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Technical and Formulation Aspects of Pharmaceutical Co-Crystallization: A Systematic Review

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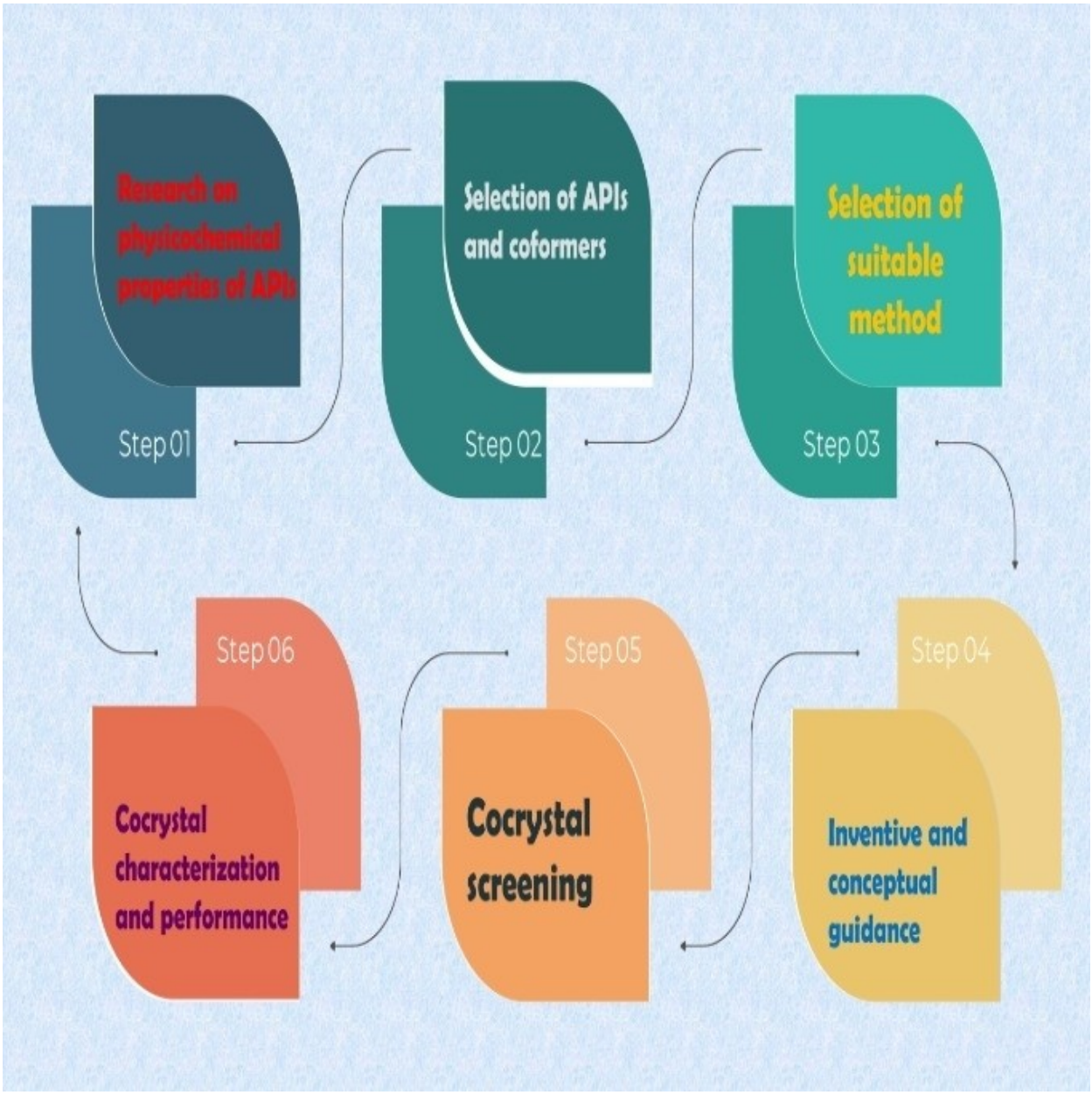

Crystal engineering provides a unique approach to modulating the physicochemical properties of forming active drug molecules so nowadays pharmaceutical companies and researchers have shown interest in designing and building cocrystals. Creating new crystalline solid structures with altered physicochemical properties such as solubility, bioavailability, tabletability, melting point, stability, and so on. The intermolecular interactions of molecules in the crystal lattice are used to investigate these properties. Numbers of methods for crystallizing the drug are summarised and analyzed, pointing to the advantages and disadvantages that have been highlighted in the literature. This literature review discusses in detail the different types of cocrystals, their mechanisms, methods of cocrystals, applications of cocrystals, and their characterization. The main purpose of this article is to look at what has changed in this field in the last ten years and show what could be learned from better research on cocrystal formation and how it can be used.

1. Introduction

Nowadays drug design is a very difficult task due to the regulations and requirements for drug design and its formulation. The discovery of a new drug is a time-consuming process. Pharmaceutical scientists have suggested a new idea for drug design involving existing drug molecules.[1,2] Modification of the physicochemical properties of existing drugs and novel drug molecules to address issues with existing drug molecules.[3] Most drug molecules have problems with their solubility, dissolution, hygroscopicity, chemical stability, thermal stability, ability to pass through biological membranes, etc.[4] They are very critical factors that define the effectiveness of the drug molecules. According to the WHO(World health organization) survey, 82% of API(Active Pharmaceutical Ingredients) is available in solid dosage form and of those, 40% of the API has poor water solubility.[5] The majority of the drugs are available in BSC classes II and IV. The major problem that arises during the drug formulation is its poor solubility. Prodrugs,[6] size reduction,[7] solid dispersion,[8] complexation,[9] salt formation,[10] solvates, polymorphs,[11] and co-crystallization[12] are among the approaches being investigated to improve solubility. All methods have their own advantages and disadvantages. Scientists are asked to help when new chemical entities are made, with most of their attention on salts, polymorphs, hydrates, and solvates. (Figure 1)

1.1. Crystal Engineering

Crystal engineering must have developed to the point by the discovery of the first urea-sodium chloride cocrystals in 1783.[13] Cocrystals are a subclass of multicomponent molecular crystals that have been demonstrated to enhance or alter the physicochemical characteristics of active pharmacological molecules including their solubility, bioavailability, and stability.[14] According to the latest United Food and Drug Administration (USFDA) guidelines, cocrystals are crystal structures that contain two or more molecules in the same crystal structure.[15] Recently, researchers have concentrated on cocrystals of active pharmaceutical ingredients.[16] In the last few years, pharmaceutical cocrystals have become a possible way to improve the physical and chemical properties of a drug.[12,17,18] Cocrystals also have a long history but in the past cocrystals have been categorized with various names such as molecular complexes, complexes of donor-acceptors, and species of associations. Stahly documented the history of cocrystals before 2000 and this survey included the discovery and history of organic components and explained cocrystal chemistry concepts with descriptive examples.[19] There are three different types of classification for cocrystals.[20,21](Figure 2)

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2. Multicomponent crystal classification

Cocrystals that include two or more distinct residues inside their crystalline structure are referred to as multicomponent crystals. It is generally accepted that a residue is made up of a full complement of components that are covalently linked. It describes the theoretical classification of solvates, salts, and cocrystals and it was shown in Figure 3. The above aggregation states apply to the pure unionized residues at room temperature. Solvate crystals have solid residue and liquid residue. Salts have two solid ions, and cocrystals have two solid residues. These groups are not mutually exclusive and give rise to seven subclasses.

3. Three different regulatory classification

I. One class: all solid forms of active pharmaceutical ingredients are listed together under this category.
II. Two classes: (i) single component active pharmaceutical ingredients and their polymorphs and solvates. (ii) Salts, cocrystals and polymorphs or solvents.
III. Three classes (i) single component active pharmaceutical ingredients and their polymorphs (ii) Salts, cocrystals, salt-cocrystals, binary salts and their polymorphs (iii) single component and multiple component active pharmaceutical ingredient and polymorphic solvates and hydrates.

4. FDA regulatory classification

The Food and Drug Administration (FDA) published a draught guidance document on cocrystal classification as "dissociable

API-excipient molecular complexes" in 2011.[22] The academicians then objected to the proposed regulation by issuing a document in which they demanded a new regulatory classification. This was done in response to the proposed regulation. After that, the Food and Drug Administration (FDA), the pharmaceutical industry and academic institutions met to discuss the myriad of perspectives and concerns regarding pharmaceuticals. Following these discussions, various classes of pharmaceuticals were established based on specific guidelines based on a number of crystal structures as well as how to use crystallographic databases, and the following subclasses were formed based on those criteria:

I. Single component crystals and pseudo polymorphs
II. Salts and pseudo polymorphs
III. Cocrystals and pseudo polymorphs

5. Types of cocrystal

Cocrystals are single crystalline substances having two or more components present at room temperature in a stoichiometric ratio and are usually solids. Investigators suggested different types of cocrystals depend on the number of components present in the crystal structure.[4] The following are the types of cocrystals:

1. Binary Cocrystal
2. Ternary Cocrystal

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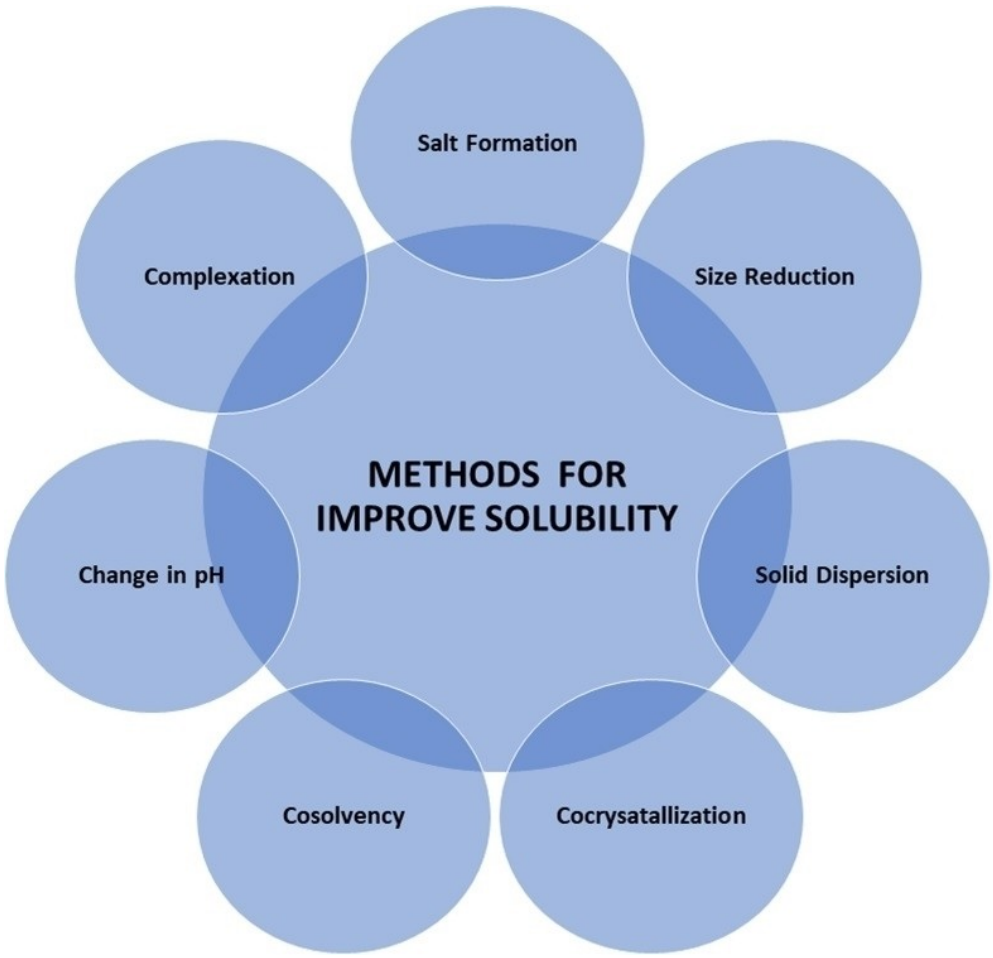

Figure 1. Methods for improve solubility.

3. Quaternary Cocrystal
4. Ionic cocrystal
5. Polymorphic cocrystal
1. Synthon polymorphic cocrystal
2. Conformational polymorphic cocrystal
3. Packing polymorphic cocrystal
4. Tautomeric polymorphic cocrystal
5. Hydrates/solvates

5.1. Binary Cocrystals

Investigators reported that binary cocrystals have two crystalline structures; API and coformer. A coformer has the potential to change the physicochemical properties of active pharmaceutical ingredients without a change in their pharmacological properties. The alteration of physicochemical properties of an API is based on the selection of a type of coformer. Synthesis of binary cocrystals depends on H-bonding propensity,[23,24] supramolecular synthon,[25] supramolecular compatibility by cambridge structure database,[26–28] pKa values,[29] and Hansen solubility parameters.[30] The advantages of this method are that the drugs will achieve their desired properties and also prevent any unintended toxic effects. The success rate in binary cocrystal design can be very high because during formation there are only two separate chemical units involved so there would be more chances of potential interaction.[31,32] A very large quantity of binary cocrystals have been planned, formulated, and characterized depending on various theoretical and experimental strategies and modulating the physicochemical properties such as stability, solubility, tabletability, hygroscopicity, melting point, etc. For example, scientists have prepared binary cocrystals of indomethacin and saccharin and the crystalline part was characterized using infra-red spectroscopy, Raman and powder X-ray diffraction, and differential scanning colorimeter.[33] As proven by Basavoju et al., the acid dimer synthon of indomethacin and the imide dimer synthon of saccharin have interacted with the aid of H-bonding and the binary cocrystal has a greater dissolution rate as compared to pure drug. (Figure 4) Srirambhatla et al. studied the binary cocrystals of paracetamol with various coformers.[34]

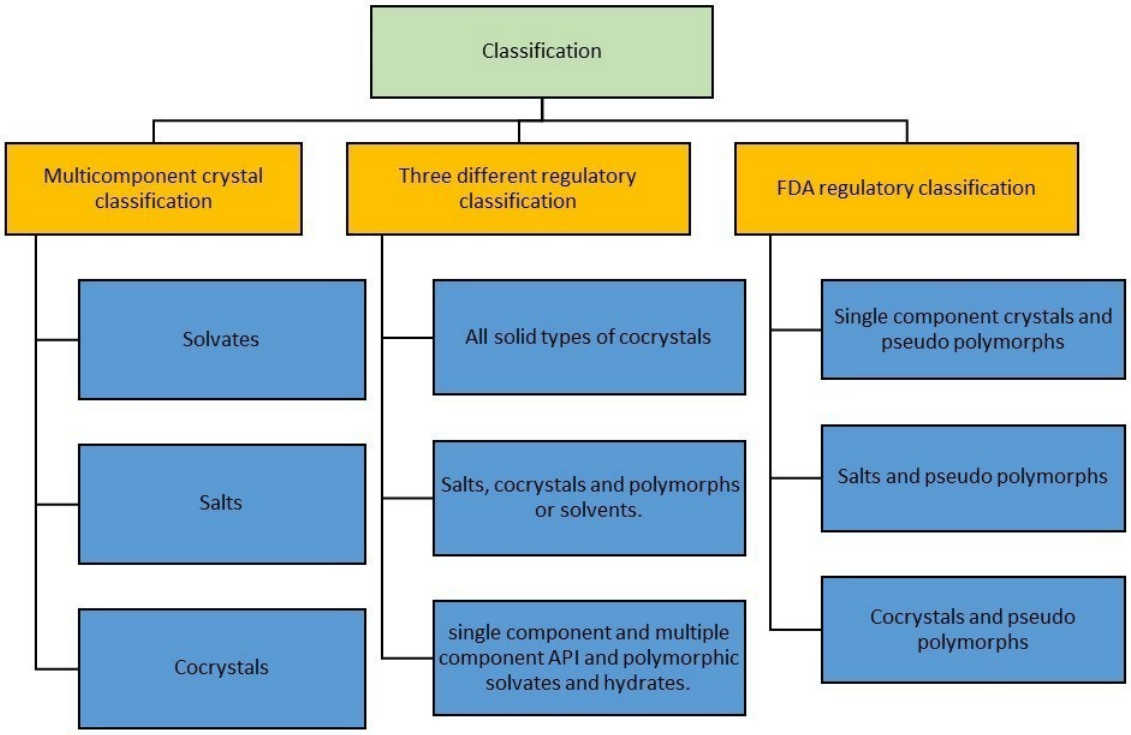

Figure 2. Classification of Cocrystal.

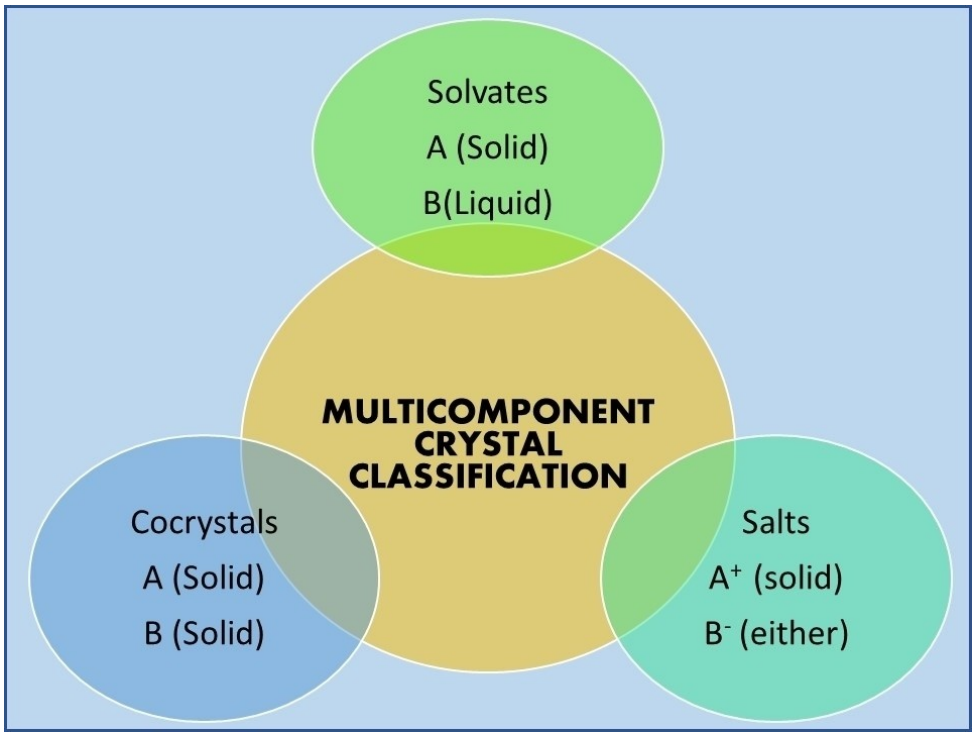

Figure 3. Multicomponent cocrystal classification.

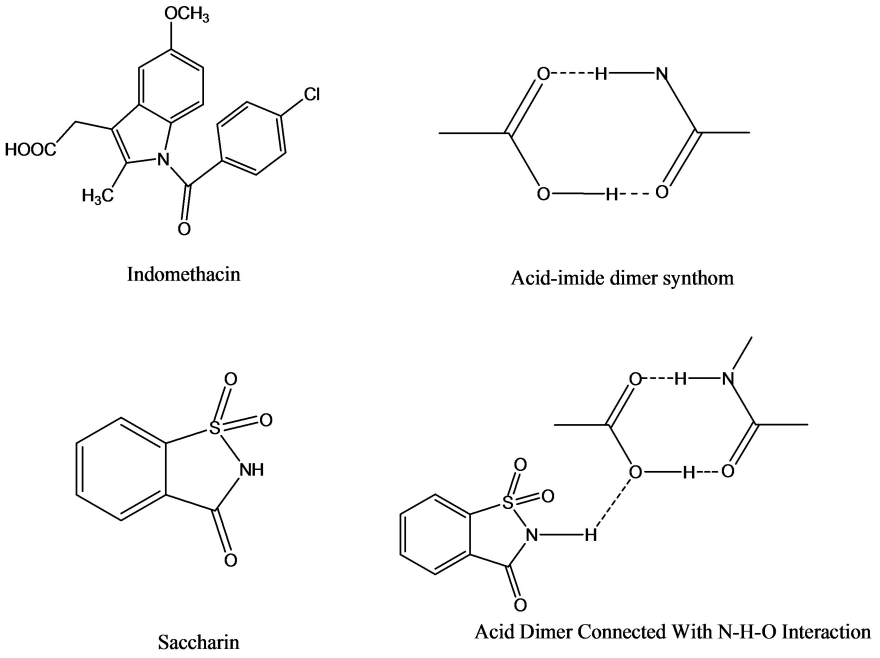

Figure 4. Carboxylic acid and amide dimer synthon.

5.2. Ternary Cocrystal

A ternary cocrystal is made up of three distinct neutral solid compounds in one crystal structure with an exact stoichiometric ratio. Investigators synthesized and isolated the three ternary cocrystals of 3, 5-dinitrobenzoic acid, isonicotinamide, and various acids based on the H-bond hierarchy. For example, the acid pyridine moieties from 3, 5-dinitrobenzoic acid, and isonicotinamide formed the primary strongest heterosynthon followed by the second acid-amide heterosynthon with another acid.[35] Aitipamula et al. reported ternary cocrystals isoniazid formed a cocrystal with nicotinamide, fumaric acid, and succinic acid, and the crystal structure with an acid pyridine heterosynthon was determined.[36]

Formulation and isolation of ternary cocrystals is a very difficult task for research. Co-crystallization experiments with three components prefer the formation of single component crystals or binary cocrystals or polymorphs or hydrates or solvates but ternary cocrystals are very rare. In the crystallization of ternary cocrystals, the balance and the interplay among the intermolecular interactions of the three distinctive chemical units are critical. Scientists have not explored the functional utilities of ternary cocrystals, but a ternary cocrystal has a tremendous role in intellectual and aesthetic application in crystal science.[31,32]

5.3. Quaternary Cocrystals

A wide variety of binary cocrystals has been reported but the variety of ternary and higher cocrystals is limited.[37,38] This is due to the difficulties in introducing three or extra factors stoichiometrically into a molecular solid. Hypothesis-driven synthetic protocols for greater cocrystal stability depend on supramolecular synthons which means on the intermolecular interactions and their geometry, like the shape and size of the starting molecules.[39,40] Scientists have reported the profitable format of a six-component molecular solid using both interaction-based and strong solution-based strategies.[41] This strategy has been in consequence used by others. For example, Paul has reported quaternary cocrystals of resorcinol, tetramethyl pyrazine, phenazine, and pyrene. This four-component solid contains a closed tetrameric resorcinol heterocycle synthon with two linker bases. Two resorcinol molecules and two pyridine bases (tetramethyl pyrazine and phenazine) produce tetrameric synthon. The stoichiometric quaternary cocrystal forms epitaxially on the surface of resorcinol. Phenazine binary cocrystal produced from mother liquor.[42] possible mechanism for the development of such a unique supramolecular architecture has been proposed by indexing the frequent crystal faces of the binary and quaternary cocrystals and observing that no ternary strength is gained.[43]

5.4. Ionic Cocrystals

In 2010, Braga invented the term "ionic cocrystal" for the sodium bromide barbituric acid cocrystal.[44] An ionic cocrystal is defined as a multi-component pharmaceutical material having at least one salt in a crystal lattice.[45] The basic formula is A+B−N, where A+ is a cation, B is an anion, and N is a neutral molecule or another salt. These are considered three components of an active pharmaceutical ingredient. When an ionic cocrystal is created with an API (cation) as one component and an anion or neutral molecule as the other, the solid form's(API) physicochemical properties can be varied.[45,46]

For example, Zaworotko research group designed and formulated the ionic cocrystal of inorganic lithium with a series of amino acids, zwitter ionic molecules "N" by utilizing the strength of lithium carboxylate bonds. Within this ionic cocrystal, lithium cation and amino acids were reacting with each other via coordinating bonds, while remaining anions balanced the composition charge. Coordinated bonds are stronger than hydrogen bonds so stronger bonding will improve lithium's in vivo efficiency and thus change its pharmacokinetics and pharmacodynamics.[47]

5.5. Polymorphic Cocrystal

Crystalline polymorphes are substances that have the same chemical composition but different lattice structures and/or different molecular conformations.[48] Various investigators have reported the impact polymorphism has on the output of cocrystals. Most cocrystal polymorphs identified by researchers were accidentally discovered during the experimental study and identification of new polymorphic cocrystals.[49–51] Identification and isolation of new polymorphs of active pharmaceutical ingredient cocrystals is a demanding exercise in the production of pharmaceutical drugs. Various parameters are affected in the cocrystallization of polymorphic substances such as solvents of different polarities, solvent mixtures, solvent evaporation rates, and various cocrystal formulating methods. A group of scientists used a variety of techniques, including solution crystallization,[52] pressure-induced polymorphs,[53] rotary evaporators,[54] spray drying,[55] freezing drying,[56] and grinding[57] to discover numerous unique polymorphic cocrystals. There are many different kinds of polymorphic cocrystals, including hydrates and solvates; conformational polymorphic cocrystals, packing polymorphic cocrystals, and synthon polymorphic cocrystals, based on their synthons, crystal shapes and molecular structures.[58]

6. Pharmaceutical cocrystal design strategies and its mechanism

The synthesis of cocrystals is a multistep analytical process. There are a number of methods used for cocrystal production. The type of the reactant and the solvent are two factors that impact the development of new cocrystals. Nevertheless, major scientific problems such as no control over nucleation, crystallization, and phase evolution of the cocrystals. For example, the probability of cocrystallization may be increased by drug molecules having carboxylic acids as coformers with acidic substituents or amides.[59] In addition, there is no guarantee of cocrystal formation. Mechanical chemistry approaches the best cocrystal methods using green chemistry and inexpensive synthetic route methods. In history 1893, cocrystal was formed using the grinding method to manufacture quinhydrone cocrystal from the equimolar quantities of p-benzoquinone and hydroquinone.[18] After that, a number of drug molecules, cocrystals were formed using neat grinding and wet grinding, but still, there is a mechanism of cocrystal synthesis that is not properly understood. Researchers have studied the cocrystallization method by changing its factors such as temperature range, the stoichiometric ratio of drug and coformer, speed of stirring, acidic or basic pH, and effect of container material but no one can say about drug and coformer stability at high temperatures. Jones and his team have reported that the cocrystallization method is not based on a single mechanism but rather on a sequence of mechanisms that involve such things as eutectic formation,[60] molecular diffusion, and cocrystallization via an amorphous phase.[61] The relevant point in these three mechanisms is the presence of an intermediate phase such as gas, liquid, or amorphous solid that has increased mobility or higher energy of reactant molecules in comparison to the initial crystalline forms. Eutectic development is an important mechanism in the synthesis of cocrystal. In this mechanism, grinding improves the use of this method by means of two strategies: (i) increasing reactant surfaces and (ii) improving cocrystal nucleation.[62] For example; a crystal of benzophenone and diphenylamine formed a cocrystal and it was examined by a microscope where the surface of both crystals was converted into the liquid phase.[63]

In molecular diffusion, either one or two reactants have remarkably high vapor pressure in the solid state. This mechanism is mainly dependent on the pure drug surface quality and also on the mechanical force which is responsible for the breakdown of intermolecular bonds of the reactant drug molecule crystals.[64] Molecular diffusion is mainly used by heavier aromatic hydrocarbons such as naphthalene.

Cocrystallization may occur in an amorphous phase (liquid or gas) in which there is no special route for the transfer of mass. Scientists have reported that the grinding occurs at a temperature underneath the glass transition temperature of drug molecules, which is responsible for the development of the amorphous phase. Moreover, the rate of grinding increases, resulting in the synthesis of metastable polymorphs.[65] (Figure 5)

7. Method of preparation of cocrystals

Figure 6 illustrates the different methods for the preparation of cocrystals. These methods are described here in detail with examples.

7.1. Solution based cocrystal

A number of methods are available to crystallize the molecule from the solution. In the beginning, it's worth considering some principles of universal solution crystallization. The key factor for crystallization at this temperature in that solvent is supersaturation, the distinction between the original concentration of the study and the specified concentration of solubility. One concentration to remember for a cocrystal system is the target molecule and the second coformer.[62] The concentrations of the target molecule and coformer relative to cocrystal solubility, which is determined by cocrystallization supersaturation. There would be a eutectic point where the stable solid phase of the system is a mixture of cocrystals and

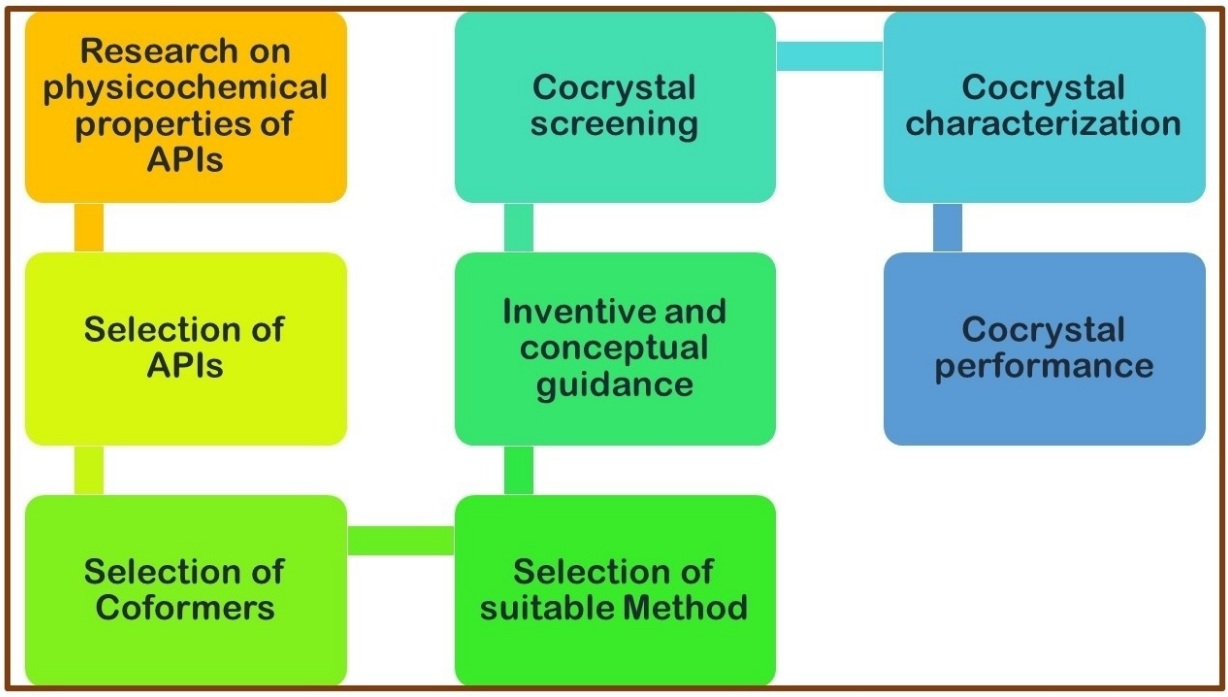

Figure 5. Steps for cocrystal design and preparation.

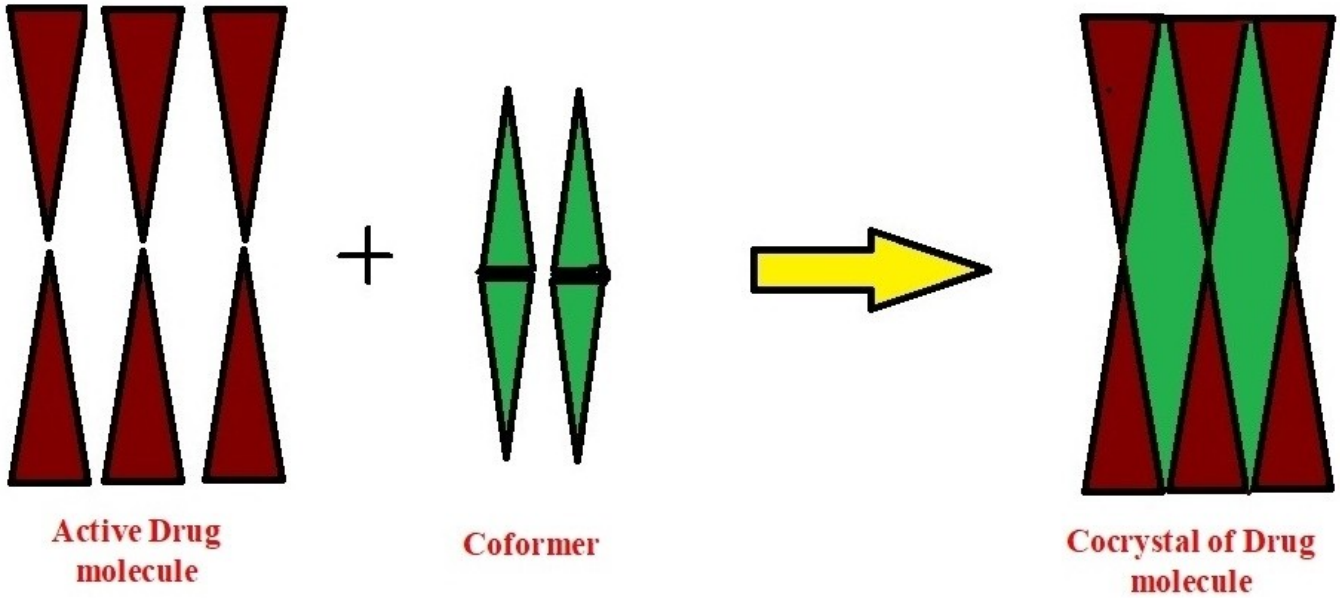

Figure 6. Mechanism of cocrystal formation.

the target molecule in a fixed concentration of a solution and a second eutectic point where cocrystals and coformers mix.[66] Eutectics is a diluted solution with the least level of solvent content indicating the solubility is at its peak. The cocrystal would only be stable at concentrations between the eutectic points and be less soluble than the target molecule or coformer.[67] It is important to know about the concentration range for successful solution cocrystallization. The solubility of cocrystals is most effectively represented in a ternary-phase diagram (TPD). This triangular diagram shows how solid phases can dissolve in a solvent at a constant temperature and pressure. It also shows the stability regions of the system for different solid phases and the cocrystal preparations.[21] ■■Dear author please mention Figure 7 in your text■■

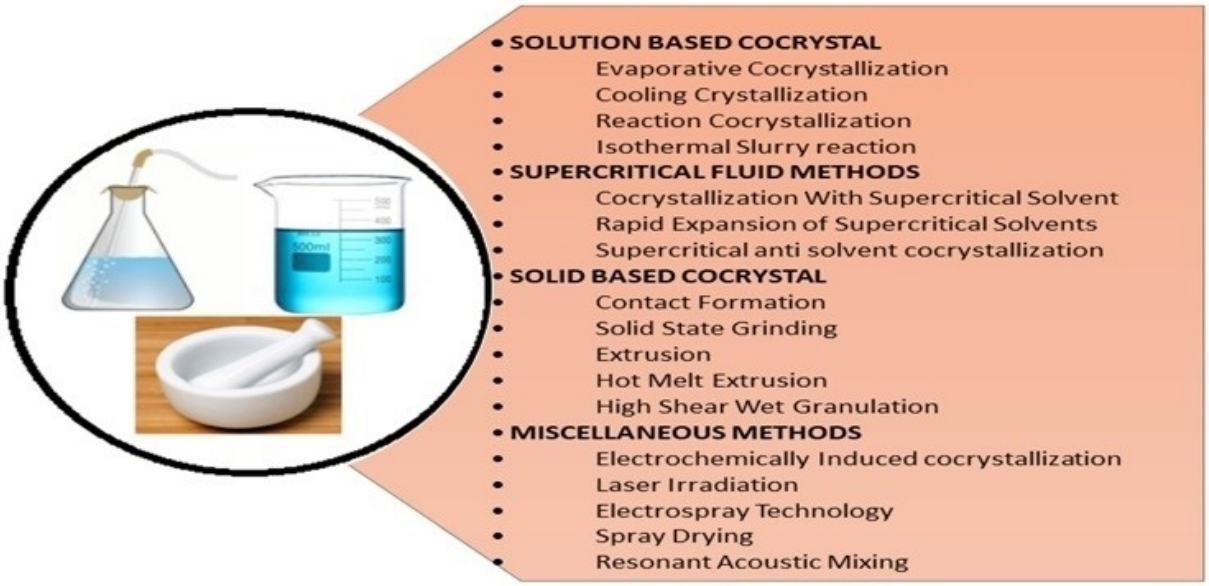

Figure 7. Preparation methods of cocrystal.

Figure 8 describes a schematic representation of the ternary phase diagram with (a) similar solubility and (b) different solubility. All regions are colour coded, with pink representing drugs and solvents. The blue region contains the drug and the cocrystal; the red region contains the cocrystal; the green region contains the cocrystal and the coformer; the white region contains the coformer and the solvent; and the yellow region contains the solution.[68] As shown in Figure 8, the ternary phase diagram of the multi-component system includes the following: solvent, active pharmaceutical ingredient, co-former, and cocrystal.

7.1.1. Evaporative Cocrystallization

It is a basic method for cocrystal formation. Generally, it is used to produce single cocrystals that are appropriate for diffraction studies to summarize the cocrystal structure. This method includes cocrystal synthesis from a coformer solution in a suitable solvent, and supersaturation is produced by solvent removal. Generally, the rate of evaporation is slow so it ensures the formation of a small number of larger crystals instead of a large number of smaller crystals.[69] It is required to identify the crystal structure for the formation of new cocrystal forms such as solvates, hydrates, salts, or other polymorphic forms of the active drug or coformer.[70] Researchers have reported the best

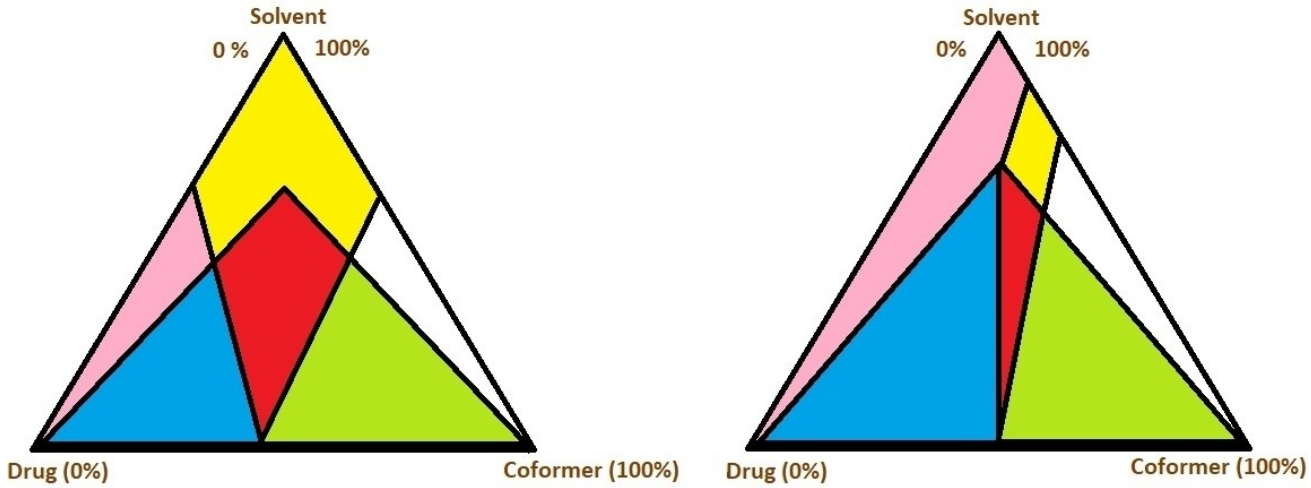

Figure 8. schematic representation of ternary phase diagram

example of evaporation cocrystals. Preparation of cocrystal of norflaxin-isonicotinamide from chloroform: Norflaxin (0.1 MMOL): Isonicotinamide (0.1 MMOL) is dissolved in 8 ml of chloroform. On evaporation of chloroform, results in a rod-shaped cocrystal of 1:1 norfloxacin: isonicotinamide cocrystal.[71] This method is not widely used because there are some disadvantages such as this method is not used for the bulk quantities of cocrystal. This method's optimization is similar to any other method of crystallization, and it works with very dilute solutions. This is often because of a lack of solubility data of precursors in the solvent but can also be done intentionally to try to minimize the cost of supersaturation to promote the synthesis of large crystals.[72]

7.1.2. Cooling Crystallization

To design the cocrystal using the cooling cocrystallization method, it should be considered solvent selection to identify thermodynamically stable cocrystal and desupersaturation kinetics at a 1 litre scale with a higher yield. For example, the preparation of the cocrystal of carbamazepine: nicotinamide from ethanol. Holari and colleagues conducted another study to prepare agomelatine: citric acid cocrystals. The effect of cooling rate and seed amount on crystal size distribution in the final product was checked.[73]

7.1.3. Reaction Cocrystallization

This method is used for the formation of carbamazepine-saccharide cocrystals by mixing individual feed solutions from any reactant.[74] The ternary phase diagram has implemented this method and represents a robust cocrystal operating range and relationship between supersaturation and induction time. An example of reaction cocrystallization is the preparation of carbamazepine: nicotinamide cocrystals.[75]

7.1.4. Isothermal Slurry Conversion

This method requires the suspension of drug and coformer in suitable media in an exact molar ratio which boosts the solid fractions. The strategy may also work in direct terms by adding the target molecule to a solvent solution or coformer suspension.[76] Although this is a solution-based process, there is no need for a clear starting solution that is completely dissolved like in the reaction cocrystallization method. Slurry conversion depends on the solubility driving force, the relative concentration of the target molecule and coformer, nucleation, and growth kinetics of the system. It is the most accepted method due to its high effectiveness. Investigators reported the conversion time for theophylline to turn into a 1:1 glutaric acid cocrystal. Its conversion time for full conversion varied from 15 minutes to 5 hours. The rate of conversion depended on the solution and selection of solvents and also suggested that conversion time for cocrystals was reduced with an increase in solubility.[77,78] D. R. Weyna reported that meloxicam-aspirin slurry conversion with the help of tetrahydrofuran as a solvent produced a 96% yield at atmospheric conditions.[79] The purity and process effectiveness of the isothermal slurry conversion method for toluene sulphonamide: triphenylphosphine oxide crystals were confirmed by Rasmuson.[80] Some downsides of this process are (i) a large quantity of starting product. (ii) product loss due to residual solvent solubility.[81]

7.2. Supercritical Fluid Methods

Cocrystals were successfully developed using supercritical fluid technology, specifically using supercritical carbon dioxide (CO2), utilizing three specific techniques based on distinct supercritical CO2 properties: solvent, antisolvent, and enhancement of atomization.[82]

7.2.1. Cocrystallization with Supercritical Solvent

In this method, coformers in solid forms are mixed with supercritical fluid for a fixed period of time. The Cocrystallization of Supercritical Solvent (CSS) methodology utilizes the supercritical CO2 solvent to suspend the drug molecule and the coformer as a liquid or supercritical CO2 slurry, preventing the use of hazardous organic solvents.[83] Cocrystal density and solvent power can be completely fine-tuned by controlling the temperature and pressure which gives control over cocrystallization between cocrystal components. L. Padrela et al. correlated cocrystallization results of multiple APIs such as theophylline, acetylsalicylic acid, caffeine, and carbamazepine with saccharin in liquid and supercritical CO2.[83] Those authors indicated that cocrystallization is facilitated by its dissolution in CO2, considering the normal low solubility of most cocrystal components, such as active pharmaceutical ingredients and conformers, in CO2.[84] Generally, they have noted that the rate of crystallization is increased by increasing the concentration of cocrystal components in the CO2 phase. In addition, cocrystal components are blended with a CO2 slurry to promote effective mass transfer by convection, which has been found to be critical for achieving successful cocrystallization and getting co-crystalline products free of traces of their starting constituents.

7.2.2. Rapid Expansion of Supercritical Solvents

In this method, CO2 is depressurized through a nozzle into a drying chamber at atmospheric pressure then supercritical CO2 is used with an active drug molecule and coformer to form cocrystals. Mullers et al. used this method to produce ibuprofen-nicotinamide cocrystals with microparticles.[85] Mostly, pharmaceutical compounds have very poor solubility, so it is a major drawback of this technique that the active pharmaceutical ingredient and coformer must be solubilized in supercritical CO2.

7.2.3. Supercritical Antisolvent Cocrystallization

This method is defined as "A solution of coformers forms cocrystals as a result of the addition of a supercritical antisolvent." In this case, CO2 is used as a supercritical antisolvent

based on the solubility of active pharmaceutical ingredients and coformers, which is reduced in supercritical CO2. It helps them to catalyze in a cocrystalline structure together. This strategy offers the potential to control the polymorphic form of the active pharmaceutical ingredient (API) or cocrystals that are formed.[86,87,88] Antisolvent cocrystallization is a viable alternative to evaporative and cooling cocrystallization for cocrystals with lower solubility. In addition, this procedure can be performed at an ambient temperature, which requires less energy than solvent evaporation and drying.[89] The advantage of this method is that it selects a solvent antisolvent mixture for cocrystallization and produces the cocrystal with a remarkable yield and high purity. Additionally, it was utilized in the manufacturing of nanoscale cocrystals. Wang et al. synthesized carbamazepine and saccharin cocrystals using an antisolvent technique, with 84% yield and exceptional purity.[90] Velaga et al. demonstrated the method of Supercritical Antisolvent or the formation of indomethacin-saccharin cocrystals into micron-sized needle and block-shaped particles.[82]

7.2.4. Supercritical Spray Drying

This method is explained as the quick elimination of saturated solutions of a drug molecule and coformer by spraying them through a nozzle using supercritical CO2. Supercritical CO2 as an atomization enhancer is required to facilitate the fragmentation of liquid jets into fine droplets when depressurized at the same time as liquid solutions. It is a one-step method involving the spraying into a drying chamber at atmospheric pressure of a solution having the dissolved starting cocrystal molecules through a nozzle with supercritical CO2. Investigators are using the supercritical enhanced atomization (SEA) process to study the conversion of theophylline to nanosized cocrystals with many coformers. This is done to fine-tune the cocrystals' shape and how well they dissolve.[91,92] This strategy was also effectively used as a controlled release preparation to produce micro composites of theophylline-saccharin cocrystals dissolved in hydrogenated palm oil. These approaches reflect the most common cocrystal forming strategies.[93,94]

7.3. Solid State Methods

7.3.1. Contact Formation

Random cocrystal formation by mixing natural API and coformer was recorded under regulated atmospheric surroundings.[95,96] No mechanical forces are applied in this method during cocrystallization.[97] Moreover, in a few examples, rapid grinding of pure additives was performed directly faster than blending. Researchers analyzed the effect of starting material pre-milling on carbamazepine and nicotinamide cocrystallization prices.[98] It was known that the cocrystallization charge for pre-milled reactants turned out to be considerably faster than unmilled reactants (12 versus 80 days, respectively). In addition, higher cocrystallization levels were identified at high temperatures and relative humidity, irrespective of the mechanical activation for the same method. Scientists documented the development of cocrystal Isoniazid-benzoic acid by spontaneous cocrystallization.[99] They noted the rate of reaction improved at higher pre-milling speeds of the pure reactant. In addition, A. Y. Ibrahim et al. examined the effect of particle size on the spontaneous cocrystallization of urea and 2-methoxybenzamide from starting materials. Smaller partition size distributions have been shown to contribute to faster cocrystal synthesis. In the situation of the small particle size distribution of 20–45 μm, in which no hidden eutectic or amorphous intermediate phase was identified, a rapid increase in cocrystallization rate was observed.[97] The cocrystallization route in the presence of moisture under deliquescent environments is composed of three phases: (1) moisture absorption, (2) reactant dissolution, and (3) cocrystal growth and nucleation.[100] D. J. Berry et al. utilized cocrystal screening under hot-stage microscopy. Scientists have used the Kofler method to check the binary phase activity of a given co-crystal system and show co-crystal phases in a mixture of active drug molecules. Throughout the study, nicotinamide was selected as a prior molecular scaffold with a range of active drug molecules, e.g., fenbufen, ibuprofen, ketoprofen, flurbiprofen, and salicylic acid. In the whole process, one component is melted and then allowed to solidify till another component is placed in contact with it and a part of the first reactant is solubilized. Therefore, a mixing layer is formed after the recrystallization of all the materials. That is comparable with the two components' binary phase diagram. Using this approach, nicotinamide: ibuprofen, nicotinamide: salicylic acid, nicotinamide: flurbiprofen, and nicotinamide: fenbufen were reported.[101]

7.3.2. Solid State Grinding

This approach has been employed to produce cocrystal powder. There are two sub-methods: (1) dry grinding and (2) liquid-assisted grinding.

Dry grinding is also known as neat grinding. A dry grinding method includes the combination of dry powder of a target molecule and dry powder of a coformer using a manual or mechanical method. Starting materials are melted during grinding in the melt crystallization method but it is not possible in the neat grinding method.[102] Temperatures are maintained and recorded throughout the grinding process. Two cocrystals of sulphathiazole and carboxylic acid were made by grinding stoichiometric variants of sulphathiazole with the essential carboxylic acid for 90 minutes at 37 °C or less in a 25 Hz frequency Retsch mixer mill.[103] There is no loss of product with solvent in the solid-state method, so yield is good compared to the solution-based process.[60] Problems with dry grinding can involve failure to prepare a cocrystal, incomplete cocrystal conversion, and crystalline defects with potential amorphous material. An incorrect transformation of cocrystal leads to a mixture of cocrystal and excessive starting material in the drug. It is not ideal, as it requires additional purification steps to obtain a pure cocrystal. It can often be overcome by increasing the grinding time but product mixtures can also be indicative of non-stoichiometric cocrystal formation. Dry grinding usually

occurs with mixtures of target and coformer solids in a molar ratio. The starting material is totally used in the formation of stoichiometric cocrystals.[66] The development of a non-stoichiometric cocrystal would result in an excess amount. Theoretically, molar equivalents and an excess of each starting material will be used to complete dry grinding. It will promote the search for existing alternate cocrystals.[104]

Liquid-assisted grinding requires applying a solvent to the dry solids. Milling is typically started in very small volumes. The solvent has a catalytic role in helping to form cocrystals and will continue for the duration of the grinding method. By using a liquid-assisted method, it produces good quality crystals compared to the neat grinding method.[105] Investigators first reported that cocrystals of caffeine and maleic acid were formed using a liquid-assisted and neat grinding method. They suggested that grinding time is 30–60 minutes, and a 1:1 or 2:1 cocrystal is produced, which is based on the solvent selection. But it contains some impurities.[106] This impurity was overcome by an ultrasound-assisted solution cocrystallization method in 2010. It was proposed to form a pure caffeine and maleic acid cocrystal.[107] Cocrystals of benzoic acid were synthesized by wetting an equimolar mixture of benzoic acid and carboxylic acid coformer in methanol, wetting and grinding it to dryness.[108] Scientists used coformers such as caffeine, picolinic acid, and nicotinamide to increase bioavailability. Their work has contributed to the optimization of pharmacokinetic properties. Furthermore, dissolving prepared cocrystals in an aqueous buffer revealed that the concentration of hesperetin is 4–5 times higher than the pure one.[109]

7.3.3. Extrusion

Different from Hot Melt Extrusion (HME), Twin Screw Extrusion (TSE) works at temperatures below the melting point of the reactant and occurs in a different piece of equipment, a suitable twin-screw extruder. This device contains a single barrel with two co-rotating screws. Screw action allows for the continuous mixing and movement of content along the length of the barrel. Daurio et al. developed four model cocrystals using a 16 mm twin-screw extruder with four temperature controllable zones.[110] Theophylline: citric acid, carbamazepine: saccharin, caffeine: oxalic acid, and nicotinamide: cinnamic acid cocrystals were synthesized by passing through the extruder stoichiometric mixtures of the dry powder from each starting content. It has been suggested that the effect of temperature on the preparation of cocrystals has been examined and suggested that carbamazepine: saccharin cocrystal was not based on a specific temperature but nicotinamide: cinnamic acid cocrystal was affected by the temperature.[110] Medina and the group first implemented the twin screw extrusion method for the manufacture of caffeine cocrystal and AMG 517. Their work has shown that twin screw extrusion helps to achieve a highly efficient mixing and close packing of material that leads to improved surface contact between cocrystal components. The cocrystal formation would thus be allowed without the application of any solvent.[111] Twin screw extrusion was also used as a continuous cycle in the production of ibuprofen-nicotinamide cocrystal. With various extrusion conditions, PXRD has shown that cocrystal purity ranges from 20 to 99 percent. This study has shown the temperature of the extrusion, the orientation of the screw, and the speed of rotation of the screw. These three parameters are important for evaluating the purity of cocrystals. The best way to get the purest ibuprofen: nicotinamide cocrystal is to have the highest residence time (lowest speed) and the highest processing temperature with the most powerful mixing screw.[112]

7.3.4. Hot Melt Extrusion

Solid state methods include hot melt extrusion in which the concurrent melting and interaction of the target molecule and the coformer are integrated by heated screw extruder application. In a molar ratio, the starting materials are combined and fed to the heated extruder. Melting takes place and allows the intimate mixing of the reactants. The cocrystal nucleates melt and the pure cocrystal extrudate is continuously removed from the extruder. The method is recommended due to its ability to avoid the use of organic solvents. It is not a time-consuming method; it improves conversion compared to solution-based processes; it reduces waste and the technique is well suited for continuous pharmaceutical manufacturing. A scientist has identified the development of cocrystals containing carbamazepine and cinnamic acid using a single screw and twin-screw extruder.[113] Cocrystals formed from the twin-screw extruder represent good dissolution properties compared to those obtained from single screw/solution methods. Hot melt extrusion was used to manufacture indomethacin-saccharine cocrystals as a continuous manufacturing method, and research studies have shown that the temperature profile, feed rate, and velocity of the screw are the three critical process parameters (CPP) that are required for high-quality cocrystal engineering. They have also reported that the cocrystal dissolution rate is not affected by temperature.[114] but it is affected by the particle size of the cocrystal.[115] Investigators have developed the ibuprofen and nicotinamide agglomerated cocrystals using this method and also examined the influence of various manufacturing parameters such as the speed of the screw, the temperature specification, and the screw configuration. It was shown that the barrel temperature must be above the eutectic point of the physical mixture for cocrystallization to proceed, and also the maximum sheer screw configuration should be used to get the purest crystal. Moreover, it has been shown that the introduction of xylitol matrix polymer in the production of ibuprofen-isonicotinamide cocrystal has a major effect on extrusion torque and residence time. They examined the effects of 10%, 30%, and 50% xylitol polymers and found that the torque decreased with an increase in the amount of xylitol and the residence time increased.[116]

7.3.5. High Shear Wet Granulation

High shear wet granulation exact mechanism for cocrystal formation is not known, but it is similar to liquid-assisted grinding. This method involves agglomerating powder particles

in the presence of a binder via a liquid medium. The process is performed in a high-shear granulator, which exerts shear through impellers and choppers on the powder mixture. There is a study that reported that a 1:1 piracetam: tartaric acid cocrystal was developed using a Bohle mini granulator.[117] It is prepared by using a mixture of piracetam and tartaric acid in the water and a variety of excipients, and 95% cocrystal is obtained within 5 min. The number of parameters, such as the amount of granulation liquid used, the speed of the impeller, and the mixture of the excipients, affect the rate of cocrystal formation.

7.4. Miscellaneous Methods

7.4.1. Electrochemically Induced Cocrystallization

Researchers reported that electrochemistry can be used to transfer the pH locally to obtain neutral carboxylic acids and to produce a local key factor for cocrystallization. Horst et al. have proven it by forming a cocrystal of cinnamic acid and 3-nitrobenzamide.[118]

7.4.2. Laser Irradiation

This approach requires the use of a high-power CO2 laser to irradiate cocrystal powder and trigger its recrystallization into a cocrystal structure. Gaisford noted that, first of all, cocrystal formers require sublimation up to a significant time duration, in which molecular rearrangement between the active pharmaceutical ingredient and coformer molecules and nucleation of cocrystals occurs in the vapor phase. For example, oxalic acid and malonic acid are used to prepare caffeine cocrystal.[119]

7.4.3. Lyophilization

This method, also known as freeze-drying, is primarily used in the manufacturing of food and pharmaceutical products. It works by freezing the substance and then decreasing the ambient pressure so that the frozen water in the sample can be sublimated from the solid state to the gas state. Recently, these have been shown to be a promising route for designing new solid forms of cocrystal.[56] This method, in which the amorphous phase is sublimated and cocrystallization happens, led to a new type of theophylline: oxalic acid cocrystal.

7.4.4. Electro spray Technology

Electro spraying is the simultaneous generation and charging of droplets through an electrical field. In this method, a solution having the dissolved substances flows through a high-potential capillary nozzle through an electrical field that induces a jet to form the deformation of the solution droplets. The solution jet is dried, and the particles generated are deposited on a charged powder collector. Investigators studied this process' ability to develop carbamazepine and itraconazole cocrystals with specific coformers.[120]

7.4.5. Spray Drying

Spray drying is a single-step continuous process of converting solutions into solid powders. Because it solidifies quickly, it is used a lot in the making of amorphous solid dispersion. It was also used in cocrystal synthesis. Cocrystallization was observed in highly super-saturated drug regions due to rapid evaporation of solvents, coformer presence, and interaction between drug and coformer. It can also be used to manufacture cocrystals trapped in a matrix of excipients with increased rheological properties. It is a continuous, controllable, and fast method. Investigators have illustrated the synthesis of poorly soluble sulfadimidine cocrystals and 4-aminosalicylic acid as coformers in the presence of an excipient matrix.[121]

7.4.6. Resonant Acoustic Mixing

This method is based on the principle of mixing drug and coformer in the presence of a suitable solvent to form a cocrystal in the absence of any grinding media. There is mechanical energy transferred into a wetted powder mixture and it allows the material to be properly mixed using a labRAM resonant acoustic mixer operating at 80–100 G and 60 Hz. For example, a number of carbamazepine cocrystals have been successfully developed. The cocrystal products were extracted in the lab at 100 mg, 1.5 g, and 22 g scales, and the method seemed perfect for going bigger.[122]

8. Characterization of cocrystal

Recently, investigators have been interested in modifying the active drug molecules by improving their physicochemical properties, which form the salts, polymorphs, or cocrystals of the existing drug molecules. These modified drug molecules are characterized by different techniques such as analytical methods, spectroscopic methods, diffraction methods, and thermal methods. (Figure 9) A detailed study on the latest advances in characterization methods for salts, polymorphs, and cocrystals has been published by Pindelska. All characterization methods are important for studying active drug molecules in their inherent complexities at the molecular level and collecting information regarding drug molecules' structure, purity, configuration, and physicochemical properties so the characterization becomes effective and systematic. Such techniques can also be used to control and examine physical phenomena that are involved in drug production in situ and in real-time. The main purpose of this review is to learn about the new analytical methods and show how important they are in the field of pharmacy.[123] (Figure 9)

8.1. Structural Study (Single crystal and powder X- ray diffraction study)

The crystal structure is essential, which is identified by the single crystal and powder X-ray diffraction methods. Single crystal and powder x-ray diffraction (PXRD) comprise the primary methods used for crystalline active drug character-

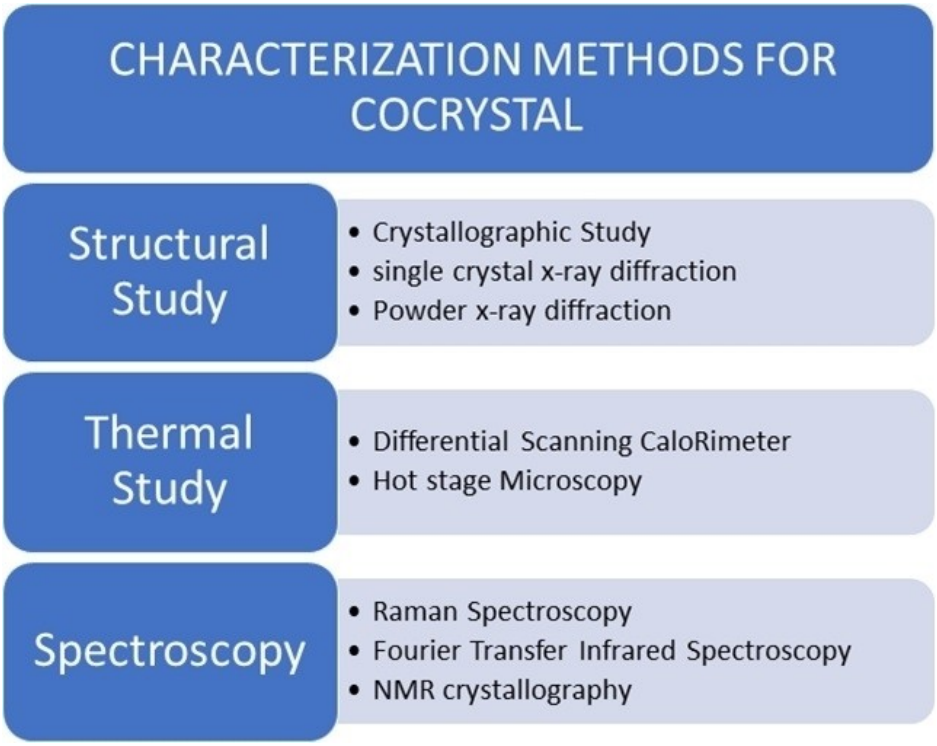

Figure 9. Characterization methods for cocrystal.

ization. Active drug molecules can be made as microcrystalline powders. Single crystal and powder diffraction data hold exactly the same structural data, but this data is presented in three-dimensional (3D) space in a single crystal diffraction model while it is compressed into one dimension in the powder diffraction pattern, so the different peaks in the powder diffraction pattern overlap, with data on the individual diffraction rate concealed. Researchers have designed and used the PXRD method for the quantification of indomethacin-saccharin cocrystals in the crystallization mixture.[66,105] Generally, software programmes such as DIFFRAC.TOPAS (Bruker AXS, Karlsruhe, Germany) allow structural determination and refining depending on the Rietveld study. The Rietveld method, first established for the processing of crystal structures, has proven to be very useful in the quantitative phase analysis, as the Rietveld scale parameter of the phase relates to its relative quantity in a multi-phase mixture. In recent times, this approach has been effectively applied to the quantitative application of pharmaceutical solids.[124] The qualitative characterization of drugs is widely applicable and has played a key role in the invention and detection of new salts, polymorphic types, and drug cocrystals. There is a new method developed and it is named the Hirschfield atom refining method, which offers enhanced and tailored spherical atomic electron densities, which are derived from crystal field-embedded quantum chemical electron densities.[125] This approach has used an in-depth analysis of two solid forms of the polymorphic neuralgic drug, carbamazepine, i. e., polymorphic Type III and dehydrated.[126] The results obtained from the HAR and the high-resolution X-ray data set for Type III CAR are highly promising in that the positional and anisotropic parameters of the H-atom are identical to those derived from the neutron diffraction analysis. This indicates that the HAR strategy has great potential for charge density analysis.

8.2. Thermal Study

This study is used to measure changes in physicochemical properties of the active drug molecule due to heating, cooling, or constant maintenance of temperature. Thermal analysis of cocrystals is performed by different methods such as Thermogravimetric analysis (TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC) with hot stage microscopy. These methods give important information about the enthalpy of cocrystal fusion, melting point, crystallinity, thermal transition temperature, and the formation of solvates or hydrates.[127] Hot stage microscopy provides details about the physical properties of solid drug molecules based on the effect of temperature. Cocrystal of the drug is heated and shows changes in melting point, melting range, and crystal growth; it is examined using a microscope. Hot stage microscopy is a very simple and inexpensive method. Hot stage microscopy instruments may be paired with other instruments such as the Fourier-transform infrared spectroscope (FTIR), the DSC, or the heating-cooling system for controlling the flow of hot or cold air. The relevant application of thermal microscopy is in situ cocrystal forming, also identified as the Kofler contact preparation.[128] Some cocrystals are melted at temperatures

distinct from their dug molecule and coformer. Thermal analysis is performed using temperature-controlled PXRD or simultaneous DSC-PXRD systems, which identify physical changes in the cocrystal observed. A chemical study of thermally modified drugs is performed by High performance liquid chromatography

(HPLC), Raman, and FT-IR, which helps to illustrate modifications of the drug molecule. Thermogravimetric analysis and residual water analyses allow the identification of solvents and hydrates. Differential calorimetry was used in the analysis of the cocrystal synthesis. For example, analysis of in situ carbamazepine-nicotinamide cocrystal formation kinetics of equimolar components in an amorphous state after melting.[129] This technique is also used for the construction of binary phase diagrams for the screening of cocrystal synthesis and for the presence of a eutectic mixture or eutectic impurities which is responsible for reducing the melting point.[130] It checks fusion heat, transition heat in solid transitions and heat capacity. It can also be used to determine the degree of crystallinity.

8.3. Spectroscopic Study

This study involves infrared spectroscopy, raman spectroscopy, and nuclear magnetic resonance. IR is highly susceptible to changes in crystalline form, polymorphism, and cocrystal detection. Different regions of the infrared are used for the characterization of cocrystals, such as mid-IR (4000–400 cm^{-1}), near-IR (14,000–4000 cm^{-1}), and far-IR (400–10 cm^{-1}). Fourier-transform IR (FTIR) is concerned with the continuous analysis of the spectra of the single cocrystal components and their final mixture with polymer matrices. It is a significant method for the identification of cocrystal formations and for the elucidation of their structures. Due to the presence of hydrogen bonds, especially when carboxylic acid is used as a coformer, the cocrystal gives a specific range from that of the product mixture. It is difficult to quantify cocrystals by IR due to the high absorption of additives or other ingredients because most excipients form bonds at a high dipole moment, and multiple absorptions occur that cannot be easily isolated and allocated to each component.[131] Rather than using an analytical technique, near IR during the process of controlling cocrystal ibuprofen-nicotinamide formation using a rotating dual-screw extruder as a real-time process method.[112] Nuclear magnetic resonance (NMR) provides specific details about the structure of organic pharmaceutical cocrystals and their complexes, and these informative studies on complex characterizations were given by the researchers.[123] Raman spectroscopy was used to control the crystallization. It is a powerful analytical tool for the distinction between polymorphs, salts, cocrystals, solid solutions, and hydrated salts because it needs limited sample preparation and uses a very small quantity of it. This is also a non-destructive tool for structure determination since the radiation dosage is minimal. In particular, the raman spectra are useful for figuring out how cocrystals form because the oscillations of cocrystals are different for each starting substance.[132]

9. Application of cocrystal

Cocrystals aim to attract investigators through their demonstrated potential applications. There are a number of cocrystal applications described as follows. (Figure 10 and Table 1)

9.1. To improve the solubility and bioavaibility

Solubility is one of the chemical properties that measures the quantity of a solute in a fixed quantity of solvent at ambient conditions. The solubility of the drug molecules may be changed due to the presence of foreign particles. The most prominent use of cocrystals has been to enhance the solubility of drug molecules. Low aqueous solubility is an obstacle to the proper distribution of active drug molecules, which results in prohibiting the use of medication. By altering its fundamental crystal structure, a cocrystal has a naturally different solubility than any drug molecule. The relationship of cocrystal solubility with the solubility reviewed with the same physical composition, or at least in the availability of a known coformer concentration, is more acceptable as compared with similar solutions. A majority of the published reports lack the predicted effect of the coformer on cocrystal solubility Improved solubility is advantageous since it can improve the bioavailability of the pharmaceutical, but excess change can be risky due to the formation of a super-saturated solution. This results in an undesirable accumulation of the precursor. Cocrystals have the capacity to improve pharmaceutical drug delivery and clinical efficiency by changing solubility, pharmacokinetics, and bioavailability. In general, a strong emphasis in many research papers reported in the journal has been the use of cocrystals to enhance the oral drug penetration of biopharmaceutics classification system (BCS) class II and IV drugs. Ketoconazole is a BCS class II drug that has a hydrophobic site in its chemical structure and low basicity, which facilitates poor aqueous solubility. Ketoconazole is a wide-spectrum imidazole antifungal agent, so Indra said that the slurry method for making cocrystals of ketoconazole and ascorbic acid made the drug 50% more soluble than the pure ketoconazole drug.[133] S. Ranjan et al. studied the diuretic drug, hydrochlorothiazide, which belongs to the BCS class IV drug. It has lower solubility and low permeability, which is a major problem for the drug's bioavailability. Investigators have prepared the cocrystal of hydrochlorothiazide with different coformers such as phenazine, 4-dimethylamino pyridine, and picolinamide. From this study, scientists have concluded that the solubility of hydrochlorothiazide cocrystal is enhanced in the following order: hydrochlorothiazide: dimethyl aminopyridine (4-fold) > hydrochlorothiazide: phenazine (1.4-fold) > hydrochlorothiazide: picolinamide (-0.5-fold).[134] Researchers have identified a new crystalline form of telaprevir, which is a protease inhibitor antiviral drug. Cocrystallization of telaprevir with coformer 4-aminosalicylic acid shows improvement in its solubility and a 10-fold increase in its bioavailability in vivo.[135]

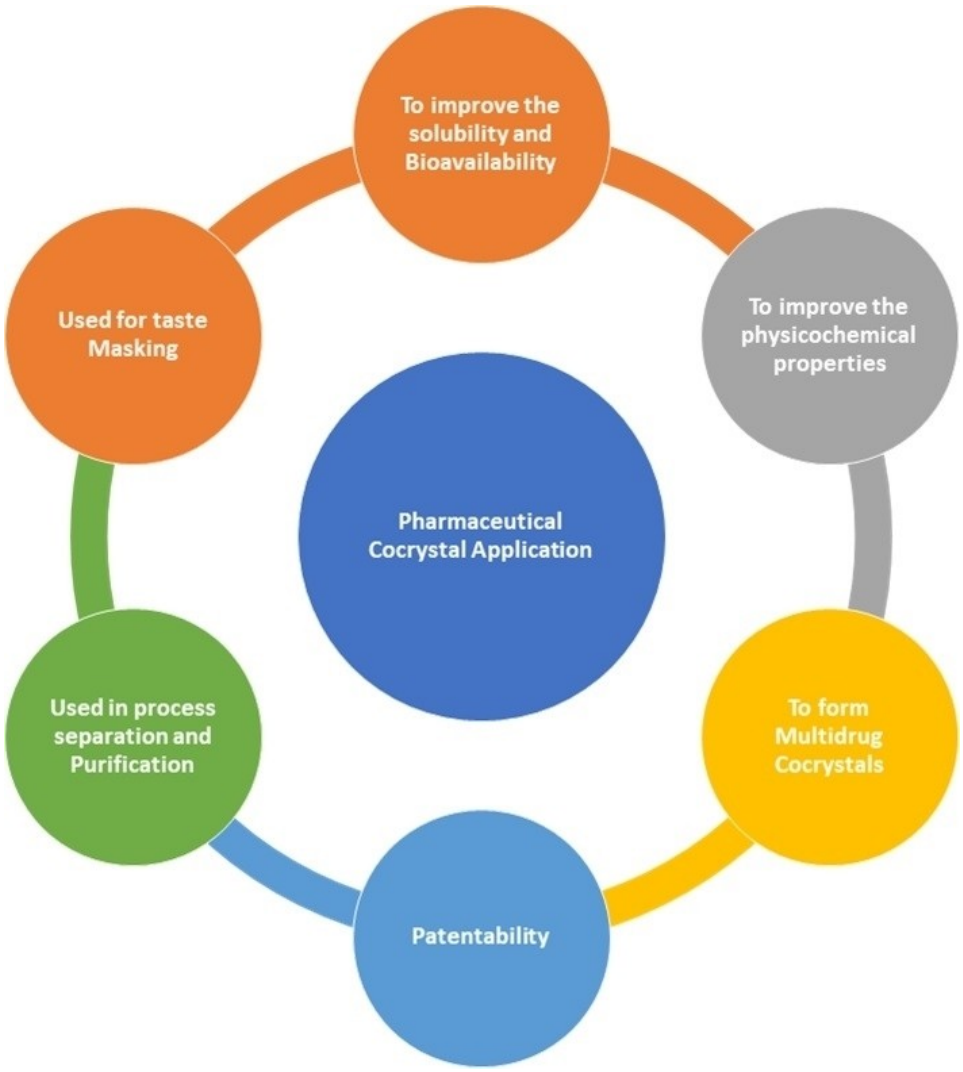

Figure 10. Cocrystal application.

9.2. To improve the physicochemical properties

Many drug molecules have a variety of physical and chemical properties that can be altered by forming cocrystals. Pharmaceutical cocrystals can modify the physicochemical properties of pharmaceuticals such as solubility, bioavailability, permeability, melting point, tabletability, etc.

A **melting point** is a thermodynamic physical property that is explained as the temperature at which the solid particles are in equilibrium with the liquid particles. It is a fundamental physical property with zero free transition energy. Generally, it is beneficial for any cocrystals of drug molecules to have a high melting point, but it leads to low solubility and it restricts some molding processes. The low melting point of cocrystals also causes problems with the drying and stability of the pharmaceutical product. A melting point is used to measure the purity of the product. A high melting point represents the thermodynamic stability of the new molecules. For example, by identifying a coformer with a higher melting point, the thermal stability of an API can be improved.[136] Cocrystals have a low melting point, which is good for thermolabile product management. Different types of methods, such as thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC), can be used for thermal studies of drug molecules and melting point measurement.[137] The melting point of cocrystals can be modified by proper selection of the coformers. When compared with their active drug molecules, less polar and lipophilic coformers displayed low aqueous cocrystal solubility. Researchers found the melting points of similar heterosynthon cocrystals were packed and researchers found the melting points of cocrystals varied due to different crystal packing. The melting point leads to a significant concern during cocrystal preparation, and it is proven by the investigators. They discovered that carbamazepine has a melting point of 192 °C while its coformer, nicotinamide, has a melting point of 128 °C, and the cocrystal of carbamazepine with nicotinamide (1 : 1) has a melting point of 151–161 °C.

Table 1. Example of Cocrystal formation and its application.

Sr. No.	Drug	Coformer	Method	Application of cocrystal	Reference
1.	Hydro-Chlorothiazide	phenazine	Slow evaporation crystallization method	1.4-fold improved solubility	[132]
		4-dimethyl amino pyridine	Slow evaporation crystallization method	4-fold improved Solubility	
2.	Baicalein	caffeine	Slow evaporation crystallization method	Great thermo stability and shows 2.5-fold and 1.5-fold oral bioavaibility enhancement in pH 2.0 and pH 4.5 buffer solution	[134]
3.	Fluoxetine HCl	Fumaric acid	Slow evaporation crystallization method	Enhanced the solubility than pure fluoxetine HCl	[155]
4.	Indomethacin	saccharin	Twin screw extrusion	Enhanced dissolution than raw indomethacin	[67]
5.	Ketoconazole	Fumaric acid	Reaction Crystallization Method	Improved solubility	[114]
6.	Carbamazepine	Vanillic acid	Slow evaporation crystallization method	Improved the dissolution rate	[156]
7.	Curcumin	Hydroxyquinol	Solid state Grinding	cocrystals showed enhanced dissolution than raw curcumin. (1 : 2)	[157]
8.	Carbamazepine	p-amino salicylic acid	Grinding Method	cocrystal showed enhanced dissolution than raw carbamazepine (1 : 1)	[158]
9.	Fenofibrate	Nicotinamide	Solution crystallization and Solvent-drop grinding method	Enhanced dissolution rate than raw nicotinamide (1 : 1)	[159]
10.	Agomelatine	Urea, Glycolic acid, Isonicotinamide, methyl-4-hydroxy benzoate (1 : 1)	solution crystallization	Enhanced powder dissolution rate than raw agomelatine	[160]
11.	caffeine	Citric acid	Isothermal Slurry method	higher stability than the pure alkaloid	[161]
12.	Meloxicam	aspirin	Evaporation method	Improved aqueous solubility and accelerate the onset of action	[162]
13.	sildenafil	acetylsalicylic acid	Solution crystallization method	75 % improved dissolution rate than sildenafil citrate	[163]
14.	Isoniazid	Pyrazinamide	Liquid assisted grinding	Improved aqueous solubility	[79]
15.	Isoniazid	4- amino salicylic acid	solution crystallization	Improved aqueous solubility	[164]
16.	Quercetin	Caffeine	Liquid assisted grinding method	14 times more solubility than quercetin	[165]
17.	Fluoxetine HCl	Succinic Acid	Slow evaporation	Two-fold increase in solubility	[166]
18.	Febuxostat	L-pyroglutamic acid	Liquid assisted grinding method	Improved solubility	[167]
19.	Hydrochloro-thiazide	nicotinamide	Liquid assisted grinding method	Improved solubility	[168]
20.	Ritonavir	Adipic acid	Solvent grinding method	6 times higher solubility	[169]
		nicotinamide	Solvent Grinding Method	3-4 times higher solubility	
21.	Dipfluzine	benzoic acid	Solvent assisted co grinding method	500 times improved the solubility	[170]
22.	furosemide	adenine	Liquid assisted grinding method	7-fold increase the solubility	[171]
		caffeine	Liquid assisted grinding method	6-fold increase the solubility	
23.	Telmisartan	Oxalic acid	Solvent drop grinding method	1.7 times fold improved solubility	[172]
24.ac	Acyclovir	malonic acid	Solvent evaporation method	6 times enhancement in aqueous solubility	[173]
25.	Posaconazole	4-aminobenzoic acid	Slow evaporation method	Enhanced dissolution rate	[174]
26.	Nifedipine	Isonicotinamide	Solution cocrystallization	Superior Photo stability	[175]
27.	Aspirin	Simvastatin	Grinding method	Enhanced dissolution rate than raw drug	[176]
28.	Praziquantel	cyclodextrins complex	Neat grinding method	Improvement in drug solubility and dissolution rate	[177]
29.	Resveratrol	4- aminobenzamide	Liquid assisted grinding	improved aqueous solubility, intrinsic dissolution rate, and tabletability properties.	[178]

Table 1. continued

Sr. No.	Drug	Coformer	Method	Application of cocrystal	Reference
30.	itraconazole	1,4-dicarboxylic acids	Solvent assisted grinding	Improved the dissolution rate	[179]
31.	Olanzapine	nicotinamide	Solution method	Improved dissolution profile of drug	[180]
32.	Lornoxicam	saccharin sodium	Neat grinding method	enhance the solubility and dissolution rate	[181]
33.	chlorbipram	gentisic acid	liquid assisted grinding method	1.45 folds higher solubility	[182]
34.	Telaprevir	Salicylic acid	Liquid-assisted grinding	Improved solubility and stability,	[183]
35.	Ticagrelor	Ticagrelor	Solvent evaporation, reaction crystallization	Improved solubility and dissolution properties	[184]
36.	Vismodegib	Maleic acid	Reaction crystallization	Enhanced solubility, enhanced dissolution, improved bioavailability	[185]
37.	Teriflunomide	Cytosine	Liquid assisted grinding	Enhanced dissolution and diffusion	[186]
38.	Pomalidomide	Gentisic acid	Reaction crystallization, liquid assisted grinding	Enhanced solubility, stable cocrystals	[187]
39.	Dabrafenib	Fumaric acid	Liquid assisted grinding	Improved dissolution	[188]
40.	Ibrutinib	Succinic acid	Reaction crystallization	Enhanced solubility, stable cocrystals, improved flowability	[189]
41.	Apremilast	Caffeine	Reaction crystallization	Enhanced dissolution rate, stable cocrystals, good flowability	[190]
42.	Lesinurad	Proline Glycolic acid	Reaction crystallization	Improved kinetic solubility, stable cocrystals	[191]
43.	Brexpiprazole	Catechol Succinic acid	Neat grinding	Improved solubility, improved dissolution rate, stable cocrystals	[192, 193]
44.	Lumacaftor	Nicotinamide	Reaction crystallization	Improved solubility, improved dissolution rate, stable cocrystals, improved mechanical properties	[194]
45.	Obeticholic acid	Ursodeoxycholic acid Chenodeoxycholic acid	Reaction crystallization	Stable cocrystals	[195]
46.	Ribociclib	Saccharine	Solvent evaporation, slurry, solid-state grinding and cooling crystallization	Enhanced solubility, enhanced dissolution, improved flowability, stable cocrystals	[196]
47.	Cannabidiol	L-Proline D-Proline Tetramethyl pyrazine	Solvent evaporation, liquid assisted grinding and reaction crystallization	Stable cocrystals	[197]
48.	Nebivolol hydrochloride	4- hydroxy benzoic acid	Liquid-assisted grinding and solvent evaporation method	Enhanced the solubility of the parent drug molecules	[198]

Permeability plays a major role in drug absorption and distribution through biological membranes. Generally, it is based on the partition coefficient of the n-octanol/water system by using log P and clogP values for the drug unchanging.[136] Scientists have reported that 5-fluorouracil, BCS class-III drug permeability has been improved by cocrystallization with various coformers like 4-aminobenzoic acid, cinnamic acid, and 3-hydroxybenzoic acid.[138] Permeability of the cocrystals can be checked by Franz diffusion cells. The results concluded that the permeability of cocrystals was enhanced by forming a heterosynthon of drug molecules and coformer.

Stability is a key point in the development of new chemical entities. Different types of stress are based on the nature of the active drug molecule and its structure. There are a number of stability studies performed during the development of drug molecules, such as chemical stability, photostability, relative humidity measurement, thermal stability, etc.[139]

Chemical stability study means there is any modification in the chemical degradation of a drug molecule that can be checked. Researchers have published that the cocrystal of glutaric acid with the drug molecule has the best chemical stability and no chemical degradation in different conditions.[106] When high-temperature stress is put on cocrystals of carbamazepine and saccharin, they show strong chemical stability under different conditions and good physical and chemical stability.[140]

Photostability study was carried out to check the impact of light on light-sensitive drugs. Some drugs are not stable in the presence of light, so it is required to perform this stability study. The author has reported that nitrofurantoin cocrystals with various coformers display greater photostability. Except for one cocrystal after 168 hours, all cocrystals showed little degradation (3%), indicating that cocrystallization will prevent photo-degradation of light-sensitive drugs.[141]

Relative humidity means automated water sorption and desorption studies. It is carried out to assess the impact of water on the formulation. Using a suitable humidity chamber, the moisture absorption can be regulated by exposing the cocrystal to specific relative humidity and then examining the sample after achieving equilibrium. Scientists have checked the relative humidity of theophylline cocrystals with distinct co-formers such as malonic acid, maleic acid, oxalic acid, and glutaric acid. The results are noted for specific time intervals (24 h, 72 h, 1 w & 7w) at various relative humidity intervals (0, 43, 75, and 98 percent), and they revealed an increase in physical property and stability, particularly by avoiding the formation of hydrate.[142]

Thermal stability of pharmaceutical drug molecules is examined under high temperatures. Cocrystals of paracetamol with 4,4-bipyridine have demonstrated greater stability than other coformers.[129] Another stability study of phosphodiesterase IV inhibitors cocrystal with tartaric acid was evaluated in multiple stoichiometries ranging from 0.3:1.0 to 0.9:1.0. From this range, cocrystals with 0.5:1.0 stoichiometries were found to be the most stable due to their acid content, which can fill the crystal channels and create various binding modes.[143]

9.3. To improve mechanical properties

Mechanical characteristics such as tensile capacity, force to rupture, thermal deformation, compressibility, and tablet material capacities. The mechanical properties of drug molecules can be modified by changes in their crystal structure. Tableting is a common and widely accepted dosage form in the market because of its technological advantages such as high production, ease of use, low manufacturing cost compared to other dosage forms, and ease of storage and handling.[144] There are also some problems existing due to the mechanical properties of the tablet, which are solved by cocrystallization of the active drug molecule. Cocrystallization has also been used as a process to enhance the physicochemical properties of powders, including mechanical strength and flow properties. Some of these methods include the application of silicon dioxide to increase the mechanical strength of tablets and magnesium stearate to enhance flowability. Investigators have studied the cocrystal of paracetamol with various co-formers which show an improvement in mechanical properties. In particular, 5-nitroisophthalic acid cocrystals of paracetamol could be made into tablets with the right tensile strength without affecting how well they dissolve. This was possible because the cocrystals had slip planes.[145]

9.4. Produce the multidrug cocrystals

Nowadays, a new trend in drug development has been the incorporation of multiple active drug molecules into one unit dose. There are two key factors for this growing trend the need to target numerous receptors for successful treatment of chronic illnesses such as HIV/AIDS, cancer, and diabetes, in addition to the increased need to promote the cost reduction of drug development. Multiple active drug molecules are combined into a single delivery system using salts, cocrystals, and co-amorphous systems.[146] Comparison of co-amorphous structures with multidrug cocrystals (MDCs) is beneficial in terms of their improved stability and decreased payload relative to the mesoporous and cyclodextrin complexes. Scientists have described multiple drug cocrystals as "dissociable solid crystalline supramolecular complexes," which consist of two or more therapeutically efficient components in a stoichiometric ratio within the same crystal lattice where components can interact primarily through nonionic interactions and occasionally through hybrid interactions.[146] Investigators reported that there are some future benefits of multiple drug cocrystals over pure drug components due to advantages of multiple drug cocrystals such as improved solubility and dissolution of at least one of the components, increased bioavailability, improved stability of unstable drug molecules via intermolecular interactions, increased mechanical strength, and flowability. For example; Ethenzamide and gentinsic acid formulations with multiple drug cocrystals were documented with an improved intrinsic dissolution rate. Meloxicam and numerous drug cocrystals containing aspirin were formulated with a 12-times drop-in time to achieve therapeutic concentrations and a four-fold improvement in bioavailability.[147]

9.5. Used for taste masking

The preparation of oral disintegrating tablets requires rapid disintegration of tablets with fast dissolution. This technique allows tablets to be used without the need to chew or consume water, which enhances the level of drug consumption for geriatric, pediatric, and travelling patients. Nevertheless, the disintegrating tablets require the use of taste masking agents to enhance the comfort of the patients, so scientists have mainly used sugar-based excipients, but there are some limiting factors, such as the low rate of dissolution in the synthesis of oral disintegrating tablets. Therefore, scientists have overcome this problem by synthesizing the cocrystal of active drug molecules with a sugar-based coformer. For example, synthesis of cocrystal of hydrochlorothiazide with sucralose as a co-former. These cocrystals have taste masking and a high rate of dissolution rate at the same time.[148] Aitipamula et al. have studied theophylline and xanthine derivatives, which act as phosphodiesterase inhibitors. Generally, it is marketed as a solid oral preparation and it is recognized for its bitter taste and therefore not widely accepted by patients. Therefore, scientists have developed a 1:1 stoichiometric cocrystal using artificial sweeteners such as sodium saccharin, sodium gluta-

mate, d-sorbitol, and coffee using the liquid-assisted grinding method. The resulting cocrystal has improved both the rate at which cocrystals dissolve and their sweet taste.[149]

9.6. Patentability

Intellectual property is essential to pharmaceutical manufacturers. Intellectual property security of new concepts, technologies, methods, or goods allows for exclusive production and marketing of pharmaceutical products or services. Such intellectual property is protected by patents, copyrights, and trademarks, which allow individuals or organizations/companies to gain acknowledgment or economic benefit from their own research or contributions to development. Patentability leads to the regulation of the patent life cycle of drugs or drug products. It can be achieved in a way by securing a large number of innovative features over simple innovation, preventing eventual double patent infringement, and extending the patent duration of the same drug product. Monitoring of innovative solid types of marketed products, including polymorphs, salts, and cocrystals, offers the opportunity to grant new intellectual property on certain medicines and prolong their patent life cycle.[150] Pharmaceutical cocrystals have regulatory and intellectual property benefits which create unique opportunities, benefits, and challenges.[151] When a pharmaceutical cocrystal is established with positive results, the next step will be to gain regulatory approval so that it can be put onto the market. In the last few years, cocrystal production has seen tremendous growth, and there have been several patents issued for cocrystals. For an invention to be patentable, it must meet three criteria: it must be new, not obvious, and useful or valuable.[152,153] Current patents published for cocrystal agomelatine and metaxalone with carboxylic acids represent significantly improved dissolution characteristics and bioavailability of the pure forms of the drugs.[154] Improvements in micromeritics properties, solubility, dissolution rate, bioavailability, and drug stability as described above provide powerful evidence for utility and industrial application.

10. Future perspectives and challenges

Pharmaceutical cocrystals are a class of multicomponent molecular crystals that optimize the physicochemical properties of the active drug molecules, thus a research area that is currently undergoing rapid growth. There are a significant number of choices for manufacturing cocrystals and analyzing their physical-chemical properties. This analysis offers standard explanations and details of existing and developing routes for cocrystal preparation. In addition, comprehensive perspectives are offered on the possible mechanisms for cocrystallization in different techniques. Based on knowledge of intermolecular interactions that determine their formation and stability increases, theoretical methods for predicting cocrystal formation may become a valuable tool to help in cocrystal design. Cocrystals continue to gain popularity and manifest their significance, so the number of validated cocrystal application fields continues to grow. Pharmaceutical cocrystals have useful applications for the production of new chemical moieties and for the enhancement of dosage forms containing active pharmaceutical ingredients. All presented application areas for pharmaceutical cocrystals are included in this analysis with the goal of highlighting the broad potential of these materials. With a focus on physical characterization and quality control, technical bases and concerns for the use of pharmaceutical cocrystals have been developed and addressed. As the benefits of cocrystals continue to be shown and common production methods are confirmed, it is expected that they will be used more and more in the pharmaceutical industry.

Author's Contribution

- Vishva Chauhan: Conceptualization; Data curation; Roles/Writing - original draft; Writing - review & editing
- Rajnikant Mardia: Conceptualization; Writing - review & editing
- Mehul Patel: Conceptualization; Writing - review & editing
- Bhanu Suhagia: Conceptualization
- Komal Parmar: Writing - review & editing

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: cocrystal application · cocrystallization · drug-coformer cocrystals · cocrystal preparation methods · pharmaceutical cocrystals

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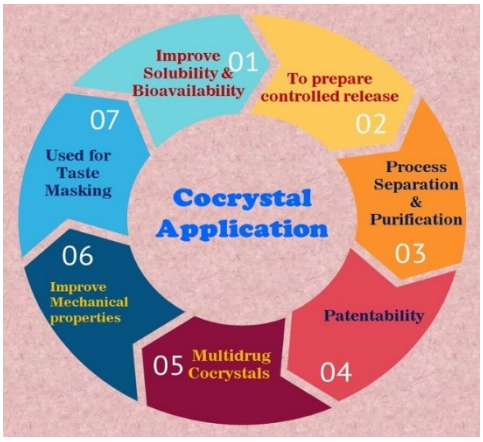
REVIEW



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Technical and Formulation Aspects of Pharmaceutical Co-Crystallization: A Systematic Review

Crystal engineering provides a unique approach to modulating the physico-chemical properties in forming active drug molecules so now-a-days pharmaceutical companies and researchers have shown interest in designing and building cocrystals. Develop and design new crystalline solid structures with modified physicochemical properties such as solubility, bioavailability, tabletability, melting point, and stability, The development and design of new crystalline solid structures with modified physicochemical properties such as solubility, bioavailability, tabletability, melting point and stability etc. These properties are studied by the intermolecular interactions of molecules in the crystal lattice. Numbers of methods for the crystallize the drug are summarized such as, solution based cocrystal, solid based cocrystal, supercritical fluid method etc. These methods used to analyse pointing to the advantages and disadvantages that have been highlighted in the literature. Applications of these methods in different drug cocrystals are discussed with examples from publications in the last decade. Number of pharmaceutical substances belongs to BSC class II/IV which having solubility/dissolution and bioavailability issues. To fix this problem cocrystallization has been an interesting research area for the investigators which act by modifying physicochemical properties of drugs. Further, it also facilitates drafting of regulatory guidelines for pharmaceutical cocrystals by various regulatory bodies, preceded by approval for the pharmaceutical cocrystals available in different countries. Pharmaceutical cocrystals have a crucial advantage than active drug molecule. This literature review discusses in detail the different types of cocrystals, its mechanism, methods of cocrystals, application of cocrystals and its characterization. The main purpose of this article is to collect data on novelties in this field and to illustrate what knowledge might be collected from more reliable research. Our attention has concentrated on pharmaceutical examples of the last century or so, because of the interest in this subject.