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Research Article

AN OVERVIEW ON FABRICATION, PHARMACEUTICAL PROPERTIES, CHARACTERIZATION AND APPLICATIONS OF PHARMACEUTICAL COCRYSTALS

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ABSTRACT

Cocrystals are the idea of supramolecular chemistry to what end they are obtaining the substantial attentiveness of researchers belonging to chemical and pharmaceutical science and the medicament regulatory agencies. Although, these cocrystals set up their site in pharmaceuticals, mainly because of their capacity to change the physicochemical effects without understanding the constitutional coherence of API and consequently, maybe, the bioactivity. This article is deliberated to merge literature working on cocrystallization, a gadget for increasing solubility and for developing the properties of active pharmaceutical ingredients with exceptional significance on the mechanism behind it. Although, the formation of pharmaceutical cocrystals can be challenging, consequently decreasing the translation into feasible drug by-products. This review additionally furnishes a short introduction to the cocrystals nature. These pharmaceutical cocrystals are appearing as a new category of solid drugs with the upgraded physicochemical effects, to what end fascinated improved interests belonging to both academic and industrial researchers. The properties of different drugs had been accessible on the pharmaceutical market for an old-time required to be upgraded. The impact of choosing suitable preparation and design on these challenges has been discussed. Cocrystallization is an appearing proceed towards to increase dissolution profile, solubility, bioavailability, and some other mechanical and physicochemical effects of an active pharmaceutical ingredient Cocrystals the collection of active pharmaceutical ingredients and pharmaceutically tolerable coformer.

Keywords: Cocrystals, Coformers, Polymorphs, Dissolution, Solubility.

INTRODUCTION

According to the US FDA cocrystals can be defined as "dissociable active pharmaceutical ingredient- excipient molecular complexes (with the neutral guest compounds being the excipient named coformers) in that active pharmaceutical ingredient and excipients both exist in the same crystal lattice". Not long-ago United States food and drug administration publicize draft guidance, according to that cocrystals are defined as" crystalline materials are made up of 2 or more different molecules within the same crystal lattice that is associated by unionized and noncovalent bonds". The character of crystal engineering theories bin the choice of suitable coformers and the identity of supramolecular synthons nearby inside the crystals are reported. In modern times, the cocrystal development has appeared as an applicable plan of the act to upgrade the bioavailability and solubility of imperfectly soluble drugs. The cocrystal and salt development are the most frequently utilized procedure of improving dissolution and solubility rate of pharmaceutical combinations and are of specific attentiveness for the combinations at a low aqueous solubility with an intermediate. There is a short exchange of the influence on polymorphism and the main utilization of stoichiometric amorphous amalgams and the salts for stabilizing the amorphous structures and some more

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important matters for the compensation belonging to the pharmaceutical formation perspective.

Active pharmaceutical ingredients and co farmers should contain functional groups, to get the cocrystals that can form either homo or hetero super molecular-super molecular synthon formation of the noncovalent bond between Active pharmaceutical ingredient and coformers leads to the generation of crystal lattice repeatedly. In the general, the ratio of API and coformer is either 1:1, 1:2, 1;3 or vice versa (Korotkova *et al.,* 2014). The main purpose of cocrystal development is for enhancing the solubility and bioavailability of poorly soluble drugs. Solubility and Dissolution place an important role in detecting the potency as well as activity of the drugs. Based on physicochemical properties of the drug modifications are done to improve the stability, solubility or mechanical properties for ionized compounds its salt form is one of the best methods to enhance solubility (Rajput *et al.,* 2013; Saal *et al.,* 2013). That property can be enhanced by the synthesis of solvates (Skieneh *et al.,* 2016) and hydrates (Khandavilli *et al.,* 2014). The pharmacokinetic properties of the drug can be regulated by the use of specific polymers. Nonionizable compound properties can be altered by cocrystals formation (P. Vishweshwar *et al.,* 2006). The province of pharmaceutical cocrystals has come to a tipping point, specifically because cocrystals can be better the properties of medication without negotiating their therapeutic benefit.Recent researchers on cocrystal development and application to the pharmaceutical formulation as focus on enhancing material handling during processing, storage, stability, and dissolution of

API (Brittain *et al.,* 1979). Cocrystal can be further classified into two subclasses: Ionic cocrystals (ICCs) and salt cocrystals (SCCs) (Cerreia Vioglio *et al.,* 2017). Ionic co-crystals contain active pharmaceutical ingredients and organic alkaline or alkaline earth salt both are present in the same crystal lattice. Salt cocrystals contain active pharmaceutical ingredients and coformers within the same crystal lattice, where one of the constituents is satisfied. Although, both forms involve the same basic constituent, such as salt (inorganic or organic) and organic molecules, in the crystal lattice (Braga *et al.,* 2010). Some solid-state strategies and their respective components are displayed in Figure 1.

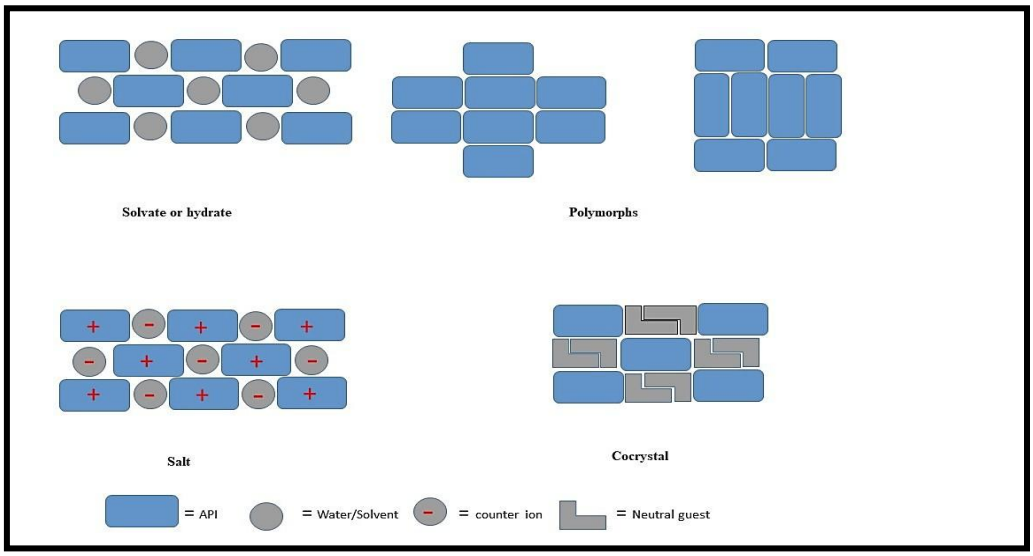

Figure 1. Pictures displaying the more common solid-state strategiesand their respected components.

POLYMORPHISM IN COCRYSTALS

Polymorphism

In Modern times, the outline and combination of multicomponent crystals like cocrystals have acquired remarkable interest because of the capacity of cocrystals to change the material characteristics for pharmaceutical and Material Sciences applications. In pharmaceuicals, in contrast to the medicaments, the cocrystals of many vital active pharmaceutical ingredients came to appear property enhancement (Schultheiss *et al.,* 2009). In substances science, effects like mechanical strength, photoluminescence, etc. came to be adjusted utilizing cocrystals (Yan *et al.,* 2011). This stimulated a remarkable scientific debate and many writers have utilized many variables to specify what accounts for cocrystals and by what means cocrystal constituents are interrelating with one another. Although, many writers accept a definition that defines the cocrystals as crystalline constituents made up of not less than two separate neutral components which are solids less than ambient circumstances and existed in specific stoichiometric quantities (Aakery *et al.,* 2005).

The Crystal in conformations with clear crystal formations of identical chemical compounds is mentioned as polymorphs (Aakeröy *et al.,* 2005). Exploring the polymorphic way of behaving of Active Pharmaceutical ingredients is the analytic role of the drug development

procedure. It is due to polymorphism can very much impact the pharmaceutical effects like solubility, hygroscopicity, stability, bioavailability, etc., and profitable importance of narrative polymorphs as cognitivecharacteristics (Brittain *et al.,* 1999). Greater than 50% of drug particles are roughly calculated as polymorphic (Aitipamula *et al.,* 2013) (Figure 2). The abundant polymorphic cocrystals being described have remarkably raised in modern years, although, because of growing interest in the n evolution of cocrystals (Aitipamula *et al.,* 2010).

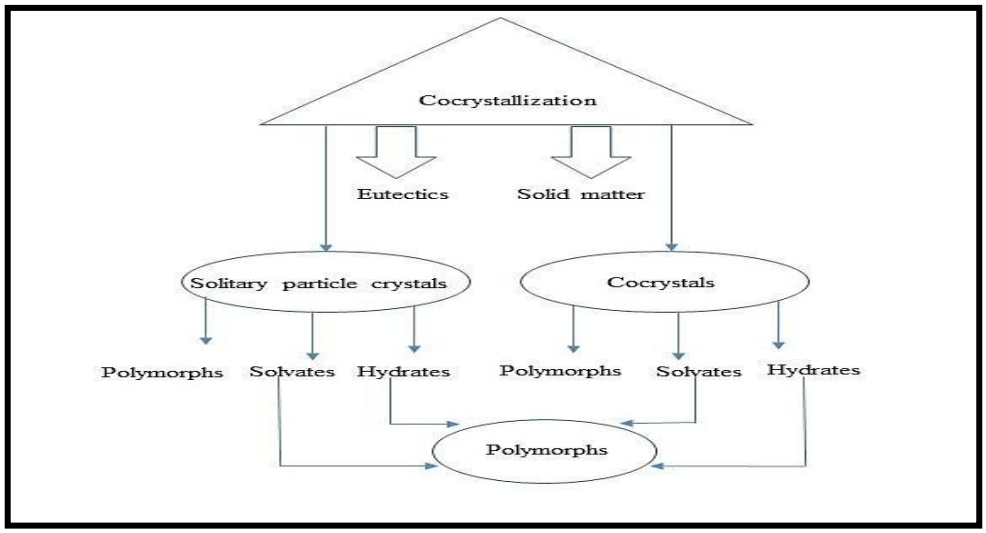

Figure 2. Several viable results of aimed co-crystallization examination**.**

Screening of polymorphs of cocrystals

Despite some results-focused especially at polymorph screening of cocrystals, they furnished variant procedures that are useful for cocrystal polymorph screening. Solid-state grinding past it extensively utilized to cocrystal screening along with the that-based co-crystallization method (Almarsson *et al.,* 2004). The method is done for proving to remarkably upgrade the Kinetics of cocrystal formation and give highly crystalline cocrystal outcomes of quantitative yields (Trask *et al.,* 2005). Through the grinding, the 1:1 cocrystal of Ethenzamide with ethyl malonic acid which is a second polymorph was initially identified.

In Modern Times, Bysouth *et al* altered a planetary mill which is having the ability to perform 48 experiments eventually. For the preparation of inorganic are metal-organic material, solvothermal synthesis or hydrothermal synthesis are mostly used methods. and besides utilized cocrystal polymorph screening. In Modern Times, this method was appealed by Wang *et al*, to make a cocrystal implying 1,2-bis(4-pyridyl) ethylene (BPE) and 4,4'- di hydroxyl benzophenone (DHB) (Brittain *et al.,* 2013). Pulham and co-workers came to be delightfully assessed regarding the high-pressure locations in inquiring about novel polymorphs recently (Sladkova *et al.,* 2015), suggesting the fastest technique for screening new cocrystals by the fast evaporation of solvent through the Rotary evaporator. By including CBZ and SC, the writer signified the amalgam of metastable polymer of cocrystals. The metastable Polymers of cocrystals are formed by facilitating the crystallization kinetics and availability of higher levels of supersaturation. Alhalaweh and Velaga revealed the nearer technique of kinetically controlled cocrystallization by utilizing spray drying. Moreover, it shall be emphasized hear that engaging through screening won't contract the cocrystal polymorphs finding. There are some outcomes by the polymorphy after screening by the 1:1 phenazine-mesaconicacid (Table.1).

Table 1. Outcomes by the polymorphy after screening by the1:1 phenazine-meraconic acid.

S. No	Co crystallization techniques	Form of Cocrystal
1	Cocrystallization of mixture, melting, crushing, hydratesdesolation	Form-1
2	Dimethyl sulfoxide solvate desolation, cocrystallization onjunction of two suspensions	Form-2
3	Thermogravimetry, melting point	Form-3

Classification of co-crystal polymers

The benefits of these classifications are the polymorphism behavior and the contrast in the middle of different cocrystal structures are simply demonstrated.

Synthon polymorphs

Synthon polymorphs are classified based on the difference in the primary hydrogen bond motifs or synthons. The classic example of these Synthon Polymers in single component crystals is Polymers of tetrolic acid: The beta form consists of a catemer synthon and the Alpha form consists of acid-acid dimer synthon (A. J. Blake *et al.,* 2004). From many hydrogen bond synthons, the Synthon polymorphism that appeared has also been described in cocrystals. For example, Synthon polymers of 2,3,5,6-tetramethyl pyrazine (TMP) and 4- hydroxybenzoic acid(4HBA) in the ratio of 2:1 have also been reported by Srikanth *et al*. In Modern Times, the same type of synthon polymorphism was reported in a cocrystal consisting of 4HBA and 4,4'- bipyridine (Bassavoju *et al*., 2006). Particles that consist of the different hydrogen bonding potentialities seem to be further liable to given synthon polymorphs.

Conformational polymorphs

The phenomenon of different atomic conformations in many polyps is mentioned as conformational polymorphism. In common, the low-energy coformers and the malleable molecules with many degrees of torsional freedom are further liable to give away the conformational polymorphism. The greatest phenomenon of polymorphism in active pharmaceutical ingredients is done for imputing to the malleable molecular structures. Regarding cocrystals, many described polymorphic cocrystals property many coformers of different cocrystal constituents, and consequently can be categorized as conformational polymorphs. For example, the modern polymorphic cocrystals of NCT-pimelic acid (1:1) (Karki *et al.,* 2009), Ethenzamide gentisic acid (1:1) (Aitipamula *et al.,* 2009), and Ethenzamide ethyl malonic acid (1:1) (S. Aitipamula *et al.,* 2010) all properties many conformers of different cocrystal constituents.

Packing polymorphs

Whenever there will be a difference in completely three-dimensional oval crystal packing, then the polymorphs are categorized as packing polymorphs. For example, chlordiazepoxide, p- nitrophenol, and sulfathiazole all show minor variations in confirmation but they will exhibit differences in complete crystal packing. The skovosgaard and Bond announced two cocrystals that appear for packing for polymorphism in cocrystals. The announced polymorphic cocrystals consisting of hard constituents are examined for recognizing the packing similarities and differences. The compelling packing polymorphism was observed in the polymorphs of 1:1 cocrystal including BPE and 4- cyano phenol(4CP) (Bailey Walsh *et al*., 2003). The polymorphic 2:1 cocrystal including 4- cyano pyridine and 4,4'- biphenol was also announced by the same authors [24]. These polymers do not show variations only in their intermolecular interlinkage, additionally, they characteristic many coformers of 4,4'- bi phenol moiety, so it can be treated as synthon and conformational polymorphs.

Tautomeric polymorphs

These tautomeric polymorphs are designated when the solidification of many tautomers amalgam in various crystal forms takes place. Normally, tautomerism takes place when the constitutional isomers are present in dynamic equilibrium accordingly with various hydrogen atom affinities. Tautomers are said to the be same chemical constituents when they are intercorrelated in a solution and consequently these types of tautomers in the Crystal forms are categorized as polymorphs (Desiraju *et al.,* 2011). Active ingredients like sulfasalazine (Blake *et al.,* 2004), omeprazole (Duggirala *et al.,* 2016) and triclabendazole (S.Tothadi *et al.,* 2012) came to be described to consist of various tautomers in polymorphic structures.

Physicochemical properties

Crystalline materials derive their key physical characteristics from the molecular arrangements within their solid structures. Modifying the positioning or interactions among these molecules can significantly influence the properties of the resulting solid (Seddon *et al.,* 1999). The physical and chemical characteristics of a cocrystal must be evaluated similarly to any other solid form to assess its potential for development into a viable dosage form (Elder *et al.,* 2013). Salt formation remains one of the most widely used solid-state approaches to improve the physical properties of active pharmaceutical ingredients (APIs), with estimates suggesting that more than half of marketed drugs are formulated as salts (Shan *et al.,* 2008). Properties such as crystallinity, melting point, solubility, dissolution behavior, and stability are vital considerations when advancing new compounds, including cocrystals, through early development stages (Qiao *et al.,* 2011).

Melting Point

The melting point is a critical physical property defined by the temperature at which a solid and its liquid phase exist in equilibrium. It represents a thermodynamic process where the free energy change for the solid-to-liquid transition equals zero, and the value is determined by the ratio of the enthalpy of fusion to the entropy of fusion (Shimanovich *et al.,* 2012). Differential Scanning Calorimetry (DSC) is the most widely utilized technique for determining accurate melting point data, also providing valuable thermal information such as the enthalpy of fusion. For example, both melting point and heat of fusion obtained via DSC are used to classify polymorphic systems as either monotropic or enantiotropic (Byrn *et al.,* 1999). Although melting point measurement is commonly used for compound identification or purity testing, in pharmaceutical sciences

it is also crucial because of its relationship to aqueous solubility and vapor pressure (Abramowitz *et al.,* 1990).

Stability

Stability is a key parameter during the development of any new chemical entity. Multiple types of stability assessments are necessary depending on the molecular structure and properties. Chemical and physical stability studies performed under accelerated conditions help predict the compound's shelf life and suitability for development (Cavallari, *et al.,* 2017). The main types of stability assessments include: a. Relative humidity stress, b. Thermal stress, c. Chemical stability, d. Solution stability

Relative humidity stress

As with many solid forms, transitions under varying relative humidity (RH) conditions are vital considerations in cocrystal development (Reutzel-Edens *et al.,* 2006). Automated moisture sorption and desorption tests are typically used to identify potential issues and guide further studies. X-ray Powder Diffraction (XRPD) analyses of samples after moisture testing can confirm the final form, though they may not always reveal intermediate transformations. Limited data exist on water sorption behavior for cocrystals. For instance, a 1:1 indomethacin/saccharin cocrystal exhibited negligible water uptake (0.05%) up to 95% RH (Basavoju *et al.,* 2008), indicating no solid-state transformation. Similarly, a 1:1 AMG 517/sorbic acid cocrystal absorbed only 0.7% water at 90% RH, with XRPD confirming retention of the initial form (Bak *et al.,* 2008). A glutaric acid cocrystal of 2-[4-(4-chloro-2-fluorphenoxy) phenyl] pyrimidine-4-carboxamide also showed minimal water uptake (<0.08%) up to 95% RH, with no form change after 2 months at 40°C/75% RH (Namara *et al.,* 2006). These results suggest such cocrystals are likely stable under normal storage and processing conditions, minimizing development risks.

Thermal stress

Thermal stress testing is another standard method used to assess both physical and chemical stability under accelerated conditions (Bethune *et al.,* 2011). For example, an 8-week exposure of a monophosphate salt cocrystal with phosphoric acid at 60°C showed no observable degradation or phase transformation (Chen *et al.,* 2007). Further studies, such as those on paracetamol cocrystals with 4,4′-bipyridine, 1,4-dioxane, N-methylmorpholine, morpholine, N, N-dimethylpiperazine, and piperazine, analyzed by DSC, demonstrated that only the paracetamol/4,4′-bipyridine cocrystal maintained the guest molecule upon heating, displaying a melting endotherm corresponding to monoclinic paracetamol (Oswald *et al.,* 2002). Such studies provide critical insight into the impact of temperature on solid-state stability, aiding in the optimization of drying, processing, and accelerated stability conditions.

Chemical stability

Chemical stability assessment is essential during both compound development and formulation to minimize potential degradation. Accelerated testing, typically conducted at 40°C/75% RH and 60°C/75% RH, is used to predict long-term performance. For example, the monophosphate salt–phosphoric acid cocrystal showed no significant degradation after 8 weeks at these conditions (Chen *et al.,* 2016). Similarly, the glutaric acid cocrystal of 2-[4-(4-chloro-2-fluorphenoxy) phenyl] pyrimidine-4-carboxamide exhibited no increase in impurity levels after 2 months under the same conditions Namara *et al.,* 2006). Such data help identify and prevent potential degradation pathways during development.

Solution stability

Solution stability refers to a cocrystal's ability to remain intact in solution without dissociating or recrystallizing. This property is particularly relevant for both liquid formulations and solid dosage forms that dissolve in the gastrointestinal tract. Stability studies in aqueous environments help identify possible transformations, such as hydrate formation. For instance, a 2:1 caffeine/oxalic acid cocrystal remained unchanged after 7 weeks at up to 98% RH and 2 days of slurrying in water (Trask *et al.,* 2005). Similarly, in a 1:1 carbamazepine/saccharin cocrystal, slurrying with carbamazepine dihydrate and saccharin in solution for 24 hours revealed only the cocrystal phase by XRPD, indicating its thermodynamic stability in the presence of its components (Hickey *et al.,* 2007).

Intrinsic Dissolution

Intrinsic dissolution measures the dissolution rate of a compound independent of particle size, typically using a compacted disk or pellet placed in a dissolution medium (Childs *et al.,* 2008). The concentration of dissolved material is monitored over time to calculate the dissolution rate (mg/cm²·min). Although limited studies exist for cocrystals, available data indicate significant improvements. For example, the glutaric acid cocrystal of 2-[4-(4-chloro-2-fluorphenoxy) phenyl] pyrimidine-4-carboxamide exhibited a dissolution rate approximately 18 times faster than the parent compound in water over 90 minutes (Namara *et al.,* 2006).

Solubility

Solubility is one of the important factors to investigate poorly soluble drugs many Approaches have been used to improve the solubility of drugs such as salt formation, solid dispersion, particle size reduction (M. C. Namara *et al.,* 2006), among them co-crystallization has been utilized, by several researchers (Martin *et al.,* 2013). Solubility of antifungal drug ketoconazole was enhanced 53 and a hundred times by synthesizing salts and cocrystals respective compared to ketoconazole. Thus, higher solubility of the drug was obtained by cocrystals as compared to salt formation (Martin *et al.,* 2013). The

solubility of cocrystal was increased about 2 times and cocrystals showed faster dissolution compared to the pure drug (Chen *et al.,* 2016) Cocrystal of antitumor drug 6-mercaptopurine with nicotinamide showed 2 times higher dissolution compared to pure drug (Wang *et al.,* 2015). Summary of some cocrystals is given in table 2.

Table 2. Some of the examples of cocrystal works.

S. No	Active pharmaceutical ingredients	Coformer	Reference
1	AMG 517	Benzoic acid	M. K. Stanton *et al*., 2008.
2	Aspirin	4-4'-bipyridine	R. D. Bailey Walsh *et al*., 2003.
3	Carbamazepine	salicylic acid	S. L. Childs *et al*., 2008.
4	Carbamazepine	Benzo quinine	S. G. Fleischman *et al*., 2003.
5	Chlorzoxazone	4-hydrox benzoic acid	S. L. Childs *et al*., 2007
6	Ethyl paraben	Ricotinamide	S. Nicoli *et al*., 2008
7	Fluoxctine HCl	Fumaric acid	S. L. Childs *et al*.,2004
8	Ibuprofen	4-4'-bipyridine	R. D. Bailey Walsh *et al*., 2003.
9	Norfloxacin	Isonicotin-amide	S. Bassavoju *et al*., 2006.
10	Piroxicam	Saccharin	Intrinsic dissolution and woods apparatus.US Pharmacooeia.,2008
11	Caffeine	Gallic acid	A.V. Trask *et al*., 2004
12	Celecoxib	S-valerolactam	G. Bolla *et al*., 2014
13	Isoniazid	Caffeic acid	B. Swapna *et al*., 2014
14	Ethenzamide	Saccharin	S. Aitipamula *et al*., 2010
15	p-coumaric acid	Nicotinamide	M.J. Bevil *et al*., 2014

SELECTION OF APPROPRIATE COFORMER AND PREPARATION OF COCRYSTALS

Co-former Selection

The selection of a suitable coformer is generally guided by the "synthon approach", which focuses on constructing a supramolecular structure within the cocrystal through specific molecular fragments known as supramolecular synthons. According to this approach, the functional groups present on both the drug and coformer play a crucial role in cocrystal formation. For effective cocrystallization, coformers possessing complementary functional groups to those of the drug should be selected. Common examples of supramolecular synthons include carboxylic acid–carboxylic acid dimers, amide–amide synthons, and acid–amide synthons. However, the synthon approach does not consider factors such as competition among multiple functional groups within the active pharmaceutical ingredient (API) or coformer, nor does it account for steric hindrance around donor and acceptor sites. Therefore, selecting coformers based on shape and polarity complementarity has been suggested to improve the likelihood of successful cocrystal formation. Hunter, Price, and their collaborators have evaluated computational techniques to predict the outcomes of different cocrystallization processes, while Galek *et al*. (2007) developed a knowledge-based approach for anticipating cocrystallization results.

Preparation of Cocrystals

Once potential coformers are chosen, several methods can be employed to prepare cocrystals, including solution crystallization, mechanical grinding, and melt crystallization. Among these, solution crystallization is the most frequently used technique. In this method, the cocrystal components are dissolved in a suitable solvent at an appropriate stoichiometric ratio, and cocrystals are obtained through solvent evaporation or cooling. Reaction crystallization, a solution-mediated process, enables cocrystal formation without the need for evaporation or cooling. Here, the individual components do not crystallize independently, as the solution becomes supersaturated only with respect to the cocrystal. This technique can also be influenced by vapor sorption of cocrystal components or moisture absorption by excipients such as sugars and polymers.

The mechanochemical approach, which involves grinding the solid components, can be conducted either without solvent ("neat grinding") or with a small amount of liquid ("liquid-assisted grinding"). Liquid-assisted grinding is often more efficient for screening purposes compared to solution methods, as minimal liquid facilitates cocrystal formation through reactions occurring in a thin liquid film or amorphous phase. Besides solution, grinding, and melt methods, other techniques like fast evaporation, supercritical fluid processing, and antisolvent addition have also been employed for cocrystal synthesis.

COCRYSTAL FORMATION METHODS

Cocrystals can be synthesized through solution-based, solid-state grinding, or other specialized methods. The solution crystallization technique is suitable when both components possess adequate solubility, though this does

not guarantee cocrystal formation. Adequate solubility of both materials is essential to prevent simple precipitation (S. Bassavoju *et al.,* 2006). The grinding method, which includes dry (neat) and solvent-assisted approaches, can yield results comparable to solution techniques. The solvent-assisted process generally produces better outcomes due to enhanced reaction kinetics and improved molecular interactions, facilitating efficient cocrystal formation (A. Yadav *et al.,* 2009).

Cooling Crystallization

Cooling crystallization is a scalable method involving temperature-induced crystallization. In this technique, reactants and solvent are mixed in a jacketed vessel, heated to dissolve all solutes, and then gradually cooled, resulting in supersaturation and subsequent precipitation of cocrystals. This method has been successfully used to prepare cocrystals of caffeine and para-hydroxybenzoic acid (B. Swapna *et al*., 2014).

Evaporation Cocrystallization

Evaporation cocrystallization involves dissolving equimolar quantities of the components in a suitable solvent, followed by solvent evaporation to form cocrystals. This approach is effective when both components exhibit comparable solubility in the chosen solvent. Prior assessment of reactant solubility is essential for designing efficient and reproducible experiments (G. W He *et al.,* 2008).

Reaction Crystallization

This method is beneficial for systems in which the two constituents have unequal solubilities. In reaction crystallization, one reactant is introduced into a saturated or nearly saturated solution of another, creating a supersaturated environment conducive to cocrystal formation. When nonequivalent concentrations are used, improved yields are often obtained. For example, carbamazepine cocrystals have been successfully prepared using this method (Bis *et al.,* 2007).

Grinding Method

The neat grinding method (also called dry grinding) involves mixing the cocrystal components in stoichiometric proportions and grinding them manually (using a mortar and pestle) or mechanically (using a ball mill or vibratory mill). Adequate vapor pressure of one or both solids is essential for effective grinding. The formation mechanism may involve molecular diffusion or eutectic formation. In contrast, liquid-assisted (wet) grinding enhances the kinetics of cocrystal formation by introducing a small amount of solvent, promoting better interaction between the components. This approach is cost-effective, environmentally friendly, and widely used for screening and synthesis of pharmaceutical cocrystals (D. Braga *et al.,* 20010).

Other Methods

Additional techniques for cocrystal synthesis include the supercritical fluid method, ultrasound-assisted crystallization, and spray drying. For instance, carbamazepine–nicotinamide cocrystals have been successfully produced using the nano spray drying technique (N. Blagden *et al.,* 2007).

MECHANISM OF SOLUBILITY ENHANCEMENT

Cocrystal solubility is influenced by two primary factors: crystal lattice strength and solvation behavior of the cocrystal components. A reduction in lattice energy coupled with enhanced solvation affinity can lead to improved solubility. Cocrystals can affect both parameters to varying degrees. When solvation resistance is minimal, solubility is largely determined by lattice interactions, whereas solvation plays a more dominant role for hydrophobic drugs in aqueous media.

The solubility of a cocrystal often correlates with the solubility of its coformer, as higher coformer solubility reduces the solvation barrier for the cocrystal. Pinal and colleagues demonstrated this relationship for carbamazepine cocrystals by separating the lattice and solvation contributions using a solvent-based graphical approach. Their findings showed that solvation can reduce the observed solubility by an order of magnitude in organic solvents and by up to three orders in water. Additionally, the melting point of cocrystals has been found to be a poor predictor of aqueous solubility, indicating that solvation effects often outweigh lattice energy considerations.

CHARACTERIZATION OF PHARMACEUTICAL COCRYSTALS

Structure of cocrystals:

Cocrystal consists of a stoichiometric group of molecules that interact through non-ionic forces. From the blend of many acidic, basic or neutral active pharmaceutical ingredients with coformers, these cocrystals are aggregated. Frequently, in cocrystals, the molecular constituents are less filled up than compared to other crystals (S. L. Childs *et al.,*2004). To the quality control for pharmaceutical cocrystals, the complete crystal composition may supply the theoretical basis, that is attained by the powerful single-crystal XRD technique.

The reasonable structural statistics regarding cocrystals a provided by recent advances in clarifying from powder XRD(PXRD) facts (S. L. Childs *et al*., 2007). The rise of polymorphs is due to a bit of API- conformer combinations, equally as caffeine- glutaric acid and carbamazepine (CBZ)- malonic acid] rely on production methods and process parameters. In many familiar coformers, the different functional groups like organic acids, and their capability to create numerous hydrogen bonds provide mixed stacking arrangements framing the crystal lattice by the many combinations of interactions.In

a few cocrystals like sulfadimidine- 4- aminosalicylic acid crystals, there will be having identical crystal lattices that differ in appearance and formulation 11 physical effects when fabricated by separate procedures.

Salts, Hydrate, Solvates, and Cocrystals

There are identical crystal structures, consisting of API and the second component in salts,hydrates, solvates, and cocrystals. Based on the identity of the organic acid the Crystal consists of active ingredients, for example, minoxidil, and organic acids are classified as salts, cocrystals, or solvates. The border in the middle of salts and cocrystals and procedures for differentiating process delighted become greater observation due to scientific interest and non-identical regulatory essentials (Aitipamula *et al*., 2010).

The attribute property of salt crystals is happening of proton training interactions reactions in the middle of the constituents (A.V. Trask *et al*., 2004) In a multi-component, the authentic and accurate data on proton move are accessible by neutron diffraction, anyway, this method persists laborious to approach (Aitipamula *et al*., 2010). Some of the methods like Raman spectroscopy, FT-IR-vibrational analysis of carboxyl groups (Yadav *et al.,* 2009), x-ray photoelectron Spectroscopy mixture with solid-state density functional theory (DFT) have also existed a field two characterization. Based on raw materials, preparation technique, storage conditions, a few crystals like theophylline-citrate crystals, can form solvates and hydrates consisting of water or solvent particles, appropriately as third constituents (A. Yadav *et al.,* 2009). The Pharmaceutical cocrystals obtained by different procedures can show contrast in compositions or physical States apart from objective cocrystal, in addition to design material.

Screening and production of co-crystal formation

Different procedures came to be evolved for screening cocrystal formating utilizing the specified APIs and Conformers. Due to its broad relevant chemicals, small sample sizes, and short processing times, their assisted grinding (LAG) has been demonstrated as most engaging. The systematic screening of fixed cocrystals is facilitated by combining an API with a Cocktail of possible coformers (S.Tothadi *et al.,* 2012). In the other use of screening procedure, the solids are distinguished by the PXRD and thermal analysis. For Quick co-crystal identification in small solid samples consisting of large water moiety, the Raman spectroscopy has delighted increasing interest to reach the need. The happening of the New Phase at material interfaces has appeared by the hot stage thermal microscopy. Through the in-situ monitoring, please data regarding the cocrystal formation was supplied by solid-state NMR studies (Thakuria *et al.,* 2013). The suitable conformer discretion prediction depends on structural data and it also provides insights into potential cocrystal arrangements. The chemicals which are recorded as generally recognized as safe (GRAS) by FDA are also familiar coformer choices due to more of them having considerable quantities of accessible safety information (Sundarmurthi *et al.,* 2014).

Challenges in translational development of Pharmaceutical cocrystals

The exploration of a drug product from the drug substance contains different steps like pre-formulation studies, process development, prototype formulation development, scale-up, and the last making of viable batches. The utilization of cocrystal like a drug substance for the evaluation of drug products provides challenges, because of their distinctive effects and structural properties. The beginning sections express the matters including formulation development, preformulation, and process development of cocrystal- depended drug products. Based on the use of salts, amorphous form, and polymorphs the pharmaceutical industry has habitually depended on product evolution. This moment is assisted by huge scientific n understanding attainability of skilled manpower and evolved regulatory environment. Before scheming cocrystal for the drug, the cautious contemplation of former safety and its quantity in cocrystal by-products is important. The choice of coformer for larger dose drug is challenging, at enough larger quantity of coformer potential needed which maybe positioned for away from the IID limit. Hence, the authority members of marketing of like cocrystal-dependent drug products consisting of these coformers intended to fabricate an extra governing burden.

The strategy for the choice of the crystal candidate in the translational development of cocrystal products. In this the activities of preformulation can be categorized into two divisions, those are critical formulation factors (essential effects) and additional pre-formulation factors (desirable effects). For the sake of developing cocrystal products, the critical formulation factors should be conveyed initially. These factors are important for decision-making and also aids in determining the appropriateness of cocrystal in additional development. The challenges created by addition preformulation must be avoided by utilizing the conventional approaches and these factors are usually less evaluative. Although, the respective significance of a specific factor looks into a BCS class of the compound, the cause for choosing the cocrystal as solid form, and deliberated the concluding the dosage forms. Current status various drugs is demonstrated in table 3

Table 3. Current status of cocrystals.

S.NO	DRUG	ACTIVE MOIETY/COMPONENT	CURRENT STATUS
1	Beta-Chlor®	Chloral Hydrate Betaine	FDA Approval in 1963

2	Suglat	Ipragliflozin Proline	FDA Approval	in 2014
3	Steglatro®	Ertugliflozin L-Pyroglutamic Acid	FDA Approval	in 2017
4	Esteve	Tramadol Hydrochloride colexib	NCT03108487	
5	Thar Pharmaceutical	Zoledronic acid CoCrystal	NCT01721993	
6	Depakote	Valproic acid	FDA Approval	in 1983
7	Iron sorbitex	Iron, Sorbitol, Sodium citrate	PubChem	CID 20715017
8	T121E01F	Zoledronic acid	NCT01721993	
9	Lexapro	Oxalic acid	FDA Approval	in 2002
10	Tetracycline phosphate	Tetracycline, phosphoric acid	PubChem	CID 54713149

FUTURE PROSPECTS

Co-crystallization is a feasible approach for the improvement of the physical and chemical properties of drugs while protecting the pharmacological activity of the active pharmaceutical ingredient. In 2011, the United States Food and drug administration released guidelines for the pharmaceutical industry related to patenting of cocrystals. FDA differentiated cocrystal as an" active pharmaceutical ingredient excipients" molecular complex, a drug product intermediate and not a new API, EMA stated that cocrystal should undergo similar principles of documentation as salt form. Even though the regulatory views of us FDA and EMA are different, it does exhibit the growing interest in the use of pharmaceutical cocrystals as potential marketable drugs. Research into cocrystals continues to develop and more pharmaceutical

formulations that are based on cocrystal research sell out the market, it can only be expected for cocrystals to gain a stronger grip in drug development. The advantage of cocrystals over salt is cocrystals can be utilized for those drugs that are Nonionizable or weekly ionizable. Thus, cocrystals help in the enhancement of melting point, solubility, stability, and bioavailability of the drugs. Cocrystals methods are not so far. Popularly explored and a combination of fact-based and experimental methods for co-former selection offers a new vintage in cocrystal formation. Industrial interest in pharmaceutical co-crystal is growing due to improved Pharmaceutical benefits the display and time for drug development in cocrystal method are decreased. However, drug dosage forms with cocrystals still need further biochemical and pathological investigation to evaluate their therapeutic outcomes in humans.

CONCLUSION

Pharmaceutical cocrystals are fetching more and more dominant as another way for making better bioavailability of imperfectly water-soluble drugs, mainly to those neutral substances or those containing poorly ionizable groups. These cocrystals can mark the obstacles in drug delivery. For the moment, there is a growing importance for good understanding regarding the mechanism of crystallization and theory by what means the Pharmaceutical cocrystals make better the bioavailability of active pharmaceutical ingredients. Besides, the drug-drug cocrystals proceed towards may be used for combination therapy and improve the drug's therapeutic effect. Through this crystallization, the life cycle of old active Pharmaceutical ingredients can be improved. Consequently, these cocrystals provide a chance for fortunate drug delivery and can distribute as support for the viability of pharmaceutical industries in the upcoming days.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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