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Pharmaceutical Cocrystals: A Review on Design, Preparation, Application and Challenges

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Abstract Pharmaceutical cocrystals have emerged as a transformative approach in drug development, enhancing the physicochemical properties of active pharmaceutical ingredients (APIs) such as solubility, bioavailability, stability, and dissolution rate without altering their pharmacological characteristics. Defined as multicomponent crystalline solids composed of two or more neutral molecules in a stoichiometric ratio, cocrystals are formed through non-ionic interactions like hydrogen bonding and π-π stacking. This review explores the evolution, design, preparation, and applications of pharmaceutical cocrystals, highlighting their ability to improve drug performance, enable controlled release, and offer intellectual property opportunities. Various preparation methods, including solvent-based (e.g., solvent evaporation, cooling crystallization) and solid-based (e.g., grinding, liquid-assisted grinding) techniques, are discussed alongside design approaches like hydrogen bonding propensity and the supramolecular synthonic approach. The review also addresses challenges such as molecular compatibility, thermodynamic barriers, and regulatory considerations. With regulatory acceptance from agencies like the FDA and ongoing advancements in crystal engineering, pharmaceutical cocrystals hold significant promise for optimizing drug delivery and formulation, necessitating further research to fully realize their potential in commercial applications.

Keywords Cocrystal, Ionic cocrystal, molecular cocrystal, APIs, Coformers, Supramolecular Synthons, Crystal Engineering

Introduction

The concept of pharmaceutical cocrystal engineering has advanced greatly over the past 15 years. Cocrystals are multicomponent molecular crystals made up of two or more chemically distinct molecules with all of the elements at a stoichiometric ratio(1,2). The creation of supramolecular hetero synthons of particular active ingredients, such as carboxylic acid heterocyclic nitrogen, carboxyl acid-amide, and alcohol-pyridine, which are not structurally related, is necessary for the formation of cocrystals. Intermolecular interactions of homo synthons, such as acid carboxylic and amide–amide synthons, can also produce cocrystals (3,4,5).

Cocrystals are neutral, crystalline, single-phase solids that are either solvates nor simple salts and are

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made up of two or more distinct molecular and/or ionic compounds, usually in a stoichiometric ratio. It is considered a pharmaceutical cocrystal if not less than one of the co formers is a the API and the other is appropriate for use in pharmaceuticals. As demonstrated by the carbamazepine:4-aminobenzoic acid co-crystal system, which can exist in 1:1, 2:1, and 4:1 proper configurations, cocrystals of varied stoichiometry with the same co former are feasible. The physicochemical parameters of a cocrystal differ from those of either of its precursors due to its distinct crystal structure(6). Because they can be made to have better physical qualities than either of the raw initial components, cocrystals are appealing(2). Because they can change the crystal structure of APIs without changing their pharmacological character, pharmaceutical cocrystals have garnered a lot of interest from the pharmaceutical industry and academics over the past 20 years(8).

The most practical way to develop and administer APIs, or active pharmaceutical ingredients, is through solid forms of dosage that contain a specific crystalline form of the API. A co-crystal is a form of crystal made up of two or more distinct molecules with weak intermolecular forces like π-π stacking and hydrogen bonding. The majority of pharmaceutical firms use co-crystals as an enabling technology in formulation and medication development for both new and existing drug delivery methods. There has been a lot of interest in the idea of changing a drug molecule's characteristics by creating a medicinal co-crystal with one API and a pharmaceutically relevant co-former that has better qualities than the pure drug crystal (9).

Defination

"Dissociable multicomponent solid crystal supramolecular compounds made up of multiple elements within the identical crystalline structure where in all of them are in balanced mode and interact via non ionic interactions" is how the FDA defines co-crystals(10). There is much disagreement over what constitutes a cocrystal on both the scientific and legal level. "Cocrystals are crystals that are crystalline in one phase substances that consist of two or more distinct molecules and/or ionic substances usually in a stoichiometric ratio," referring to the broadest definition(11). Crystals that consist of two or more distinct neutral compounds at a ratio that is stoichiometric and are joined by a noncovalent bond relationship are known as pharmaceutical cocrystals(8).

Importance

a. Increase Bioavaibility and Solubility

A promising method for increasing the dissolution and absorption of poorly soluble medications and improving their therapeutic efficiency is co-

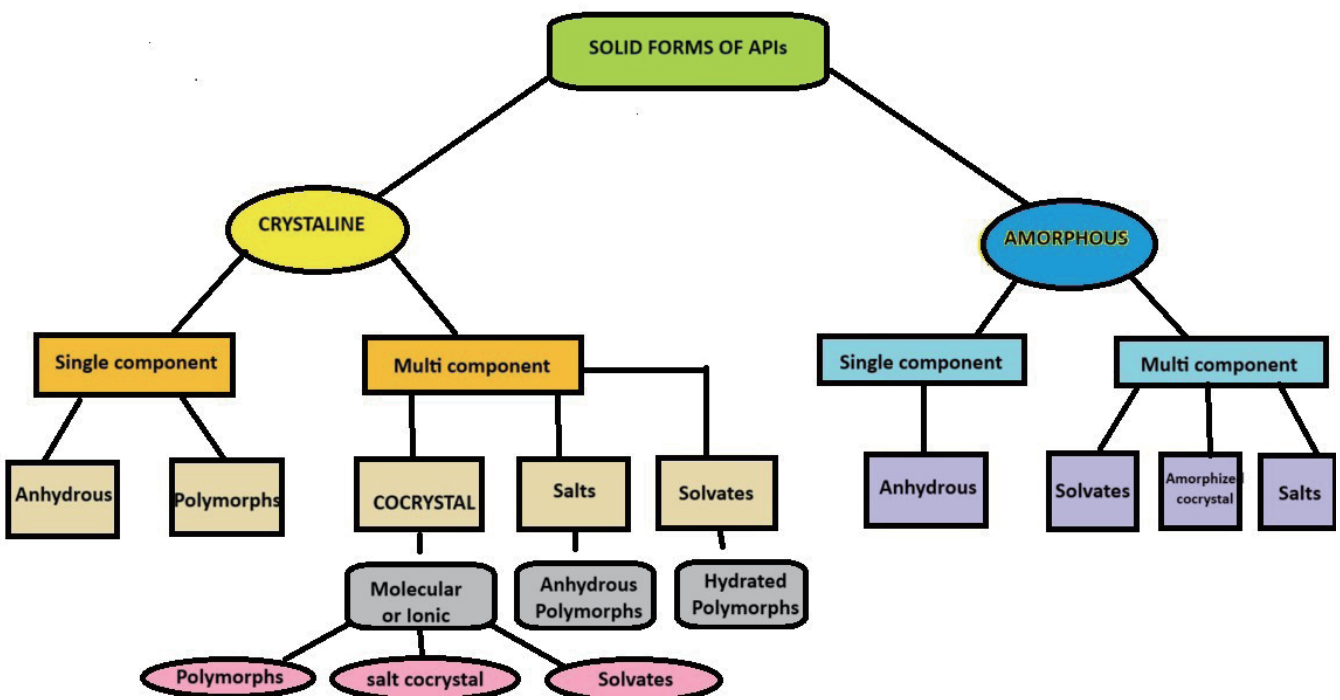

Figure 1. Solid forms of API

crystallization. This method has been demonstrated to increase in vivo bioavailability and in vitro dissolution rates, which are positively correlated with improved solubility(13).

b. Increased Stability

Certain medications may deteriorate over time as a result of crystalline form instability. Cocrystals can provide increased stability, which lowers the risk of medication deterioration. This is essential for sustaining a drug's medicinal efficacy and guaranteeing long shelf life.

c. Properties That Can Be Customized

Cocrystals make it possible to adjust a number of characteristics, including stability, solubility, and rate of dissolution. Scientists can modify these characteristics without changing the active pharmaceutical ingredient's (API) molecular structure by choosing the right coformers. This personalization enhances the medication's effectiveness.

d. Diminished Adverse Reactions

Cocrystals may lessen adverse effects linked to elevated medication levels in the body by enhancing the drug's solubility and regulated release. In time, medications made as cocrystals might also exhibit better therapeutic results.

e. Regulated Drug Dispensation

It is possible to build cocrystals to alter a drug's release rate. This can be particularly helpful for developing formulations with extended release, which can improve therapeutic adherence by lowering the frequency of doses.

f. Acceptance by Regulation

The FDA and other regulatory agencies have acknowledged cocrystals as a promising method for medication development. If the coformer is well-characterized and considered non-toxic, cocrystals are generally regarded as safe, which facilitates their acceptance.Flexibility in Formulation Cocrystals give medicinal formulation versatility. They can be readily added to different dosage forms, such as pills powders, or capsules, because they are stable forms, expanding the options for medication delivery(14).

History and Development

As previously stated, cocrystals are supramolecular assemblies that comprise many molecule types within the crystalline lattice. We define a cocrystal more precisely for the sake of this review as follows: A multiple element crystalline solid is created when two chemicals that are crystalline in structure in ambient conditions combine in a stoichiometric ratio. At least one of these substances is polymer (the cocrystal former), and it combines with the other component or components to generate supramolecular synthons. According to this description, reports of cocrystals date back to the 1840s, and several words have been created to describe them: complexes, heteromolecular crystals, organic molecular compounds, and addition compounds (15). The melting the point, the humidity, chemical and chemical stability, filterability, color, and crystallinity of an API are other characteristics that might be changed by the formation of a co-crystal or salt (16). Despite the fact that cocrystals have been around for a while, there wasn't much agreement on the term's definition until a recent paper written by experts in the subject. Cocrystals are minerals that are crystalline single-phase minerals made up of two or more distinct molecular and/or ionic compounds, usually in a stoichiometric ratio, that are neither simple salts nor solvates, according on the viewpoint. It is regarded as a medicinal cocrystal if at least a single of the coformers is the API and the remaining one is approved for use in pharmaceuticals. The idea of grouping cocrystals according to the kind of coformers was first proposed by Paul Pfeiffer in 1922. Stahly published instances of cocrystals with inorganic components in 2009(17). By this definition, cocrystals are therefore different from solvates and hydrates. It should be mentioned that because of their nature, APIs are a prime candidate for crystal growth since they contain one or more external functional groups that can interact with biological targets to produce molecular recognition events, particularly hydrogen bonds. These same reactive group(s) may interact with water ions to generate hydrates and are frequently in charge of various crystal packing configurations (polymorphism) But it wasn't until MC Etter popularized the phrase "cocrystal" in the 1980s that it became generally used, and it wasn't until the 2000s that the term "pharmaceutical cocrystal," or a cocrystal between a pharmaceutical ingredient and a medicinally acceptable cocrystal formation, became frequently utilized. It's interesting to note that pharmaceutical cocrystals have a lengthy history as well, having been recognized since the 1930s at the latest. An even older example of an ionic cocrystallization of a salt and a sugar was glucose:sodium chloride monohydrate(15).The idea of grouping cocrystals

according to the kind of coformers was first proposed by Paul Pfeiffer in 1922. Stahly published instances of cocrystals with inorganic components in 2009. Cocrystals have also been categorized by our study team as "molecular" or "ionic" based on the type of coformers. Molecular cocrystals (MCCs) are usually, but not always' supported by hydrogen or halogen bonds and comprise two or more distinct neutrality coformers in a balanced ratio. This group includes the majority of documented pharmaceutical cocrystals. Braga's research team came up with the phrase "ionic cocrystal" in 2010. Usually, charge-assisted hydrogen bonding and/or bonding by coordination (if metallic cations are present) support ionic cocrystals (ICCs).

Ionic Cocrystals

Ionic Cocrystals (ICCs) have been around since at least 1783, when Romè de l'Ise noticed that when NaCl crystallized from aqueous urea, it changed its behavior. This habit alteration was later ascribed by Bunn (1933) and Steinberg (1937) to the deposition of the urea on certain NaCl crystal faces. Bunn added, "There is one complication; there is a substance NaCl.CO(NH2)2.H2O in the aqueous system, whose structure is unknown." Gerhardt first described ICCs based on the acids carboxylic and carboxylate salts in 1853. Gerhardt examined the chemical that was created when stoichiometric quantities of benzoic acid and potassium hydrogen benzoate were cooled in an alcohol solution. In 1954, the makeup of this ICC was verified. This family of ICCs was categorized as "acid salts" in a later review by Speakman, who also pointed out that "in certain cases the acid salts is easier to made than the moderate salt; it may crystallized selectively while one makes an effort make the neutral salt."(17)

Molecular Crystal

In 1844, W,hler reported quinhydrone, the MCC of quinol and hydroquinone. It wasn't until the 1960s that single-crystal X-ray research verified the composition, revealing that it was a 1:1 MCC supported

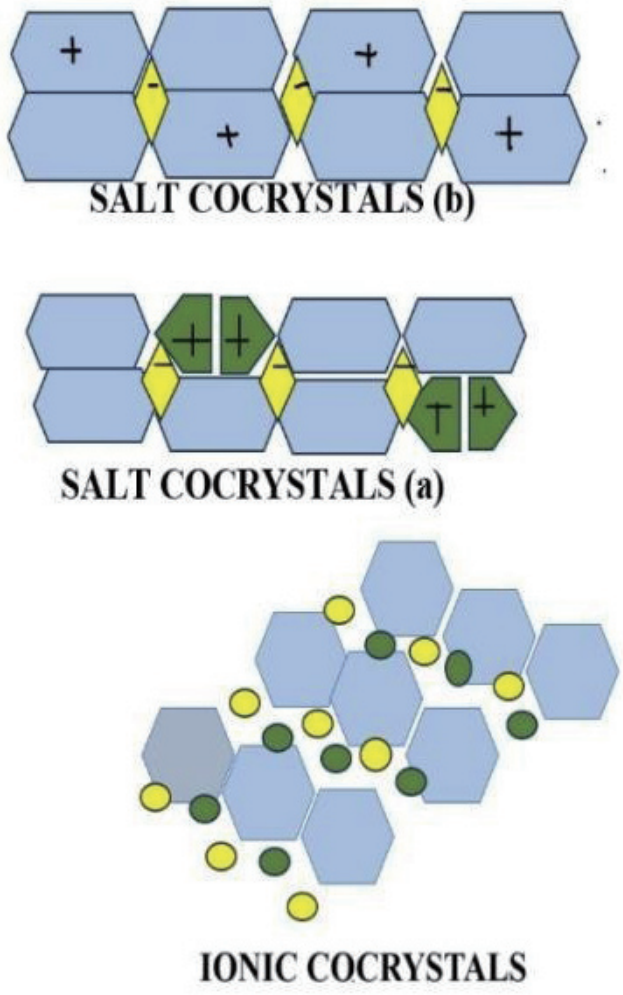

Figure 2. Ionic cocrystal forms

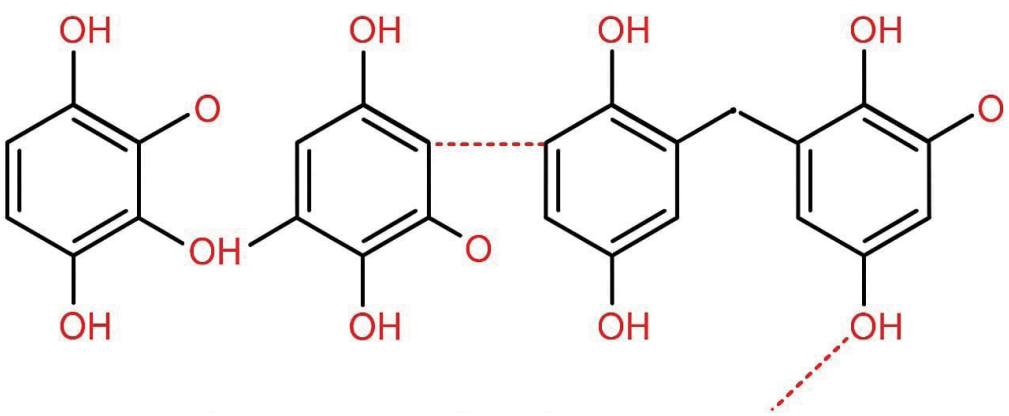

Figure 3. Molecular cocrystals

by a C=O···H-O supramolecular heterosynthon. Von Heyden et al. invented barbiturates including 4oxy-5-nitropyridine, 2-ethoxy-5-acetaminopyridine, Nmethyl-α-pyridine, and α-aminopyridine, which is an early example of an MCC having medicinal application. In the early literature, the terminology of MCCs was inconsistent: Buehler and Heap used the term "molecular organic compounds" to describe the MCCs of 1,2-dinitrotoluene, 2,4-dinitrobenzene, and 2,4-dinitrophenol (D with amino derivatives as a of naphthalene, benzidine, and aniline; Anderson used the term "organic molecular compounds" in 1937. Digoxin and hydroquinones were used as examples of the use of MCCs (referred to as "complex") to improve the efficiency of a drug substance. Digoxin is shown as a therapy of mild mild to moderate heart failure, but its bioavailability and dissolution rate are low, and Higuchi and Ikeda discovered that the mobility of digoxin is increased in the presence of hydroquinone(17).

Classification

Types of Cocrytals	Coformers
Binary cocrystal	Indomethacin: Saccharin (1:1) Naproxen : Nicotinamide (2:1)
Tertiary cocrystal	Isoniazid:4-hydroxybenzoic acid: Fumaric/succinic acid (1:1:1) 3,5-dinitrobenzoic acid: isonicotinamide: 4-(N,N-dimethyl)aminobenz
Qauternary cocrystal	1,3cis,5cis-cyclohexanetricarboxylic acid: 4,4’-bipyridine bases
Ionic cocrystal	Lithium salicylate: L-proline and Nicotinic acid Liþ salts : Amino acids (1:2) Lithium Br/Cl: Glucose (1:1) 6-mercaptopurin: zinc trifluoromethanesulfonate
Synthon polymorphic cocrystal	4-hydroxy benzoic acid: 2,3,5,6-tetramethylpyrazine (2:1) 4-hydroxy benzoic acid: 4,4’-bipyridine (2:1)
Confirmational polymorphic cocrystal	Pimelic acid: 4,4’-bipyridine Nicotinamide: pimelic acid
Packing polymorphic cocrystal	Benzoic acid: 2-aminopyrimidine (2:1) Salicylic acid: N,N’-diacetylpiperazine
Tautomeric polymorphic cocrystal	Piroxicam: 4-hydroxybenzoic acid
Polymorphic cocrystal hydrates/solvates	Isoniazid: 4-hydroxybenzoic acid monohydrate 18-crown-6: 2,5-dichloropicric acid and water (18)

Design of Cocrystal

In the 1990s, rapid advancements in crystal engineering allowed for the design of novel multiplecomponent pharmaceutical compositions (as opposed to high-throughput screening) and greater comprehension of crystal-form variation as represented by polymorphs, salts, solvates, and hydrates. Methodology practitioners have focused testing on identifying the functional categories in medications. A logical method for creating two-component crystals resulted from the realization that the chemical functionality of an API molecule can be addressed by choosing similar groups of function from a different molecule, the coformer(15). The ability to create cocrystals using a simple structure that utilizes supramolecular synthons and the design's modularity, which permits the transfer of cocrystal elements with the goal of enhancing a specific solid-state property, are the two main factors contributing to the quick advancement of cocrystallization as a technique for creating advanced materials. Supramolecular synthons and halide or hydrogen-bonding group functions are constantly being added to the synthon-based layout of cocrystals, increasing the variety of possible compounds and cocrystal components(19). Manufacturability and physico-chemical evaluations are the last stages. Early in the drug development process, salt screening is essential for choosing the best form or forms of an ionized API to move on to the following phases. The experimenter has to evaluate a large number of saltforming agents by selecting those that provide a pKa variations equal to or higher than two units with regard to the drug, since the formation of salt is an acid-base reaction that primarily depends on the pKa that exists between the acid and the base.

When performing salt screening, other factors such solvents, crystallization settings, methods, solubility, chemical properties, and toxicity should be taken into account in addition to pKa(11). In addition, cocrystals were noticeably more soluble than transcinnamic acid. In a different study, coformers were chosen using HSP in order to generate itraconazole cocrystals. Cocrystal formation was predicted using the solvent solubility factor difference (Δδt <7MPa) and the HSP parameters for itraconazole and coformers(20).

Impact of Cocrystalization on API

As was previously mentioned, pharmaceutical companies can enhance API qualities including permeability, bioavailability, and solubility by using multicomponent crystalline materials. When creating a new multicomponent system, these enhanced properties in comparison of a single component API must be experimentally evaluated as they are difficult to forecast or predict. Only a few techniques, such building artificial neural networks, have proved successful in predicting cocrystal qualities. Improved solubility, dissolving rate, and bioavailability are just a few of the positive impacts that might result from these changed qualities. However, there are also some negative effects, such increased toxicity, which may necessitate extensive research before a new cocrystal system is patented (21).

Design Approches

Coformer selection, computational modeling, and cocrystal characterization are the three processes in the medicinal cocrystal design process. Finding appropriate coformers for an API is the primary challenging stage in the formation of a pharmaceutical cocrystal. A choice of coformers cannot be done using any methodical or precise computational technique. some approaches are listed further:

1. Hydrogen Bonding Propensity

This predicts how likely a molecule is to form hydrogen bonds, helping in the selection of coformers for potential cocrystal development.

2. Cambridge Structural Database (CSD)

A vast collection of crystal structures, used to examine intermolecular interactions and guide the identification of viable cocrystal formers.

3. Supramolecular Synthonic Approach

Focuses on identifying and utilizing common intermolecular interaction patterns (synthons) to design cocrystals in a rational and targeted manner.

4. Fabian's Method

A predictive tool that uses statistical and structural data to assess the compatibility of molecules for cocrystal formation, with an emphasis on hydrogen bonding.

5. pKa Rule

Helps distinguish between salt and cocrystal formation based on the pKa difference between interacting components. Large differences favor salts; smaller ones favor cocrystals.

6. Hansen Solubility Parameters (HSP)

Assesses the compatibility of compounds by comparing their solubility characteristics— especially dispersion, polar, and hydrogen bonding forces—to predict cocrystal potential.(18).

Cocrystal Preparation

Numerous techniques, including solid-state grinding, solvent evaporation, solution reaction crystallization, slurry conversion, and hot melt extrusion, have been reported for the creation of cocrystals. The choice of an appropriate cocrystallization technique is still empirical, nevertheless. The most popular techniques for cocrystal production can generally be divided into two categories: solutionbased techniques and solid-based techniques.

Solution-based Method

When the cocrystal is overloaded and its responses (API and coformer) have been either saturated or deficient in the laboratory setting, these approaches work well. There are ternary phases in the solution (solvent, coformer, and API). Consequently, the levels of coformer and API can be utilized to adjust excessive amounts in relation to the cocrystal liquid the solution, which happens to be the key cocrystallization factor. To guide the cocrystal formation process, a phase diagram explaining the criteria for thermal stability must be made. This will stop pure reactions from breaking down and guarantee that the cocrystal stays in the equilibrium temperature zone. The location of mathematically secure The cocrystal phase zones is mostly determined by the reactants' capacity to

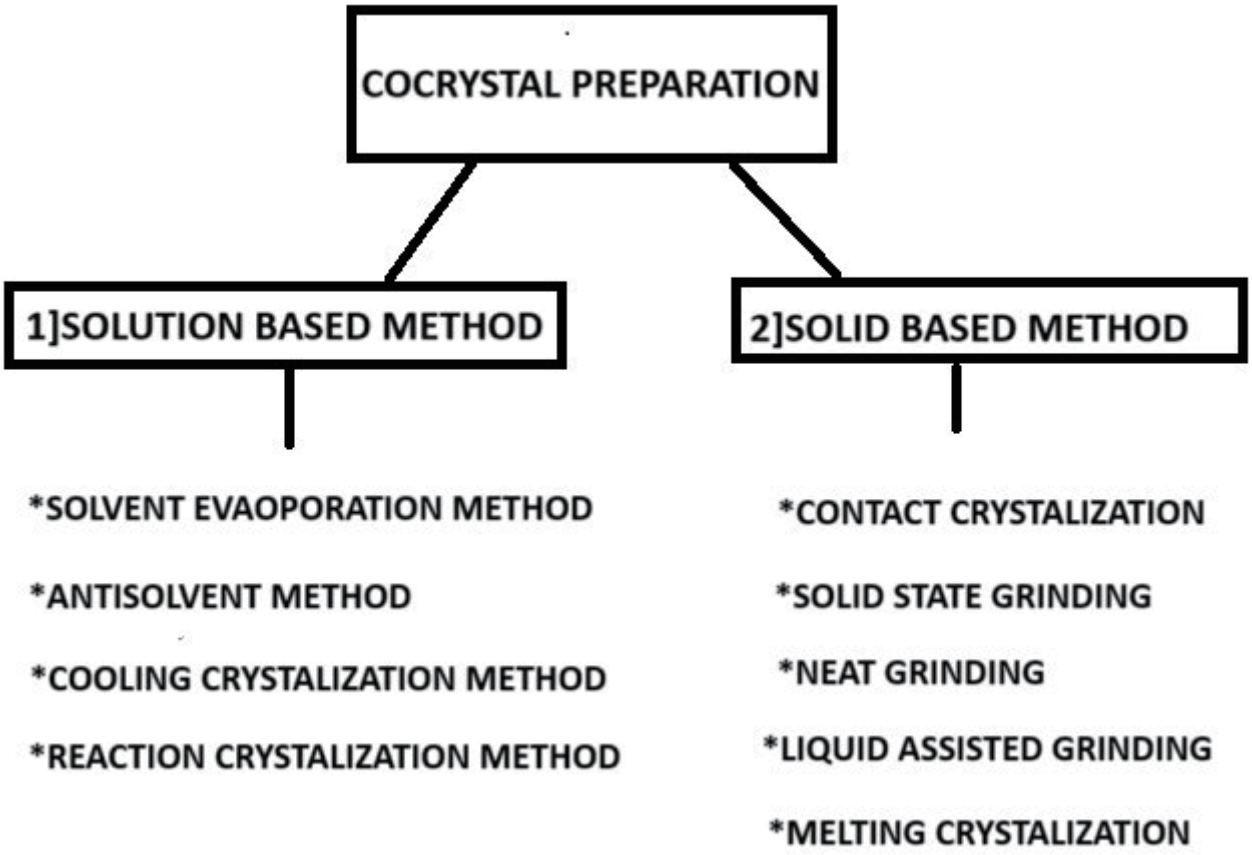

Figure 4. Flow Chart of Cocrystal Preparation

dissolve.

Solvent Evaporation Method

The most popular technique for creating cocrystals is solvent evaporation, which is usually used to create premium single-crystal cocrystals that may be used for single-crystal X-ray diffraction structural investigation. This method involves thoroughly dissolving the cocrystal's ingredients in an appropriate liquid at the right stoichiometric ratio, followed by the solvent's evaporation to yield the cocrystal. The solvent choice affects cocrystallization, which may have an effect on the reactants' solubility. For instance, gradual evaporation of acetonitrile at ambient temperature for 3–5 days produced a blockshaped individual crystal of a 1:1 febuxostat–piroxicam crystals that connected via a carboxylic acid– azole synthon. Compared to the comparable components, the resultant cocrystal showed superior tablet ability and higher solubility. Solvent evaporation was used to extract the nebivolol hydrochloridenicotinamide cocrystals with a higher rate of dissolution.

Antisolvent Method

Antisolvent crystallization, which is carried out in semi batch or ongoing manufacturing processes, has been thought to be an efficient method for controlling the quality, particle size, and characteristics of cocrystals38–42. Chun et al.42, for example, used an anti-solvent approach to create the indomethacin–saccharin cocrystals. Since the solvent's composition may affect the ability to dissolve of the cocrystal and its constituent parts, the cosolvent ratio can have a substantial impact on the yield of cocrystals. At a volume ratio of 1:2 between methanol and water, the yield of carbamazepine-saccharin (CBZ-SAC) cocrystals peaked, while CBZ hydrates would develop below that ratio.

Cooling Crystalization

One popular technique for creating large-scale, pure crystals is cooling crystallization. The local overabundance which is dictated by the process variables, including the alteration of mass and heat, is what determines the crystal the characteristics of dispersal size, purity, morphology, and crystal polymorphism in this procedure. Therefore, in order to make cocrystals, these components must be carefully regulated in accordance with certain solid–liquid equilibria. The cocrystal's stoichiometry and

thermodynamic stability zone at the beginning and ending temperature S determine the operational region during the crystallization process. Numerous research have demonstrated that this approach is a successful plan for increasing the production of cocrystals.

Reaction Crystalization

When the components of a cocrystal have various solubilities, reaction cocrystallization works well. Cocrystal precipitation results from the mixing of reacting agents with nonstoichiometric concentrations to create cocrystal supersaturated solutions. The capacities of reactants to reduce the dissolution of cocrystals governs the nucleation and development of cocrystals in this approach. Through reaction crystallization, meloxicam-salicylic cocrystals50, carbamazepine-saccharin cocrystals, and indomethacin-saccharin cocrystals have been formed. When the components of a cocrystal have various solubilities, reaction cocrystallization works well. Cocrystal precipitation results from the mixing of reacting agents with nonstoichiometric concentrations to create cocrystal supersaturated solutions. The capacities of reactants to reduce the dissolution of cocrystals governs the nucleation and development of cocrystals in this approach. Through reaction crystallization, meloxicam-salicylic cocrystals, carbamazepine-saccharin cocrystals, and indomethacin-saccharin cocrystals have been formed(3).

Solid Based Method

There are two methods for using grinding to create cocrystals. The first technique is tidy grinding, also known as dry grinding, which is combining the balanced cocrystal components and grinding them mechanically in a ball mill or vibratory mill or manually using a pestle or mortar. For this approach to work, one or both of the reactants must have high solid-state vapour pressures. To date, neat grinding has been used to successfully synthesize a wide variety of pharmaceutical cocrystals. Numerous mechanisms, including particle diffusion, electrostatic formation, and transparent phase, have been employed to explain the procedure of neat grinding. In this process, one of each of the distinct temporary bulk phases—a gas, fluid, or an amorphous solid—should show greater movement and/or greater energies of reactant molecules compared to their initial crystalline forms (22).

Since the middle of the 1800s, solid-body grinding has been used to generate co-crystals. Solid-state grinding has gained popularity as a co-crystal production method as a result of the latest technique of injecting tiny volumes of solution during the method of grinding, which was demonstrated to improve the kinetics and encourage co-crystal formation .

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Liquid-assisted grinding, also known as kneading, solvent drop, or wet co grinding, is the second method for cocrystal formation through grinding. The addition of small amounts of the right solvent can result in significant improvements in the dynamics of the creation of cocrystal by grinding. The increased orientational and structural freedom available to molecule at the different interfaces, along with the increased likelihood of molecular collisions, may account for the kinetic gains. To speed up the co crystallization process, it is also possible to envision that during the grinding process, microscopic cocrystal seeds will develop within the solvent.

The type of solvents used in grinding can significantly impact the mechanochemical reaction's course. It has been shown that the SDG approach is a revolutionary way to create a specific cocrystal polymorph of caffeine and glutaric acid. One fundamental criterion for the solvent utilized in grinding is that it must be able to disintegrate at least some of its original parts. Since SDG uses less solvent than the slow evaporation cocrystallization method, it seems to be a dependable, economical, and ecologically friendly technique for both the preparation of pre-existing cocrystals and the finding of new ones(12).

Applications Of Cocrystal

• DDCs of NSAIDs

The most widely used and successful medications for treating soft tissue, low back, and arthritic pain are NSAIDs. These medications function by preventing the cyclo-oxygenases (COX) class of enzymes from producing prostaglandins.

• DDCs of antitubercular drugs

Antitubercular medications are utilized to treat tuberculosis, a chronic infectious condition brought on by the mycobacterium tuberculosis. The Digital control units of antitubercular medications reported within the past ten years. Three of the thirteen DDCs

that were reported have not had their pharmacological characteristics assessed. The ten additional DDCs showed a range of pharmacological improvements.

• DDCs of diuretic drugs

The only medication used to treat hypertension is a diuretic. To treat more severe types of hypertension, diuretics can also be used in conjunction with other antihypertensive medications.

• DDCs of the other APIs

Seven DDCs' pharmacological qualities had not been assessed. Eight of the nine DDCs had better dissolving characteristics, while two of them had better stability. According to Sathyanarayana et al., a DDC made of nicotinamide and zoledronic acid has a 20-fold more soluble content than zoledronic acid. A DDC with an improved IDR that contained nicotinamide and febuxostat was described by Nangia et al (10).

Challenges

Molecular Compatibility

• **Hydrogen bonding and interaction mismatch:** Not all APIs have compatible functional groups or sufficient intermolecular interactions to form a stable cocrystal.

• **Molecular size and geometry:** Structural incompatibilities can prevent effective packing in a crystal lattice(24).

Thermodynamic and Kinetic Barriers

• **Polymorphism and phase transitions:** For example, the cocrystal that forms between pimelic acid and nicotinamide has polymorphic behaviour, with different forms showing varying phase transition temps and stabilities (25).

Solubility and Bioavailability

• **Dissolution behavior:** The intricacy of forecasting cocrystal dissolution profiles was highlighted by a study that examined the mechanism of dissolution of carbamazepine cocrystals and discovered that the solvent advantage over the parent drug changed with the pH level and the presence of solubilizing chemicals. The study was published in Molecular Pharmaceutics (26).

Analytical and Characterization Challenges

• Stability testing difficulties: Theophylline cocrystal stability studies, for instance, showed that temperature and humidity affected the cocrystal's stability, highlighting the significance of thorough stability evaluations (28).

• **Drug-drug interaction concerns:** A careful assessment of possible pharmacological and pharmacokinetic interactions is required when co-forming APIs (29).

Previous Work Done on Cocrystal

Author(s)	Year	Focus Area	Key Findings	Reference / Link
Aitipamula et al.	2012	Overview of pharmaceutical cocrystals	Cocrystals enhance solubility, stability, and bioavailability without altering pharmacology.	Aitipamula, S. et al. (2012), Adv. Drug Deliv. Rev., DOI:10.1016/j.addr.2012.04.003
Shan and Zaworotko	2008	Crystal engineering for drug delivery	Crystal engineering enables design of cocrystals using supramolecular chemistry.	Shan, N. & Zaworotko, M.J. (2008), Drug Discovery Today, DOI:10.1016/j.drudis.2008.01.006
Schultheiss and Newman	2009	Pharmaceutical cocrystal landscape	Reviewed over 130 pharmaceutical cocrystals.	Schultheiss, N. & Newman, A. (2009), Cryst. Growth Des., DOI:10.1021/cg900005u
Duggirala et al.	2016	Pharmaceutical applications and challenges	Addressed manufacturing, regulatory, and formulation concerns.	Duggirala, N.K. et al. (2016), J. Pharm. Sci., DOI:10.1016/j.xphs.2015.10.002
Berry and Steed	2017	Therapeutic applications of cocrystals	Cocrystals applicable in pain, antimicrobial, and inflammation therapy.	Berry, D.J. & Steed, J.W. (2017), Adv. Drug Deliv. Rev., DOI:10.1016/j.addr.2017.03.003
Vishweshwar et al.	2006	Structural aspects of cocrystals	Explained hydrogen bonding motifs crucial for cocrystal design.	Vishweshwar, P. et al. (2006), J. Pharm. Sci., DOI:10.1002/jps.20526

Garg & Azim	2021	NSAID cocrystals and formulation strategies	Discussed opportunities and formulation approaches for NSAID cocrystals, focusing on development challenges.	Garg & Azim (2021), DOI:10.1039/D0MD00400F
Xu et al.	2023	Flavonoid-based pharmaceutical cocrystals	Summarized recent advances in flavonoid cocrystals and their potential in improving pharmacokinetics.	Xu et al. (2023), Molecules, https://doi.org/10.3390/molecules28020613
Nangia	2008	Improving drug properties with cocrystals	Highlighted the emerging role of pharmaceutical cocrystals in modifying drug properties.	Nangia, A. (2008), Cryst. Growth Des., DOI:10.1021/cg700736x

Conclusion

Pharmaceutical cocrystals offer notable enhancements in drug solubility, dissolving rate, strength, and mechanical behaviour, making them a revolutionary approach to drug development. In contrast to traditional techniques, co crystallization offers a flexible and effective way to enhance the functionality of less soluble APIs without changing their inherent pharmacological characteristics. The path for their use in business formulations is growing more feasible due to the variety of cocrystal synthesis and screening methods that are now available as well as the advancement of regulatory recognition. To fully exploit the promise of cocrystals as a vital tool in the toolbox of pharmaceutical scientists, more research and cooperation amongst the two sectors are essential.

Conflict of interest

The authors declare that there is no conflict of interest.

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