of Medical Sciences, Chandrakona Town, Paschim Medinipur, West Bengal, India, Pin – 721201.

Article Received on 24 Sept. 2025,
Article Revised on 13 October 2025,
Article Published on 16 Oct. 2025,

https://doi.org/10.5281/zenodo.17366023

***Corresponding Author**

Deepayan Kar

Department of Pharmaceutics, P.G. Institute of Medical Sciences, Chandrakona Town, Paschim Medinipur, West Bengal, India, Pin – 721201.

How to cite this Article: Deepayan Kar, Mousumi Das, Susmita Maiti, Nilanjan Adhikari, Biplab Kumar Chakra. (2025). Cocrystal Technique For The Improvement Of Solubility. World Journal of Pharmaceutical Research, 14(20), XXX–XXX.

ABSTRACT

Over 80% of the market's formulations are solid dosage forms meant to be taken orally. 40% of these medications, associated with a comparable proportion of novel chemical entities, have poor water solubility, particularly those classified as BCS Class II and Class IV. Research and development of new products are also hampered by low oral bioavailability and poor water solubility, which may reduce the effectiveness of oral administration in patients. Co-Crystallization is one of the latest approaches which used for the enhancement of solubility of poorly aqueous soluble drugs also helps to improve physicochemical properties such as melting point, tabletability, solubility, stability, bioavailability and permeability with preserving the pharmacological properties of the active pharmaceutical ingredient. Cocrystals are multicomponent systems of two components, a coformer and an active medicinal ingredient, present in a stoichiometric ratio and bound together via π-π stacking interactions, hydrogen bonding, and Vander Waals forces. For the synthesis of cocrystals, a variety of techniques have been employed, including the Slurring Technique, Solution Methods, Colling Crystallization, Solution Crystallization, Grinding Method, Dry Grinding, Liquid Assisted Grinding, Anti-solvent Addition, Solvent Evaporation Method, Super Critical Fluid Technology, Spray Drying, and Hot Melt Extrusion

Method. A comprehensive discussion of pharmaceutical cocrystals is provided in this article, along with information on how cocrystals differ from other methods of enhancing solubility, the difficulties in developing cocrystals, their use, and their prospects for the future.

KEYWORDS: Cocrystal, Co-crystallization, Coformer, Bioavailability, Solubility, Stability.

INTRODUCTION

Poor aqueous solubility is a significant issue in modern drug development, with a significant proportion of active pharmaceutical ingredients (APIs) having this limitation, which poses a significant barrier to drug formulation, bioavailability, and therapeutic efficacy.[1] Solubility of drugs is a significant rate-limiting step in the absorption of drugs in the gastrointestinal tract and, consequently, their efficacy in the clinic. Various solutions such as salt formation, particle size reduction, and solid dispersion, have been explored in an attempt to rectify this limitation. These have their shortcomings, especially in drugs that are non-ionizable or chemically unstable in their altered forms.[2] A new and promising method for improving the solubility and rate of dissolution of medications those are not very soluble in water is cocrystallization. Solid crystals made of an API and a pharmaceutically approved coformer in a certain stoichiometric ratio that are held together by non-covalent forces like hydrogen bonding, van der Waals forces, or π-π stacking are known as pharmacological cocrystals.[3] In contrast to conventional modifications that can change the chemical structure or pharmacological activity of the drug, cocrystals preserve the original identity of the API but enhance its physical properties.[3,1]

The simplest advantage of cocrystallization is that it can alter the physicochemical characteristics of drugs, particularly solubility, without interfering with chemical stability and therapeutic activity. With proper choice of coformers, frequently compounds that are established to be safe and biologically inert, researchers can engineer cocrystals that significantly improve drug dissolution and absorption. This increases bioavailability and enhances therapeutic action.[4] Various researches have determined the potential of cocrystals to increase the solubility of drugs like ketoconazole, curcumin, and carbamazepine. Aside from improving dissolution profiles, such cocrystals have the benefit of increased stability, processability, and intellectual property protection.[4,1] Regulators such as the FDA have also determined cocrystals as unique solid forms of APIs, thereby confirming their use in pharmaceutical development.[1]

"The understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties" is the definition of crystal engineering, which offers a chance to improve the physical properties of active pharmaceutical ingredients (APIs).[5] Typically, a compound's molecular configurations and intermolecular interactions determine its physical characteristics. Thus, the parent API's qualities can be enhanced by adjusting these variables through the creation of salts and co-crystals. By co-crystallizing an API with a pharmaceutically acceptable substance (a coformer), a new multicomponent crystal with distinct or improved physical properties can be produced. The new multicomponent crystal is referred to as a salt or pharmaceutical co-crystal. The coformer only improves some of the API's physical characteristics; it doesn't affect its functionality.[6,7] Co-crystallization offers partial advantages for BCS Class IV drugs and has shown promise in improving the formulation of BCS Class II (Table 1) drugs by greatly increasing their solubility. This strategy fits in nicely with the pharmaceutical industry's need for stable, effective, and scalable drug delivery systems.[8,9]

Table 1: Comparison of BCS classes for cocrystal use.

Feature	**BCS Class Ⅱ**	**BCS Class Ⅳ**
Solubility	Low (primary focus)	Low
Permeability	High (no intervention needed)	Low (may require additional strategies)
Cocrystal Impact	High (solubility-driven bioavailability gains)	Moderate (dual solubility-permeability challenge)
Example Drugs	Ezetimibe, Progesterone,	Entacapone, Carvedilol

An effective method for improving the solubility and bioavailability of active pharmaceutical ingredients (APIs) that are poorly soluble in water is cocrystallization. By using non-covalent interactions like hydrogen bonding, π–π stacking, and van der Waals forces, an API and a pharmaceutically acceptable coformer are assembled to form multicomponent crystalline systems. In order to enhance dissolution and absorption characteristics, the resulting cocrystals alter the physicochemical characteristics of the API while maintaining its molecular identity.

DIFFERENCE BETWEEN COCRYSTALS, SALT, SOLVATES AND HYDRATES

The cocrystal, salt, and polymorphs were defined by the USFDA in the proposed guidance. Compounds that exist in both amorphous and crystalline forms, such as solvates or hydrates (sometimes referred to as pseudo-polymorphs), are designated as polymorphs. The crystal

lattice structures of polymorphs result in distinct lattice arrangements and, consequently, variable physicochemical properties. The full transfer of a proton from one chemical to another is what creates salts. When an acid transfers a proton to a base, salts and cocrystals can be separated from the other. While no proton transfer happens during cocrystal formation, a complete proton transfer happens between acid-base couples. Non-covalent interactions including van der Waal forces, π-π stacking, and hydrogen bonds bind two components to one another. It is possible to predict whether or not cocrystals will form based on the ΔpKa value. If the ΔpKa value is larger than 3, it is generally considered that a salt will develop; if the ΔpKa value is less than 0, cocrystals will form. Although the development of cocrystals in solids between ΔpKa values 0 and 3 cannot be accurately predicted by this parameter, the likelihood of salt formation will rise as ΔpKa increases.[10,11] The physical state of the constituents allows for the differentiation of cocrystals and solvates. Solvates are substances that are liquid at room temperature, while cocrystals are substances that are solid at room temperature. The solvates are referred to as hydrates if they have water as a solvent in their crystal lattice.[12] The physicochemical characteristics of APIs can be changed by solvates or hydrates, which are frequently produced during co-crystallization via solution or liquid assisted grinding. Because the solvent is present in the crystal lattice, the stability of solvates will differ from that of unsolvated forms. Because they lose water and solvent at high temperatures and low humidity levels while being stored, and because the physiochemical characteristics of hydrated and dehydrated forms differ, solvents and hydrates are highly unstable.[13,14] The drug's rate of dissolution was accelerated by the solvated spironolactone forms.[15] Liquid-assisted grinding was used to create several polymorphic cocrystals and solvates of caffeine and anthranilic acid using various solvents.[16]

CO-CRYSTAL

A pharmaceutical cocrystal is a complex of non-covalently bonded components, one of which is an API and the other is a co-former. Cocrystals can form hydrogen bond, pie bond, and wander wall forces due to a variety of interactions. Friedrich Hander studied the first known cocrystal quinhydrone in 1844. For a drug to have pharmacological action, it must be absorbed from the site of administration. A cocrystal is a line-shaped crystal that contains numerous compounds. A cocrystal is a multi-component crystal in which, in its pure state, each component is solid at room temperature.[17]

Nano cocrystals

Crystalline substances with particle sizes in the nanometer range (1–1000 nm) are known as nano cocrystals. A widely applicable method for increasing the solubility of medications that are not very soluble in water is nanocrystallization. The physicochemical characteristics of active pharmaceutical ingredients (APIs), especially their solubility and rate of dissolution, can be synergistically improved by combining this dual approach with cocrystal technology.[18] Nano cocrystals have shown promise in recent studies for a number of traditional drug delivery methods, such as oral, intravenous, intramuscular, pulmonary, and dermal. Their much higher saturation solubility enhances both therapeutic efficacy and bioavailability. Significantly, nano cocrystals have been demonstrated to improve solubility and lessen local tissue irritation in subcutaneous and intramuscular administration, making them a viable substitute for traditional medication.[19]

ADVANTAGES OF PHARMACEUTICAL COCRYSTAL[20]

1. In contrast to amorphous solids, it is a stable crystalline form.
2. It can improve the solubility of medications that aren't very soluble in water.
3. Because it is more soluble, it can increase bioavailability.

The purification step may employ the cocrystal formation technique.

DISADVANTAGES OF PHARMACEUTICAL COCRYSTAL

Cocrystallization is a practical method for increasing the solubility of medications that are not very soluble in water by creating crystalline complexes with coformers. Nevertheless, a number of restrictions impact its efficacy and expandability:

1. **Unpredictable Solubility:** Improvements in solubility are highly dependent on outside variables such as pH and coformer concentration, which makes reliable performance difficult.[21]
2. **Formulation Constraints:** The procedure becomes more difficult when using solvent-based and supercritical techniques, which need exact control and drug-coformer compatibility.[22]
3. **Stability Issues:** Long-term stability and bioavailability may be impacted by cocrystals reverting to their constituent parts under specific circumstances.[23]
4. **Manufacturing Challenges:** Scaling up can be challenging with mechanical and thermal approaches since they might be energy-intensive and inappropriate for medications that are sensitive to heat.[22]

5. **Inconsistent Physicochemical Behaviour:** Complex molecular interactions might cause desired enhancements (such solubility and stability) to conflict with coformer qualities.[24]
6. **Regulatory and Analytical Demands:** Structure and stability must be confirmed by extensive testing, and regulatory mechanisms are not as well-defined as they are for conventional drug forms.[25]

Table 3: Other solubility enhancement methods.

Technique	Applicable to all APIs	Solubility enhancement	Stability	Key limitation
Cocrystal	Yes	High, tunable	Good (if well-designed)	Coformer selection critical
Salt formation	No (needs ionizable)	High (not always > cocrystal)	pH-dependent	Not suitable for all drugs
Solid dispersion	Yes	Very high	May be lower	Physical/chemical instability
Hydrotropy	Yes	Moderate-High	Good	Limited by agent compatibility
Complexation	Yes	Moderate	Good	Efficiency/cost
Particle Size Reduction	Yes	Moderate	Good	May not suffice for all drugs

PHYSICO-CHEMICAL PROPERTIES

Melting Point

The melting point, which indicates the change from solid to liquid, is a crucial physical characteristic for recognizing and assessing the purity of cocrystals. The best technique for measuring it accurately and gaining knowledge of the material's thermal characteristics is differential scanning calorimetry or DSC.[26]

Stability

The stability of pharmaceutical co-crystals is often examined using four important factors: moisture stress, heat stress, chemical stability, and solution stability. Moisture content is important in determining the best storage conditions since water can degrade the quality of the co-crystal.[23]

Photo Stability

Drug photostability depends on the distance between rings in the crystal lattice. The anticipated photo stability increases with the ring distance. Carbamazepine-saccharin and carbamazepine-nicotinamide cocrystals were discovered to be able to withstand degradation

in this way by moving the molecules within the crystal grid due to their longer ring distances.[23]

Solubility

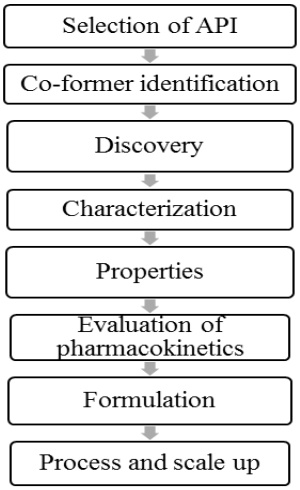
Cocrystals' increased solubility accelerates dissolution, a crucial stage in gastrointestinal absorption. Co-crystals can improve solubility beyond typical methods like salt configuration, solid dispersion, and the marinization process by using thermodynamic and kinetic approaches.[23]

Bioavailability

Improved crystal solubility raises the bioavailable portion of the medication that enters the bloodstream, which subsequently affects any API's therapeutic efficacy.

THE COCRYSTAL DEVELOPMENT PATHWAY

The process of creating medicinal co-crystals has been divided into eight phases.



API Selection

A crucial stage in the pharmaceutical co-crystal preparation process is choosing an API.

Identification of Co-formers

A candidate for a complimentary coformer to a medicinal molecule is first chosen from a library. The pharmaceutical co-former and co-crystal are chosen mostly from the FDA's list, which also includes all FDA-approved ingredients added to US food.

Discovery

A phase in which co-crystal synthesis is done. Techniques include mechanical grinding (both neat and solvent-drop or liquid-assisted), slurry-mediated transformation, and gradual solvent evaporation. Other techniques for cocrystal screening are also mentioned.

Characterization

A step in which various methods are used to evaluate the physical and chemical characteristics. Novel co-crystals are characterized using techniques such as solid-state nuclear magnetic resonance (ss-NMR), powder X-ray diffraction (PXRD), single crystal X-ray (SCXRD), infrared and Raman spectroscopy, thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC). Properties: This was defined as a phase where decisions about subsequent actions would be made. Pharmacokinetics, formulation, reproduction, and scale-up will be carried out if the generated cocrystal exhibits improved desired characteristics such as water solubility and dissolution rates. Additionally, co-crystallization makes it possible to enhance the features of properties.

Properties

Decisions regarding the subsequent actions were supposed to be made at this stage. If the produced cocrystal has enhanced desired properties such as aqueous solubility and dissolution rates, pharmacokinetics, formulation, replication, and scale-up will be conducted. Furthermore, cocrystallization makes it possible to improve characteristics.[27]

Clinical pharmacokinetic evaluation

A crucial phase in the creation of novel medications is pharmacokinetic analysis. This stage involves examining the drug's performance and flow at the action site. As the foundation for This technique of administering drugs involves figuring out the dosage of any medication. A popular definition of PK is the study of physiological processes such as drug distribution, metabolism, absorption, and excretion. Subsequent to changes in API thermodynamics, supramolecular structures, including co-crystals, exhibit different physical characteristics. The processes outlined in the paragraph above, which include but are not restricted to the prompt investigation of drug quantity (concentration) in biological fluids, tissues, and excreta, these, in turn, affect drug PK in addition to drug bioavailability.[28]

Formulation

Developing a dosage form for a co-crystal is a challenging process. It becomes dangerous for co-crystals held together by hydrogen bonds to be stable when excipients containing hydrogen bonding groups are also present. It is crucial to choose the right excipients to lessen the possible source of interactions with the co-crystal. In formulation, the stability of co-crystals is one of the primary issues. The use of excipients that already include H bonds entails a variety of risks, especially when those excipients are meant to enhance a drug's formulation properties. This is because H bonds stabilize co-crystals. Furthermore, because of their enhanced physicochemical characteristics, pharmaceutical co-crystals behave differently from their pure API. Need to be altered regardless of how stable they are with respect to H bonds.[29]

Procedure and expansion

There are difficulties in scaling up the co-crystal created by conventional solution co-crystallization techniques including solvent evaporation and slurry. Solution crystallization, a technique typically employed to purify chemical compounds like APIs, yields high-quality co-crystals. Along with the issues of solvent cost and component solubility, there is also the propensity to crystallize, which varies for These elements lessen the likelihood that the same cocrystals will be produced with the intended results. The required high mechanical stress and the difficulties of producing a homogenous final product for larger-scale processes are issues for many co-crystals made employing straightforward and popular solid-state techniques known as the mechanochemical method.[30]

METHODS OF PREPARATION

The first stage in creating a co-crystal is choosing a suitable co-crystal former, which could be an excipient or a medication's-crystallization success is mostly determined by the compatibility and molecular configuration of the chosen coformers. Ascorbic acid, isoniazid, nicotinamide, acetamide, and saccharin are a few of the safe and widely used coformers.[31] In the production of pharmaceutical co-crystals, choosing coformers that are compatible with particular active pharmaceutical ingredients (APIs) continues to be a major difficulty. Researchers have used a number of techniques, including the Cambridge Structural Database (CSD), pKa-based models, hydrogen bonding considerations, supramolecular synthons, Hansen solubility parameters, and the Fabian approach, to find appropriate coformers. In

pharmaceutical co-crystal formulation, a broad range of compounds that have been approved and maintained by the USFDA are available and may act as coformers.[32]

Slurring Technique

To make co-crystals, the slurrying technique uses water and a variety of organic solvents. Using this procedure, the active pharmaceutical ingredient (API) is added to the solution after the coformer has been dissolved in an organic solvent. The final co-crystal product is obtained by filtering and drying the resultant suspension after it has been properly agitated. As an illustration, the multi-drug co-crystal that resulted from the celecoxib–venlafaxine patent showed an improved therapeutic benefit of the anti-inflammatory medicine celecoxib.[33]

Solution Methods

The homogeneous solubility of both components in a chosen solvent system is necessary for this procedure. Premature precipitation of a less soluble component from the solution is possible. Successful co-crystallization is not ensured by the components' separate solubility, though.[34]

Colling Crystallization

This process uses regulated temperature changes to induce supersaturation, which recrystallizes the medication. The medication is first dissolved in a suitable volume of solvent at 40.0 ± 0.5°C. A water bath is then used to gently chill the solution to 10.0 ± 0.5°C at a regulated rate of 0.25°C per minute while stirring constantly. After the crystallization process, the product is collected using vacuum filtration, cleaned with distilled water, and allowed to dehydrate for a full day at room temperature. In order to preserve stability, the dried crystals are lastly kept in a desiccator.[35]

Solution Crystallization

The API and coformer are mixed to a 1:1 molar ratio using a 10 mL solution of the coformer, methylparaben, in methanol. In a water bath, the mixture is kept at 35°C to encourage gradual evaporation. Once the solvent has progressively evaporated for 48 hours, the final product is filtered and allowed to air dry. White, needle-shaped crystals are produced by this method.[36]

Grinding Method

Products from the grinding process can be as consistent as those from solution-based techniques. In uncontrolled or exclusive settings, hydrogen-bonding interactions are not precisely specified, which explains this. Solution-based methods can successfully generate some co-crystals that cannot be obtained by solid-state methods. Co-crystallization of 2,4,6-trinitrobenzoic acid with indole-3-acetic acid, for instance, was accomplished by a solvent approach, but this was not detected through dry grinding because of inadequate initial solubility that hindered appropriate co-crystal formation. However, by increasing molecular mobility during the grinding process, a tiny amount of solvent can help co-crystal formation.[37] The two main categories of grinding procedures are wet grinding and neat (dry) grinding.

Dry Grinding

Both the medication and the coformer are combined in a precise ratio and ground using a vibratory mill, mortar and pestle, or dry grinding.

Liquid Assisted Grinding

Liquid-assisted grinding (LAG) is a technology that improves the grinding process by using a small amount of solvent during the process. This method's main benefits are its increased efficiency, better control over polymorph formation, and superior product crystallization. On the other hand, the quick rate of co-crystallization could result in the production of low-quality co-crystals if the grinding time and process variables are not well managed. LAG has the advantage of drastically cutting down on the amount of time needed for co-crystal preparation in spite of this. This technique, for example, was successful in producing high-purity white ezetimibe crystals as well as co-crystals of nicotinamide and ezetimibe. Across several organic solvents, the API displayed varying solubility profiles, and the solvent evaporation time was noticeably longer.[38]

Anti-solvent Addition

The benefit of anti-solvent crystallization is that it may be carried out at or close to atmospheric temperatures, which makes it ideal for materials that are sensitive to heat. Comparing this process to solvent evaporation procedures, less heat energy is needed. This method’s drawback is that it might be hard to extract and recover solvents from the combination, which restricts how often they can be used. For instance, solvent–anti-solvent crystallization, in which the API and coformer are dissolved in solvents such buffers and

organic solvents like methanol or ethanol, has been used to successfully create co-crystals of fenofibrate and nicotinamide.[39]

Solvent Evaporation Method

Pharmaceutical co-crystals are produced using this process extensively. A certain amount of the coformer and API is dissolved in an appropriate solvent until total solubilization is accomplished. After then, the solvent is left to evaporate completely. Hydrogen bonding between the API's and the coformer's functional groups during the evaporation process creates thermodynamically stable co-crystal products.[40]

Super Critical Fluid Technology

Supercritical fluid (SCF) engineering has been a valuable method in material processing over the last 20 years, especially for the creation of nanomaterials. An environmentally friendly and effective method for improving the solubility of poorly soluble medications and altering nanocrystals is to use supercritical fluids, such as CO_2 and H_2O, which display both liquid and gas characteristics above their critical point. Polymorphic co-crystals may result from novel molecular interactions in the special medium that SCFs offer. Through controlled precipitation from solution or suspension, co-crystal formation is facilitated by methods including gas anti-solvent (GAS), supercritical anti-solvent (SAS), and solution-enhanced dispersion by supercritical fluids (SEDS). For instance, SCF techniques have been used to successfully create indomethacin–saccharin co-crystals with a variety of sizes and morphologies.[41]

Spray Drying

In solid-state engineering, spray drying is a continuous and effective process that uses a stream of hot air to turn a solution or suspension into a dry powder. In situations when the coformer and API have different solubilities, which can impede the creation of pure co-crystals through traditional solvent evaporation, this method is very helpful. Pure co-crystals could not be formed by solvent evaporation for examples such glutaric acid–carbamazepine, theophylline–nicotinamide, urea–succinic acid, and caffeine–glutaric acid. However, particularly in the carbamazepine–nicotinamide system, spray drying was successful in producing pure co-crystals.[42]

Hot Melt Extrusion Method

The process of hot-melt extrusion (HME), which produces pharmaceutical co-crystals without the use of solvents, involves physically mixing and melting the coformer and active pharmaceutical ingredient (API). This procedure facilitates co-crystal formation without the need for solvents by improving surface contact and molecular interaction between the constituents. Since the approach requires high processing temperatures, it is not appropriate for thermally labile chemicals, but it is very beneficial for heat-stable APIs and coformers. One of the main advantages of HME is its adaptability, which enables the continuous, one-step production of co-crystals with adjustable crystallinity and purity. This technique is ideal for large-scale pharmaceutical manufacture since it also facilitates scale-up and industrial applicability.

The process of creating ibuprofen–nicotinamide co-crystals with a twin-screw extruder is a well-known illustration of this methodology. Well-defined, high-purity co-crystals with enhanced physicochemical properties are formed as a result of the twin-screw system's vigorous shear and mixing, which encourage thorough blending and uniform melting.[42]

CHALLENGES ASSOCIATED IN THE DEVELOPMENT OF COCRYSTALS

I. Challenges In Cocrystal Design and Screening

a) Coformer Selection: The most significant challenge is determining appropriate coformers. Since there are theoretically a vast number of possible coformers, advanced screening techniques are required in order to identify likely possibilities. There is an obvious need for more efficient screening techniques for successful pharmaceutical application, even while methods like the Hansen solubility parameter, pKa rule, supramolecular synthon approach, hydrogen bond propensity, and Cambridge Structural Database are available.[43]

b) Experimental Screening Restrictions: To verify cocrystal formation, experimental screening is essential even after identifying likely coformers. A lot of resources may be needed for this process.[43]

II. Challenges In Cocrystallization Methods

a) Solvent-Based Methods: These methods present several difficulties:

i. Solvent Selection: It is crucial to select the appropriate solvent.

ii. **Solubility Variations:** The process can be complicated by variations in the coformer's and Active Pharmaceutical Ingredient's (API) solubility in the selected solvent (congruent vs. incongruent dissolution).

iii. **Concentration Effects:** Optimizing concentrations is crucial.

iv. **Heating and Cooling Profiles:** For regulated cocrystal formation, the right heating and cooling profiles must be established.

b) **Solid-State Grinding:** For screening, solid-state grinding is frequently chosen over solvent-based techniques; however, the resulting pharmaceutical cocrystals may occasionally undergo undesired phase changes.

III. Challenges In Cocrystal Properties & Stability

a) **Undesirable Properties:** Cocrystals with the required physicochemical, pharmacokinetic, and processability characteristics won't be produced by every coformer that is chosen. This calls for a great deal of screening and characterization.

b) **Synthesis & Characterization Issues**

i. **Formation Of Undesired Products:** Occasionally, the intended cocrystal may be replaced by salts, solvates, or hybrid forms as a result of cocrystal synthesis.

ii. **Inherent Instability:** Cocrystals can exhibit inherent instability.

iii. **Conversion To Parent Drug:** The possibility of cocrystals reverting to the less soluble parent drug form in solution, which would defeat the purpose of cocrystallization, is a significant obstacle.

iv. **Polymorphism Of Cocrystals:** Cocrystals, like parent medications, can show polymorphism, resulting in many solid forms with perhaps disparate characteristics, which complicates development.

IV. Challenges In Formulation & Scale-Up

a) **Dissociation In Formulation:** When cocrystals interact with excipients (inactive components), they may dissociate within the finished medication formulation.

b) **Coformer Replacement:** The coformer in the cocrystal structure may be replaced by excipients, changing the structure's characteristics.

c) **Stoichiometry Changes:** During formulation and dissolution, it is very difficult to maintain the cocrystal's exact stoichiometry.

d) **Conversion During Dissolution:** As the medication dissolves in the body, the cocrystal may revert to the less soluble parent form.

e) **Lack Of Established Scale-Up Techniques:** Scale-up methods for pharmaceutical cocrystals are not well-established or generally applicable. Despite the existing use of techniques like Hot-Melt Extrusion (HME), spray drying, spray congealing, and supercritical fluid technologies, more advancements are required.

f) **Reproducible Stoichiometry Control at Scale:** Reproducible management of cocrystal stoichiometry in large-scale manufacturing is still a major challenge.

g) **Lack Of In Vitro-In Vivo Correlation (IVIVC):** For cocrystals, the lack of clear in vitro–in vivo correlations delay development. Finding these connections might speed up the medication development process considerably.[44] Even said, the small number of cocrystal-based medications that are already available suggests that these difficulties are manageable and can be resolved with more research and development.

APPLICATION OF PHARMACEUTICAL CO-CRYSTAL

1. Pharmacological cocrystals are molecular complexes made up of a pharmaceutically approved conformer that is solid in ambient conditions and an active pharmacological ingredient (API).
2. The design and synthesis of cocrystals have demonstrated the effectiveness of crystal engineering techniques that depend on the intermolecular between the API and conformer.
3. The use of cocrystal as a possible alternative solid form for drug development was further verified by recent endorsements from the European Medicines Agency and the United States Food and Drug Administration.[45]
4. Pharmaceutical cocrystals aid in the drug's prolonged release.
5. Moreover, pharmaceutical cocrystals help to improve solubility and bioavailability.[46]

FUTURE PERSPECTIVES AND CHALLENGES OF CO-CRYSTALS

Co-crystals, formed by two or more molecular entities bonded through noncovalent interactions, have emerged as sustainable and eco-friendly innovations in modern science. Their synthesis often avoids complex chemical reactions and extensive solvent usage, aligning well with the principles of green chemistry. Simple methods like grinding make their production efficient and environmentally conscious.

In the pharmaceutical field, co-crystals offer substantial benefits by enhancing drug solubility, stability, and bioavailability. They also present opportunities for extending the intellectual

property life of active pharmaceutical ingredients (APIs) through novel formulations. Beyond pharmaceuticals, co-crystals are gaining attention in materials science, where their superior physical and chemical properties show promise in applications like energy storage, catalysis, and electronics.

Despite their advantages, several hurdles must be addressed. The synthesis and analysis of co-crystals require advanced techniques and expertise. Scaling up production while maintaining consistency poses a major industrial challenge. Regulatory frameworks for co-crystals, particularly in the pharmaceutical sector, are still evolving and require clear guidelines for approval. Furthermore, a comprehensive understanding of the mechanisms behind co-crystal formation and stability is essential. Computational tools and predictive models can play a key role in accelerating their design and discovery.

CONCLUSION

According to FDA recommendations, crystallization improves the stability, solubility, and bioavailability of active pharmaceutical ingredients (APIs) by carefully choosing coformers to prevent toxicity. Effective cocrystal production methods improve the permeability and tableting characteristics of poorly soluble medications while also being safe and environmentally benign. Increasing the bioavailability of neutral or weakly ionizable substances requires the use of pharmaceutical cocrystals. They also make it easier for medications, like insulin, to change how they work. For new cocrystals to have potential medical and pharmacological uses, ongoing study is essential.

ACKNOWLEDGEMENT

Our profound gratitude extends to our esteemed institution, P.G. Institute of Medical Sciences for providing the necessary resources and facility. We are profoundly grateful to the remarkable individuals whose unwavering support and expertise have been instrumental in the successful completion of this study.

Author’s Contribution

Mr. Deepayan Kar designed this study.

Ms. Mousumi Das and Ms. Susmita Maiti conducted the data analysis and prepared manuscript.

Mr. Nilanjan Adhikari have supplied resource compilations.

Dr. Biplab Kumar Chakra have done Proof reading.

All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

REFERENCES

1. Kumar S, Nanda A. Pharmaceutical cocrystals: An overview. Indian Journal of Pharmaceutical Sciences, 2017 Nov 1; 79(6).
2. Kalyani Avhale*, Dr. Kawade Rajendra M., Mayuri Lodha, Shivani Matsagar, Arti Tupe, Solubility Modification of Phytochemicals via Pharmaceutical Cocrystal, Int. J. of Pharm. Sci., 2024; Vol 2, Issue 12: 587-597.
3. Patole T, Deshpande A. Co-crystallization-a technique for solubility enhancement. Int J Pharm. Sci. Res., 2014 Sep 1; 5(9): 3566-76.
4. Patole T, Deshpande A. Co-crystallization-a technique for solubility enhancement. Int J Pharm Sci. Res., 2014 Sep 1; 5(9): 3566-76.
5. Desiraju G.R., Parshall GW. Crystal engineering: the design of organic solids. Materials science monographs., 1989; 54.
6. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Crystal growth and design. 2009 Jun 3; 9(6): 2950-67.
7. Anand RA, Nanda AR. Formulation and Evaluation of Cocry-stals of a Bcs Class Ii Drug Using Glycine As Coformer. Int J. Appl. Pharm., 2022 Nov 1; 14: 68-76.
8. Dumda AK, Tidke VN, Rawat S, Tigote RM. Advanced co-crystal technologies for effective solubility enhancement in BCS Class II and IV drugs. PEXACY International Journal of Pharmaceutical Science, 2024 Feb 15; 3(02): 86-106.
9. Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: A review. Journal of pharmaceutical sciences and Research, 2018 Sep 1; 10(9): 2205-11.
10. Bhogala BR, Basavoju S, Nangia A. Tape and layer structures in cocrystals of some di- and tricarboxylic acids with 4, 4′-bipyridines and isonicotinamide. From binary to ternary cocrystals. Cryst. Eng. Comm., 2005; 7(90): 551-62.
11. Childs SL, Stahly GP, Park A. The salt− cocrystal continuum: the influence of crystal structure on ionization state. Molecular pharmaceutics, 2007 Jun 4; 4(3): 323-38.
12. Morissette SL, Almarsson Ö, Peterson ML, Remenar JF, Read MJ, Lemmo AV, Ellis S, Cima MJ, Gardner CR. High-throughput crystallization: polymorphs, salts, co-crystals

and solvates of pharmaceutical solids. Advanced drug delivery reviews, 2004 Feb 23; 56(3): 275-300.

13. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced drug delivery reviews, 2007 Jul 30; 59(7): 617-30.
14. Ross SA, Lamprou DA, Douroumis D. Engineering and manufacturing of pharmaceutical co-crystals: a review of solvent-free manufacturing technologies. Chemical Communications, 2016; 52(57): 8772-86.
15. Salole EG, Al-Sarraj FA. Spironolactone crystal forms. Drug Development and Industrial Pharmacy, 1985 Jan 1; 11(4): 855-64.
16. Madusanka N, Eddleston MD, Arhangelskis M, Jones W. Polymorphs, hydrates and solvates of a co-crystal of caffeine with anthranilic acid. Structural Science, 2014 Feb 1; 70(1): 72-80.
17. Shan N, Zaworotko MJ. The role of cocrystals in pharmaceutical science. Drug discovery today, 2008 May 1; 13(9-10): 440-6.
18. C Nagarwal R, Kumar R, Dhanawat M, Das N, K Pandit J. Nanocrystal technology in the delivery of poorly soluble drugs: an overview. Current drug delivery, 2011 Jul 1; v8(4): 398-406.
19. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Crystal growth and design, 2009 Jun 3; 9(6): 2950-67.
20. Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. Acta Pharmaceutica Sinica B., 2021 Aug 1; 11(8): 2537-64.
21. Friščić T, Jones W. Benefits of cocrystallisation in pharmaceutical materials science: an update. Journal of Pharmacy and Pharmacology, 2010 Nov; 62(11): 1547-59.
22. Yadav R, Yadav AK, Singh A. Co-crystal: A pharmaceutical technique to improve physical characteristics of Active Pharmaceutical Ingredient. Asian Journal of Pharmacy and Pharmacology, 2020; 6(6): 366-74.
23. Cao F, Amidon GL, Rodríguez-Hornedo N, Amidon GE. Mechanistic basis of cocrystal dissolution advantage. Journal of pharmaceutical sciences, 2018 Jan 1; 107(1): 380-9.
24. Reethu Shree S., Nesalin JA, Gopinath E, Ganesh NS, Chandy V. NANOEMULGEL: AN EMERGING PLATFORM FOR TRANSDERMAL DRUG DELIVERY.
25. Wang X, Du S, Zhang R, Jia X, Yang T, Zhang X. Drug-drug cocrystals: Opportunities and challenges. Asian journal of pharmaceutical sciences, 2021 May 1; 16(3): 307-17.

26. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Crystal growth and design, 2009 Jun 3; 9(6): 2950-67.
27. Wouters J, Quéré L, editors. Pharmaceutical salts and co-crystals. Royal Society of Chemistry, 2011 Nov 4.
28. Dooner H, Mundin G, Mersmann S, Bennett C, Lorch U, Encabo M, Escriche M, Encina G, Smith K. Pharmacokinetics of tramadol and celecoxib in Japanese and Caucasian subjects following administration of co-crystal of tramadol-celecoxib (CTC): a randomised, open-label study. European journal of drug metabolism and pharmacokinetics, 2019 Feb 11; 44(1): 63-75.
29. Panzade P, Shendarkar G, Shaikh S, Rathi PB. Pharmaceutical cocrystal of piroxicam: design, formulation and evaluation. Advanced pharmaceutical bulletin, 2017 Sep 25; 7(3): 399.
30. Ngilirabanga JB, Samsodien H. Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy. Nano Select, 2021 Mar; 2(3): 512-26.
31. Patole T, Deshpande A. Co-crystallization-a technique for solubility enhancement. Int J Pharm. Sci. Res., 2014 Sep 1; 5(9): 3566-76.
32. Steed JW. The role of co-crystals in pharmaceutical design. Trends in pharmacological sciences, 2013 Mar 1; 34(3): 185-93.
33. Jayram P, Sudheer P. Pharmaceutical Co-crystals: A Systematic Review. International Journal of Pharmaceutical Investigation, 2020 Jul 1; 10(3).
34. Good DJ, Rodríguez-Hornedo N. Solubility advantage of pharmaceutical cocrystals. Crystal Growth and Design, 2009 May 6; 9(5): 2252-64.
35. Sriamornsak P, Burapapadh K. Characterization of recrystallized itraconazole prepared by cooling and anti-solvent crystallization. asian journal of pharmaceutical sciences, 2015 Jun 1; 10(3): 230-8.
36. Childs SL, Rodríguez-Hornedo N, Reddy LS, Jayasankar A, Maheshwari C, McCausland L, Shipplett R, Stahly BC. Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. Cryst. Eng. Comm., 2008; 10(7): 856-64.
37. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced drug delivery reviews, 2007 Jul 30; 59(7): 617-30.

38. Sugandha K, Kaity S, Mukherjee S, Isaac J, Ghosh A. Solubility enhancement of ezetimibe by a cocrystal engineering technique. Crystal Growth & Design, 2014 Sep 3; 14(9): 4475-86.
39. Giulietti M, Bernardo A. Crystallization by antisolvent addition and cooling. InCrystallization-science and technology, 2012 Sep 19. IntechOpen.
40. Weyna DR, Shattock T, Vishweshwar P, Zaworotko MJ. Synthesis and structural characterization of cocrystals and pharmaceutical cocrystals: mechanochemistry vs slow evaporation from solution. Crystal Growth and Design, 2009 Feb 4; 9(2): 1106-23.
41. Girotra P, Singh SK, Nagpal K. Supercritical fluid technology: a promising approach in pharmaceutical research. Pharmaceutical development and technology, 2013 Feb 1; 18(1): 22-38.
42. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. Crystal Growth & Design, 2018 Aug 10; 18(10): 6370-87.
43. Kumar S, Nanda A. Approaches to design of pharmaceutical cocrystals: A review. Molecular Crystals and Liquid Crystals, 2018 May 24; 667(1): 54-77.
44. Kumar Bandaru R, Rout SR, Kenguva G, Gorain B, Alhakamy NA, Kesharwani P, Dandela R. Recent advances in pharmaceutical cocrystals: From bench to market. Frontiers in Pharmacology, 2021 Nov 11; 12: 780582.
45. Morissette SL, Almarsson Ö, Peterson ML, Remenar JF, Read MJ, Lemmo AV, Ellis S, Cima MJ, Gardner CR. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Advanced drug delivery reviews, 2004 Feb 23; 56(3): 275-300.