Available online on 15.04.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

Pharmaceutical Cocrystals: An Emerging Approach to Modulate Physicochemical Properties of Active Pharmaceutical Ingredients

[1] Suraj Ankush Tupe, [1]Shital Prabhakar Khandagale, [2]Amrapali B. Jadhav*

[1] Students, Department of Pharmaceutics, Government College of Pharmacy, Aurangabad, Maharashtra, India, 431005
[2] Assistant Professor, Department of Pharmaceutics, Government College of Pharmacy, Aurangabad, Maharashtra, India, 431005

Article Info:

Article History:

Received 11 Feb 2023
Reviewed 17 March 2023
Accepted 28 March 2023
Published 15 April 2023

Cite this article as:

Tupe SA, Khandagale SP, Jadhav AB, Pharmaceutical Cocrystals: An Emerging Approach to Modulate Physicochemical Properties of Active Pharmaceutical Ingredients, Journal of Drug Delivery and Therapeutics. 2023; 13(4):101-112

DOI: http://dx.doi.org/10.22270/jddt.v13i4.6016

*Address for Correspondence:

Amrapali B. Jadhav, Assistant Professor, Department of Pharmaceutics, Government College of Pharmacy, Aurangabad, Maharashtra, India, 431005

Abstract

Most of the Active Pharmaceutical Ingredients (APIs) are typically formulated and administered to patients in oral solid dosage forms due to ease of administration, patient compliance and cost effectiveness. Poor water solubility, low permeability and low bioavailability of APIs are major hurdles in development of oral solid dosage forms. In recent years, cocrystal development has evolved as a feasible approach for enhancing the solubility and bioavailability of poorly soluble drugs. Crystal engineering strategies have been asserted to enhance the likelihood of discovering new solid forms of an API. A pharmaceutical cocrystal is made up of two basic components, an API and a harmless material known as a coformer in stoichiometric ratio. Cocrystallization of an API with a pharmaceutically acceptable coformer can improve the physical characteristics of the API, such as solubility, hygroscopicity, and compaction behavior, without affecting the API's pharmacological efficacy. This review article offers a comprehensive overview of pharmaceutical cocrystals, their physiochemical characteristics, and methods of preparation, with an emphasis on cocrystal screening and cocrystal characterization. The review also included recent FDA and EMA guidance on pharmaceutical cocrystals as well as an outline of multidrug cocrystals.

Keywords: Pharmaceutical co-crystals, crystal engineering, coformers, supramolecular synthons, Solubility

INTRODUCTION

In recent times, there has been an awful great deal of interest towards the design and manufacturing of pharmaceutical cocrystals. The production of new drug products with superior physical and pharmacological properties, such as solubility, stability, hygroscopicity, dissolving rates, and bioavailability, is greatly facilitated by cocrystallization of active pharmaceutical ingredients.[1] The idea of creating cocrystals, or pharmaceutical cocrystals, was developed from the fundamentals of crystal engineering and inspired both industries and academics to expand their horizons in search of more effective solid forms of APIs.[2] Cocrystals are homogenous solid phases that are solid at room temperature and are kept together by weak interactions, mostly hydrogen bonding, between two or more neutral molecular components in a crystal lattice with prescribed stoichiometry.[3] The design and creation of crystalline molecular solids with the goal of influencing material properties is often referred to as crystal engineering.[4] In 1955, Pepinsky first coined the term Crystal engineering and Schmidt implemented it in 1971.[5,6] It is well known that many new chemical entities have poor permeability and/or solubility; up to 90% of new medications are classified as BCS II.[7] Cocrystals are a type of pharmaceutical substance that can improve solubility and dissolution by producing a crystal of an API and another harmless molecule or coformer with specified stoichiometric compositions. The variety of coformer characteristics and interactions in the solid and solution phases allows for a variety of ways for controlling cocrystal solubility.[8]

PHARMACEUTICAL COCRYSTALS

In the year 1844, Friedrich Wohler created the first known cocrystal known as "quinhydrone" using benzoquinone and hydroquinone.[9] In the Cambridge Structural Database, it was the first cocrystal structure that was described.[10] Etter published the first reports on the term "co-crystal" and the design guidelines for hydrogen bonding in an organic co-crystal.[11,12] Supramolecular synthons were first conceptualized by Desiraju in 1995, marking an important turning point for the development of crystal engineering and cocrystal design.[13] Cocrystals are described as solids that are neither solvates nor simple salts and are composed of two or more different molecular and/or ionic compounds, usually in a stoichiometric ratio in the crystal lattice.[14] The FDA defines pharmaceutical co-crystals as "crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers, in the same crystal lattice."[15]

A pharmaceutical cocrystal is made up of two basic components: an active pharmaceutical ingredient (API) and a harmless material known as a coformer should be a safe component from the Generally Recognized As Safe (GRAS) list by US-FDA.[16] The distinct crystal structure of a cocrystal from either of its source materials results in unique physicochemical features. Cocrystals are appealing because they can be engineered to have better physical characteristics than either of the pure starting components.[17] It is well known that the molecular arrangement within the lattice of solids determines their key physical characteristics. Any change in these molecules' positions or interactions with one another would directly affect the behavior of the material.[18] The physical characteristics of the API, such as solubility, hygroscopicity, and compaction behavior, can be improved by cocrystallization with pharmaceutically acceptable (GRAS) chemicals without affecting the pharmacological efficacy of the API. Competing molecular connections between homologous and heterologous molecules, or similar and distinct molecules, lead to cocrystallization.[19]

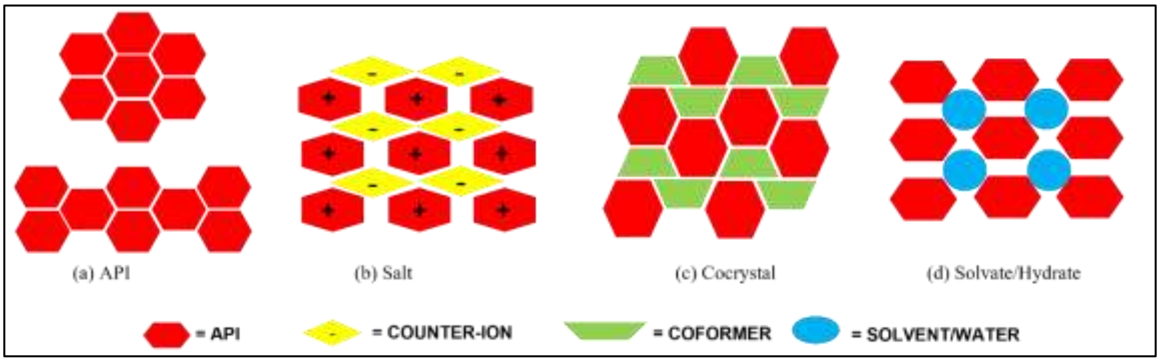

Figure 1: Schematic representation of API, salt, cocrystal, and solvates/hydrates.

ADVANTAGES OF COCRYSALS

Cocrystals have advantages over other methods for modifying the various physicochemical characteristics of pharmaceuticals without changing the pharmacological effects through noncovalent interactions.[20] When compared to amorphous solids, cocrystals are crystalline with a particular stoichiometry, which leads to superior solid-state stability and more predictable physical attributes and performance.[21] Another distinct advantage of cocrystals over more typical salts is that they can be produced for non-ionizable APIs and complex APIs that have sensitive functional groups that may not be able to withstand the extreme reaction conditions of strong acids or bases. Cocrystals have the capability to minimize the time required for drug discovery and development. Reduced development timelines lead to lower prices, which is attractive for pharmaceutical industries. Cocrystallization can modify the physicochemical characteristics of drugs such as melting point, stability, compressibility, solubility, dissolution, bioavailability, permeability, etc.[14] Green production processes such as grinding can be used to create co-crystals with high yield, no solvent use, and limited by-products.[4] Cocrystals of newer and present drugs offer new intellectual property (IP) opportunities for inventors, especially if they improve the pharmacokinetic properties of the API.[22]

DIFFERENCE BETWEEN COCRYSTALS, SALT, SOLVATES AND HYDRATES

Co-crystal, salt, and polymorphs were defined by USFDA in the draught guidance. The polymorphs are defined as the same API in different crystalline forms. Amorphous forms and solvation or hydration products, sometimes known as pseudopolymorphs, may fall under this category. The different polymorphic variants are regarded as the same APIs under the existing regulatory framework. Due to the varied crystal lattice arrangements in polymorphs, they also exhibit different physicochemical characteristics.[23,24] The physical state of the constituents is the only distinction between solvates and cocrystals. Solvates are substances in which one component is a liquid and the other a solid; nevertheless, cocrystals are substances in which both components are solid.[25] Hydrate is the term used to describe the crystalline state when water acts as a guest molecule.[26]

Salts are compounds generated by the full transfer of a proton from one substance to another.A proton transfer from an acid to a base can distinguish between salts and cocrystals. Between pairs of acids and bases, there is a full proton transfer, but not during the creation of cocrystals. In cocrystals, Van der Waal forces, hydrogen bonds, and other noncovalent interactions hold two components to one another.[27,28] When the pKa difference between the API and Coformer is in the range of negative values, there won't be any proton transfer, which offers access to cocrystal formation. The completion of proton transfer at pKa values larger than 3 results in the production of salt.[10]

PHYSICOCHEMICAL PROPERTIES OF COCRYSTALS

The primary objective of pharmaceutical cocrystallization has been to alter the properties of a drug molecule in order to produce pharmaceutical API cocrystals with an associated coformer, which would subsequently have superior properties than the crystalline form of the original drug.[29] The physicochemical properties are greatly influenced by the characteristics of APIs and coformers, the type of molecular interaction that occurs between them, and the synthetic methods used.[14] The physicochemical characteristics of pharmaceuticals, including as melting point, tabletability, solubility, stability, bioavailability, and permeability, can be improved by pharmaceutical cocrystals. These characteristics are presented here with appropriate examples.

Melting Point (M.P.): The temperature at which the solid phase and the liquid phase are in equilibrium is known as the melting point, and it is a fundamental physical property. It is a thermodynamic process with a zero free transition energy.[29] By carefully choosing the coformers, it is possible to tailor the melting point of pharmaceutical co-crystals. Due to their ability to capture additional thermal data, differential scanning calorimetry (DSC) or the Kofler method is regarded as the preferred technique for obtaining melting point data. The melting point of a compound is used to classify it and determine its purity.[19] It is also particularly useful because of its relationships with aqueous solubility and vapour pressure.[30] Many drugs have low melting points, which allows them to exist in a liquid state at ambient temperature. Through the incorporation of an appropriate coformer into the crystalline lattices, cocrystallization has the ability to change the melting point of liquid drugs.[31] Melting points of approximately 50 cocrystals were examined, and the results revealed that 51% of the cocrystals had melting points between API and coformers, 39% had melting points lower than either API or coformer, 6% had higher melting points than both API and coformer, and 4% had the similar about API or coformer.[32]

Solubility and Dissolution: Solubility and dissolution rates are critical in assessing the efficacy and activity of a drug. The variety of coformer characteristics and interactions throughout the solid and solution phases allows for a variety of ways for controlling cocrystal solubility.[8] Solubility is primarily determined by crystal lattice strength and solvent affinity. Co-crystals have the potential to decrease lattice strength while increasing solvent affinity.[33] Guzman explained the spring and parachute phenomena, which improves the solubility of hydrophobic drugs by employing a supersaturation approach. This mechanism is involved in the formation and maintenance of the supersaturated Metastable state.[34] The increased solubility of cocrystals enhances the rate of dissolution, which is the rate limiting step in the absorption of drug in the gastrointestinal tract.[35]

Sugandha *et al.* synthesized ezetimibe cocrystals using three different techniques: solution crystallization, liquid aided grinding, and reaction crystallization, with methyl paraben serving as the coformer. In the case of a cocrystal created through solution crystallization, equilibrium water solubility of ezetimibe was increased by 2-fold The solubility of cocrystals generated during reaction crystallization was strikingly similar to that of pure ezetimibe. The solubility of cocrystals synthesized using a liquid-assisted grinding technique significantly increased at 45 and 120 minutes, showing a favorable dissolution profile.[36] Wang, J.R. *et al.* showed that the improved dissolution rate of antitumor drug 6-mercaptopurine with nicotinamide using the reaction crystallization method. Cocrystals of 6-mercaptopurine have twice the dissolution rate of the pure compound.[37]

Bioavailability: Low oral bioavailability of APIs is a key problem when developing novel formulations. Bioavailability is defined as the rate and extent of a pure drug that reaches into systemic circulation.[38] Pharmaceutical cocrystals with improved water solubility and oral bioavailability are designed and created primarily through crystal engineering. Jung, M.S. *et.al.* evaluated the bioavailability of indomethacin-saccharin cocrystals, which had previously been characterized and demonstrated to have a higher solubility than indomethacin. The in-vivo bioavailability of the IND–SAC cocrystals in dogs was significantly higher than that of indomethacin.[39]

Tabletability: The crystal structure and/or packing and interaction energy of the drug powder can be greatly improved through cocrystallization, which can then be used to modify the tabletability and compaction properties of the API.[40] Zheng *et al.* created cocrystals of Resveratrol with the coformers 4- aminobenzamide and isoniazid and investigated their improved solubility and tabletability. The compaction behavior of paracetamol cocrystals with trimethylglycine and oxalic acid was shown to be superior to that of the pure drug. The synthesis of cocrystals with 4- aminobenzamide and isoniazid improved the tabletability of resveratrol.[41]

Stability: During the development of pharmaceutical cocrystals, several stability studies such as chemical stability, thermal stability, solution stability, and photostability should be carried out.[40] The application of proper stability testing provides crucial information to formulation scientists on numerous parameters that may impact product stability, potential compatible excipients, and desired storage conditions.[42] Remenar *et al.* studied celecoxib:nicotinamide cocrystals in simulated gastrointestinal fluids and revealed cocrystal dissociation and celecoxib Form I and III recrystallization. The addition of sodium dodecyl sulphate and polyvinylpyrrolidone improved the supersaturated solutions' physical stability.[43]

Permeability: For medications taken orally, adequate permeability from GI tract membranes is a need for significant systemic absorption and distribution in addition to solubility.[44] Sanphui and coworkers performed a permeability study of hydrochlorothiazide cocrystal (HCT) with coformer nicotinic acid, nicotinamide, 4-aminobenzoic acid, succinamide and resorcinol utilizing the Franz cell diffusion method. Except for HCT-succinamide, the findings demonstrated that the quantity of drug flux available in almost all cocrystals is more than the amount of pure drug.[45]

Hygroscopicity: The hygroscopicity of a pharmaceutical material is known to influence its behavior at several stages of the pharmaceutical process, including manufacture, packing, storage, and transport. It also has a significant impact on materials' stability, aesthetics, and efficiency.[46] The investigation of hygroscopicity of drug substances is needed as it could affect physicochemical characteristics such as solubility, dissolution rate, stability, bioavailability, and mechanical properties.[31] Ming-Hui *et.al.* prepared cocrystals of Oxymatrine (OMT) with urea (OMT-Urea-DH), sulfanilamide (OMT-SUA), theophylline (OMT-THP), 2-ketoglutaric acid (OMT-KTA-MH), and 3-hydroxy-2-naphthoic acid (OMTHNA) to reduce hygroscopicity. They revealed that OMT-SUA, OMT-KTA-MH, and OMT-HNA greatly decrease the hygroscopicity of OMT.[47]

SELECTION OF COFORMER

The choice of the most promising coformer is an important step in imparting desirable properties to the cocrystal, but it is also a difficult task in API crystal engineering. The non-API components used as coformers should be non-toxic without any adverse effects. Typically, the cocrystal former should be listed in the US FDA's "Everything added to food in the United States" (EAFUS) list, which includes approximately 3000 compounds that are eligible as food additives or have been designated as Generally Recognized as Safe (GRAS).[48] Coformers are primarily selected using several approaches such as knowledge-based strategies and experimental methods. Researchers used a variety of knowledge-based approaches to select suitable coformers and screen cocrystals, including hydrogen-bonding propensity, synthonic engineering, supramolecular compatibility by Cambridge Structure Database (CSD), pKa-based models, Fabian's method, Lattice energy calculation, the conductor-like screening model for real solvents (COSMO-RS), Hansen solubility parameter, and virtual cocrystal screening (based on molecular electrostatic potential surfaces-MEPS).[14]

Synthonic Engineering: Corey coined the term "Synthon" in 1967, defining it as "Structural units inside supermolecules that can be generated and/or built by known or conceivable synthetic procedures involving intermolecular interactions."[49] Desiraju described supramolecular synthons as a spatial arrangement of intermolecular interactions that serves as the basis for any supramolecular synthesis.[50] Crystal engineering uses the fundamental principles of supramolecular chemistry, or chemistry beyond the molecule, to create unique entities by altering non-covalent intermolecular interactions. Some of the interactions that are regularly observed in this aspect are hydrogen bonding, metal coordination, van der Waals forces, hydrophobic forces, electrostatic effects, and pi-pi interactions.[3] These interactions will generate patterns that can group molecules into a one-, two-, or three-dimensional arrangement in the crystal. This pattern of interaction is known as the supramolecular synthon.[51] These supramolecular synthons are categorized as homosynthons or heterosynthons based on the complimentary functional groups in the drug and coformer.[10] Homosynthon refers to the molecular interaction that occurs between two of the same functional groups present in the API and its coformers (such as acid-----acid and amide-----amide groups) , whereas heterosynthon refers to the interaction between two distinct functional groups. (such as acid-----amide, acid-----pyridine and amide-----pyridine groups).[51]

Hydrogen Bonding Propensity: According to numerous research, the hydrogen bond donors and acceptors of the partners should form a hydrogen bond. Furthermore, the best hydrogen bond donors and acceptors interact inside the crystal structure, resulting in the formation of co-crystals.[52] The hydrogen bonding propensity (HBP) tool, which was originally created to assess the likelihood of polymorphism, is also useful for knowledge-based cocrystal design.[53] Etter and Donohue developed Hydrogen Bond Rules to estimate the situations that lead to hydrogen bond interactions that result in cocrystals. In hydrogen bonding, almost all good proton donors (such as -COOH, -NH4 +) and acceptors (such as -OH, -NH3) are utilized. Intramolecular hydrogen bonds with a six-membered ring (such as C-H----O) are created first as compared to intermolecular hydrogen bonds (such as N-H----O and O-H----O). After intramolecular hydrogen bond creation, the remaining best proton donors and acceptors participate in intermolecular hydrogen bonding. All acidic hydrogen atoms are included in hydrogen bonding in the crystal structure.[10] The HBP model attempts to determine the probability of each prospective H-bond formation in the target system and the arrangement of its H-bonding propensities in a rank-wise manner. The HBP tool works by building a statistical model based on the 2D characteristics of a set of structures with functional groups and molecules similar to the target.[53]

ΔpKa Rule: ΔpKa value has been applied to evaluate the ability of a coformer with a specific API to form cocrystals. In the case of salts, the phenomena that occurs is proton transfer. The pKa value (negative logarithm of dissociation constant) reflects capacity of an acid molecule to give up a proton. There will be no proton transfer if the difference between the pKa values of the API and coformer is negative (less than 0). As a result, cocrystal formation is possible in such a circumstance. Due to the completion of proton transfer, salt formation can be seen when pKa value is greater than 3.[10] If the pKa value is between 0 and 3, salt or co-crystal can be formed. Cruz-Cabeza investigated the pKa rule in detail in order to correlate it with proton transfer in the solid state, and it was found that there was a linear relationship between ΔpKa (pKa [protonated base] - pKa [acid]) and the possibility of proton transfer between acid-base pairs.[54]

Hansen Solubility Parameter (HSP): On a molecular level, cocrystals are miscible systems. Therefore, it is believed that assessment of the miscibility of the component molecules in the solid state can predict the possibility of cocrystal formation, which would be significant for cocrystal screening.[55] The use of components with similar miscibility improves the success rate of the cocrystal synthesis.[14] The concept Solubility parameter (δ) was established by Hildebrand and Scott, who suggested that miscible substances would show similarities in Solubility parameter(δ). The Hansen solubility parameter model was proposed by Hansen and is based on the idea that the total energy of different interactions can be divided into partial solubility parameters, namely dispersion (δ_d), polarity (δ_p), and hydrogen bonding (δ_h).[53] The total solubility parameter (δ_t), also called the three-dimensional solubility parameter, can be represented as follows:

$$\delta t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5} \qquad \text{……….(eq}^{n}\text{.1)}$$

Mohammad *et al.* proposed that in order to miscible an API and coformer and form a cocrystal, the difference in HSP should be smaller than $\Delta\delta < 7\ \mathrm{MPa}^{0.5}$

Various theoretical and experimental methods based on solubility, calorimetry, sublimation, vaporization, inverse gas chromatography, and group contribution methods have been utilized to estimate a HSPs of substances. The group contribution method is a popular theoretical method for calculating HSPs that simply requires knowledge of the chemical structure of the substance.[55]

The scientists Krevelen and Greenhalgh suggested the theoretical prediction or possibility of the co-crystal formation. According to Krevelen co-crystals may form if the deviation in the solubility parameter values of the partners is $\leq 5\mathrm{MPa}^{0.5}$. Greenhalgh proposed that the formation of co-crystals may occur if the difference is $\leq 7\ \mathrm{MPa}^{0.5}$.[52]

Cambridge structural database (CSD) : The Cambridge Structural Database (CSD) is a vast collection of various compounds that provides insights into the crystal structures of molecule. Also estimates expected intermolecular interactions, and enables knowledge-based cocrystal design.[56] The CSD was developed and is currently maintained by the Cambridge Crystallographic Data Centre, which was founded in 1965 at the Department of Chemistry, Cambridge University. CSD and its related modules provide knowledge-based approaches for the construction of supramolecular synthons in relation to the screening of cocrystals in the following ways:[53]

- Analyzing the characteristics of crystal packing and looking for hydrogen bond motifs to see how often they occur.
- Identifying the hydrogen bond donors and acceptors, as well as the competition that exists between them, in order to predict the formation of cocrystals and to evaluate the possibility of polymorphism.
- Full interaction maps and Solution of crystal structures from powder diffraction data utilizing DASH.

The CSD can be used by scientists to compare existing data with data obtained from crystals generated in their laboratories. The data can also be utilized to visualize the structure via applications such as atoms, powder cells, and others. This is especially useful for analytical purposes since it allows for the identification of phases existing in a crystalline powder mixture without the necessity for crystal growth.[3]

Fabian's method: Fabian created the molecular complementarity tool by analyzing the molecular descriptors of the molecules in a cocrystal.[57] A diverse set of reliable co-crystal-forming structures was extracted from the CSD, and the molecular descriptors (single atoms, number of bonds and groups, number of hydrogen bond donors and acceptors, size and shape, surface area, and electrostatics of molecules) was calculated for each molecule. The database provided descriptions of pairs of molecules that could form cocrystals based on computed molecular characteristics.[14] It was found that the molecules that form cocrystals tend to be similar in terms of their polarity and molecular shape.[19] The Molecular Complementarity tool is especially beneficial when target molecules lack common hydrogen bonding groups. Karki and colleagues used this method to screen coformers for Artemisinin that lacked common hydrogen bonding functionalities.[58]

Phase Diagrams: Phase diagrams are used to identify the various solid phases that can develop between any drug-coformer pair. Those kinds of phase diagrams can be constructed for either two (API-coformer) or three (API-coformer-solvent) components.

(a) Binary Phase Diagrams: Binary phase diagrams are typically created using data points generated from thermal analysis methods like DSC analysis. The onset temperature of the first endotherm in a DSC thermogram is usually selected as the solidus point. The peak temperature of the second endotherm is utilized as the liquidus point for creating the phase diagram. In general, the eutectic forming binary system follows a 'V'-shaped curve, while the cocrystal forming system follows a 'W'-shaped curve, indicating cocrystal generation between the two eutectics.[10]

(b) Ternary Phase Diagrams: Cocrystals can form during solution crystallization experiments. However, due to the incongruent solubility behaviour of individual components in the solvent system, multicomponent single crystals do not always form during solution crystallization. Therefore, before attempting solution crystallization, it is necessary to determine the thermodynamic behavior of a system including ternary components.[59] When the solubilities of the two components are identical or congruent, the phase diagram displays a more symmetrical trend. On the other hand, when the solubility of the two components differs or is inconsistent, the phase diagram will exhibit less symmetrical behavior.[60]

COSMO-RS: The Conductor-like Screening Model for Real Solvents (COSMO-RS) theory, developed by Andreas Klamt, is a unique combination of quantum chemical knowledge and liquid phase thermodynamics that has been utilized to reliably predict thermodynamic equilibrium characteristics of liquids. COSMO-RS has been demonstrated to be a more efficient, accurate, and widely applicable method for screening cocrystals.[53] COSMO-therm software, based on the COSMO-RS fluid-phase thermodynamic technique, was used to describe the miscibility of coformers in super-cooled liquid (melt) phase for the purpose of screening appropriate coformers for an API.[48] Therefore, it is possible to predict cocrystallization by measuring the affinities between the API and coformer under supercooled conditions. The excess enthalpy H_{ex} of API and coformer mixture in comparison to that of the individual pure cocrystal formers represents the potential for cocrystallization of the components.[53]

$$H_{ex} = H_{AB} - x_m H_{pure,}A - x_n H_{pure,}B \qquad \text{....(eq}^{n}\text{.2)}$$

Where, H_{ex} represents the excess enthalpy, H_{AB} is the enthalpy of the stoichiometric mixture of the components A and B, H_A and H_B are the enthalpies of pure component A and B respectively and x is the mole fraction of respective components. The greater the negative value of Hex, the more likely the cocrystal system is thermodynamically favorable.[53]

COCRYSTAL PRODUCTION METHODS

Co-crystal preparation can be accomplished using a variety of methods. Some of them have been in use for decades, while others have simply recently been introduced as a result of the rapid development in co-crystal applications and commercialization. Both old and novel co-crystallization processes have been extensively reviewed.[61] Cocrystal synthesis methods can be typically classified as solid-state or solution-based. Solid-state procedures include methods that employ very little or no solvents. Solution crystallization methods include solvent evaporation, slow cooling evaporation, and reaction crystallization; also, additional techniques include supercritical fluid methods, miscellaneous methods.[62] Solvent-free approaches, in particular, are gaining popularity due to the potential of a green chemistry principle correlation.[33]

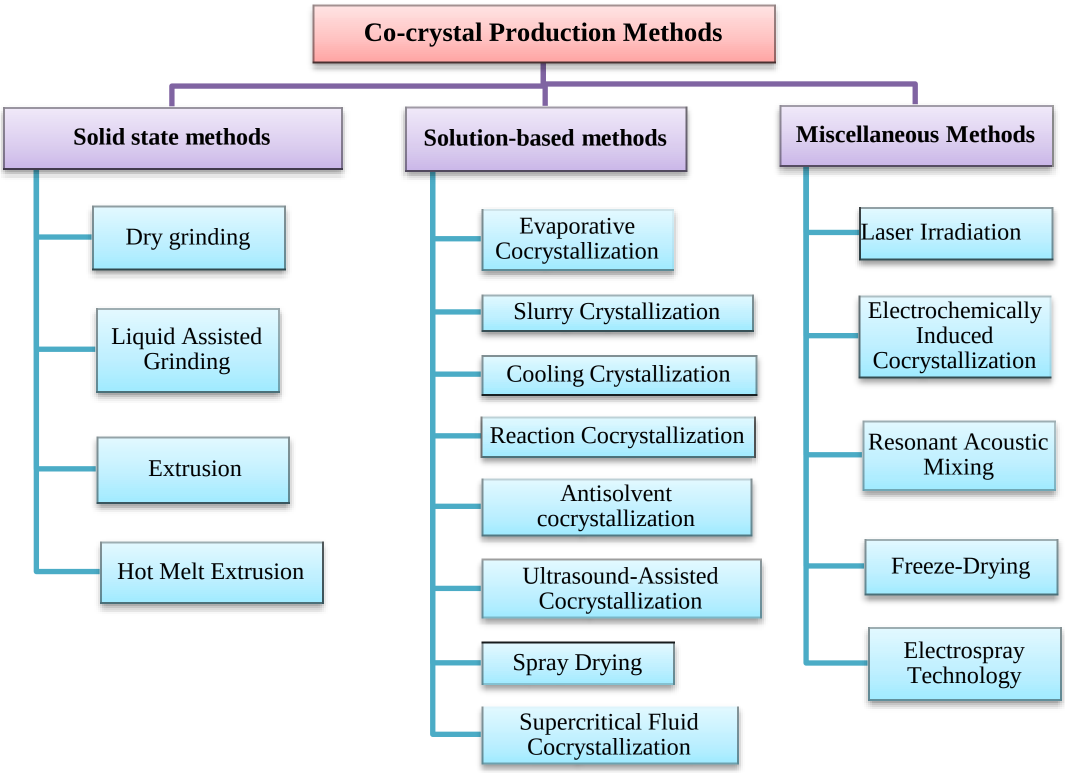

Figure 2: Various methods for cocrystal production.

Solid state methods: For the creation of cocrystals, solid-based procedures utilize very little or no solvent. They are divided into several ways, including contact formation, neat or dry grinding, liquid assisted grinding, extrusion, hot-melt extrusion, and high shear wet granulation.[2]

Contact Formation: The spontaneous formation of cocrystals through the gentle mixing of pure API and coformer in a controlled ambient environment has been reported. During cocrystallization, no mechanical forces are applied in this method.[17] The proposed mechanisms for spontaneous crystallization by contact include vapour diffusion of the two solids, moisture sorption, eutectic phase formation, amorphization, and long-range anisotropic molecular migration.[31] MacFhionnghaile *et al.* described the formation of caffeine-urea cocrystals in 3 days by individually pre-milling raw materials at room temperature and 30% relative humidity.[63]

Dry grinding: It is also called as solid-state grinding. In this method, the drug and coformer are mixed and ground together either by utilizing a mortar and pestle or by a ball mill. The stability of the material could be affected by the heat generated during the grinding process. As a result, high melting point drugs are typically used in solid state grinding for co-crystallization.[52] Panzade *et al.* created Piroxicam cocrystals utilizing the dry grinding process and sodium acetate as a coformer. The author reported changed piroxicam cocrystal characteristics and designed orodispersible tablets with faster disintegration and increased dissolution rate.[16]

Liquid Assisted Grinding (LAG): This is a modification of dry grinding in which a minor quantity of solvent is added during the grinding process, and it has been employed to improve supramolecular selectivity in crystalline systems, both polymorphic and stoichiometric.[64] The use of a solvent can be defined as catalytic because its small amount is not part of the final product. Its benefits include better crystallinity, greater performance, and the ability to control polymorph generation, while a vast variety of coformers are available for cocrystallization. This technique increases the cocrystallization rate, as some cocrystals showed poor performance in cocrystal formation using dry grinding for a considerable amount of time.[29] Thenge *et al.* developed diacerein cocrystals with urea and tartaric acid using LAG. Drug and coformer were combined in a mortar and pestle in a 1:1 ratio, and the mixture was ground for 90 minutes with addition of few drops of ethanol.[65]

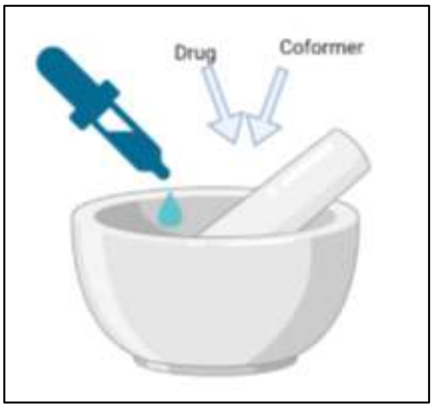

Figure 3: Liquid Assisted Grinding

Extrusion: Extrusion is a relatively new technique that utilizes a twin-screw extruder (TSE) to simultaneously mix and pressing the starting components or a mixture of starting components through a die under a controlled environment. Unlike hot melt extrusion, which requires melting the materials and mixing them at high temperatures, this technique is controlled below the melting point of the material being processed.[61] Medina *et al.* used the TSE method for the first time to synthesize cocrystals of caffeine and AMG 517. Their study proved that TSE helps to have a highly efficient mixing and close material packing, which results in improvement of surface contact between cocrystal components. Consequently, cocrystal generation will be enhanced without the addition of any solvent.[66]

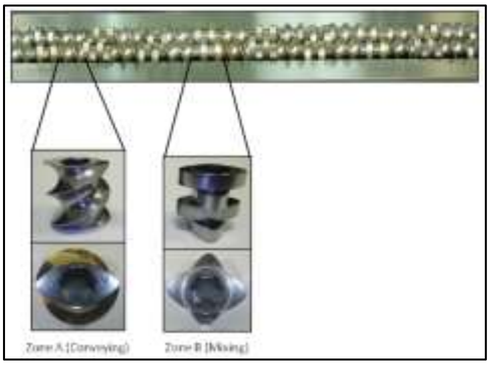

Figure 4: Screw design employed for TSE.[66]

Hot Melt Extrusion: Hot melt extrusion can be used as a continuous manufacturing method in a single step to manufacture co-crystals.[52] In this method, API and coformers are transferred into a fixed controlled temperature system where they melt and create cocrystals. Because the drug and coformer must be mixed in a molten state, this technique is not suitable for thermolabile drugs. In this method, API and coformer are mixed in molten form to improve surface contact without the use of a solvent.[67] Kevin *et al.* synthesized Carbamazepine cocrystals by Hot-Melt Extrusion. The author utilized nicotinamide as the coformer, and the cocrystal matrix was characterized using DSC, FT-IR, and powder X-ray diffraction.[68]

Solution-based methods: There are various methods available for cocrystallization from solution, and each will be covered in the following section. In these methods, drug and co-former supersaturation is necessary for the co-crystal formation from solution; this is followed by the nucleation process and crystal development. To ensure the thermodynamic stability of the co-crystalline suspension, proper precautions and conditions should be established.[61]

Evaporative Cocrystallization: This is the most commonly utilized method for creating cocrystals. With the appropriate stoichiometric ratio, the components are dissolved in a typical solvent, and the solvent is then allowed to slowly evaporate.[29] The functional groups in the API and coformer interact during dissolution to create hydrogen bonds.[14] The solvent chosen has a significant impact on solubility. If the solubility of the two components differs, the component with the low solubility will precipitate. Cocrystal synthesis by solvent evaporation is a small-scale process that does not involve complex equipment and yields high-quality and pure cocrystals.[29] Basavoju *et al.* present a typical example in the description of the formation of single crystals of a norflaxin-isonicotinamide cocrystal from chloroform. Rod-shaped single crystals of a 1:1 norfloxacin:isonicotinamide cocrystal were obtained.[69]

Slurry Crystallization: In the slurry crystallization method (or isothermal slurry conversion), drug and solid coformers are added to a solvent or solvent mixture at a fixed stoichiometric ratio for a specified equilibration period, and the solid is left in excess throughout. The suspension formed is then stirred, filtered, and dried.[2] The slurry crystallization was used to create and patent the celecoxib-venlafaxine cocrystal. By using a high solubility BCS class I drug venlafaxine, the solubility issues with celecoxib (BCS class II) are resolved.[29]

Cooling Crystallization: Cooling crystallization is another solution-based method of cocrystal synthesis. Cooling the co-crystalline solution achieves the supersaturation essential for co-crystal development. A decrease in temperature reduces the solubility of both coformers, resulting in precipitation and subsequently co-crystal development.[61] A designed seeded cooling crystallization was utilized to synthesize cocrystals of carbamazepine:nicotinamide from ethanol, in order to establish a scalable solution cocrystallization strategy.[70]

Reaction Cocrystallization: The reaction crystallization technique is utilized for the rapid creation of cocrystals at the microscopic and macroscopic scales at a nearby temperature, where nucleation and cocrystallization are dependent on the cocrystal constituents and their solubility behavior. The less soluble constituent (API) is saturated in methanol and filtered, and then the more soluble constituent (coformer) is added in an amount just below its solubility limit. Throughout the crystallization process, solution concentrations were monitored using HPLC to determine whether the examined solid looked like cocrystals (complex of the reactants). HPLC is also used to examine the solid precipitates in order to determine the stoichiometry of the complex. If the HPLC results indicated that the material was a cocrystal, it is further analyzed by DSC, TGA, and PXRD.[14] Rodríguez-Hornedo *et al.* prepared carbamazepine:nicotinamide cocrystal by reaction cocrystallization under ambient conditions.[71]

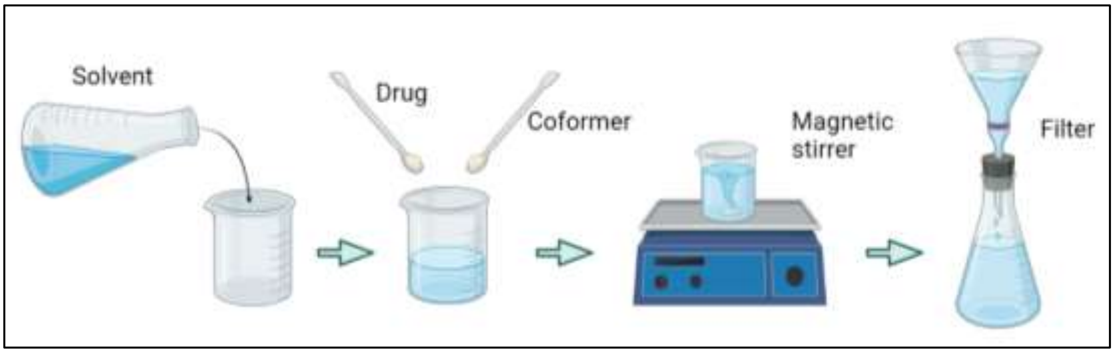

Figure 5: Illustration of cocrystal synthesis by Reaction Cocrystallization.

Antisolvent cocrystallization: Another approach for producing high-quality cocrystals is antisolvent cocrystallization, which involves the precipitation or recrystallization of the API and coformer.[52] An antisolvent is used in antisolvent cocrystallization to lower the solubility of coformers in the solvent, resulting in cocrystal formation. In general, the solvent and antisolvent should be miscible to form a single phase. An organic solvent and water mixture is the most often used solvent-antisolvent combination.[72] It has been reported that antisolvent crystallization was used to create cocrystals, indomethacin-saccharin and carbamazepine-saccharin, respectively.[29] Nano-sized cocrystals have also been created via antisolvent cocrystallization. Thakor *et al.* studied several solvents, antisolvents, and stabilizers for the synthesis of carbamazepine-nicotinamide nanococrystals.[73]

Ultrasound-Assisted Cocrystallization: Ultrasound-assisted cocrystallization or sonocrystallization is another technique that has been utilized for the production of cocrystals. Childs *et al.* synthesized cocrystals with a range of drug-coformer pairings using the SonicSlurry technique. In several experiments, sonication was repeated for 24 hours on seeded or unseeded crystal slurries.[74] Sonication causes the creation of cavity bubbles inside the solution, which act as nucleation sites and result in nucleation events at lower superstations. Sonication can increase nucleation rate while decreasing induction time and cocrystal agglomeration.[72] Rodrigues *et al.* used ultrasound-assisted cocrystallization for high-throughput screening of hydrochlorothiazide cocrystals.[75]

Spray Drying: The spray drying technology is commercially utilized to make amorphous solid dispersions, but recent research shows that it can also be used to make cocrystals. It is advantageous due to its continuous, highly controllable, and quick operation. It is a continuous single-step method of converting liquids (solutions, suspensions, slurries) into solid powders by dispersing an undersaturated solution of both drug and coformer with a hot air stream, where the solvent is rapidly removed by evaporation.[2] Alhalaweh *et al.*, prepared Theophylline cocrystals with urea, nicotinamide and saccharin utilizing spray drying technology. Author used various solvents and solution concentrations while drying was done with nitrogen gas.[76]

Supercritical Fluid Cocrystallization: Supercritical fluids are compounds that are highly compressed at temperatures (Tc) and pressures (Pc) above their critical point, where the liquid and gas phases are indistinguishable. Supercritical Fluid methods have minimal environmental impact (green solvents), fewer processing steps, solvent-free end products, customizable fluid characteristics, strong solvation power, and utilization of moderate temperatures to avoid product deterioration. Beyond the critical point, fluid possesses the diffusivity of a gas and the solvating characteristic of a liquid.[74]

i. **Co-crystallization with supercritical solvent (CSS):** CSS has been reported to promote cocrystal formation by utilizing the increased molecular mobility generated by scCO2. Typically, the solid powders are put into a high-pressure vessel, and scCO2 is supplied under temperature and pressure control. Padrella *et al.* investigated the potential of CSS for cocrystal production by suspending theophylline, indomethacin, carbamazepine, caffeine, sulfamethazine, acetylsalicylic acid, and saccharin with or without a co-solvent.[74]

ii. **Rapid Expansion of Supercritical Solvents (RESS)** : The rapid expansion of supercritical solution (RESS) approach involves rapidly depressurizing a solution of the API and coformer in scCO2 to atmospheric levels, resulting in high supersaturation of the solute in scCO2. This supersaturation causes nucleation and drives fine particles to aggregate into crystals.[2]

iii. **Supercritical Antisolvent Co-crystallization (SAC):** For the co-crystallization process, supercritical CO2 is used as an antisolvent. In contrast to RESS, this approach requires the API and the co-crystal former to have reduced solubility in supercritical CO2 in order to precipitate as one co-crystal structure. Once in a vessel, the CO2 dissolves in the utilized solvent, causing simultaneous volume expansion and lowers the solvent solubility, resulting in precipitation.[61] Courtney *et al.* investigated the production of itraconazole and succinic acid cocrystals via gas antisolvent (GAS) cocrystallization utilizing pressurized CO2. At ambient temperature, the author mixed itraconazole and succinic acid in a liquid solvent (tetrahydrofuran) and compressed the solution with CO2, which reduced the solvating ability of tetrahydrofuran and induced crystallization of itraconazole-succinic acid cocrystals.[48]

Miscellaneous Co-Crystallization Methods:

Laser Irradiation: This approach uses a high-power CO_2 laser to irradiate powder mixtures of drug and coformer and induce recrystallization to a cocrystal structure. Titapiwatanakun *et al.* employed this technique to create caffeine cocrystals with oxalic acid and malonic acid.[1]

Electrochemically Induced Cocrystallization: Urbanus *et al.* illustrated the potential of employing cocrystallization in combination with electrochemistry for in situ carboxylic acid product elimination. This research demonstrated that electrochemistry can be utilized to locally shift the pH in order to get neutral carboxylic acids and generate a driving force for cocrystallization.[17]

Resonant Acoustic Mixing: In the absence of any grinding media, resonant acoustic mixing has been utilized to blend the API molecule and coformer in the presence of a liquid to produce a cocrystal. Mechanical energy is conveyed acoustically into a wetted powder mixture in this approach, resulting in extensive mixing of the components. Using a labRAM resonant acoustic mixer running at 80-100G and 60 Hz, several carbamazepine cocrystals have been effectively produced. The cocrystal products were isolated at a variety of laboratory scales, including 100 mg, 1.5, and 22 g, and the technique appears to be scalable.[17]

Freeze-Drying: Freeze drying (or lyophilization) is another technique that has been introduced for the production of pharmaceutical cocrystals. Freeze drying is a multistep process that involves freezing a wet product and then sublimating it directly to vapour by providing a low partial pressure of water vapour.[74] Eddleston used freeze drying as a broad approach for creating new solid forms of pharmaceutical cocrystal structures. By dissolving various cocrystal systems in water or t – butanol the cocrystal synthesis of various forms was accomplished, including a novel solid solution of caffeine - theophylline and a potential new cocrystal form of theophylline:oxalic acid.[77]

Electrospray Technology: The process of electrospraying involves simultaneously producing and charging droplets with the help of an electric field. A capillary nozzle that is kept at a high potential discharges a solution containing the dissolved materials through an electric field, which causes the solution droplets to elongate and form a jet. Drying the solution jet produces particles, which are then collected on a charged powder collector. Patil *et al.* investigated the potential of this technique to produce cocrystals of carbamazepine and itraconazole with various coformers.[17]

CHARACTERIZATION OF COCRYSTAL

Characterization of newly generated cocrystals is an important step in validating cocrystallization. Various techniques have been employed to characterize pharmaceutical cocrystals and elucidate intermolecular interactions.

Single-crystal and Powder X-ray diffraction (XRD): Powder X-Ray Diffraction (PXRD) and single crystal X-Ray Diffraction (SCXRD) can be used to determine the crystalline state of cocrystals. Whereas SCXRD gives precise structural information such as lattice parameters, space groups, miller indices, unit cell volume, crystal system, inter, and intramolecular interactions. PXRD provides information regarding solid phase crystallinity, since cocrystals have distinct sharp peaks that differ from the peaks of the cocrystal components.[10] Pardela *et al.* reported quantification of cocrystals in the crystalline mixture employing PXRD. They developed and utilized PXRD to investigate the generation of indomethacin-saccharin cocrystals by mechanochemistry.[78]

Spectroscopic Analysis: A variety of spectroscopic techniques are frequently employed to characterize cocrystals.

i. **Fourier-Transform Infrared Spectroscopy:** It is a popular method for predicting and determining chemical conformation, intermolecular interactions, and communion studies between API and coformers. The API, coformers, and cocrystals were analyzed using FTIR in the 400-4000 cm^{-1} wavelength range. This method is fast, nondestructive, sensitive to changes in molecular structure, and can detect a functional group.[1] Aakeroy *et al.* differentiated cocrystals from salts by employing FTIR assessed the carboxylic acid's significance in hydrogen bond formation.[79]

ii. **Terahertz Time-Domain Spectroscopy:** Terahertz time-domain spectroscopy (THz-TDS) can be employed to characterize cocrystals in addition to PXRD. Terahertz spectroscopy can discriminate between chiral and racemic molecular and supramolecular structures.[14] Parrott *et al.* studied the sensitivity of terahertz spectroscopy to changes in the molecular and supramolecular structure of structurally similar cocrystals of theophylline with different coformers.[80]

iii. **Solid-State Nuclear Magnetic Resonance:** ssNMR spectroscopy offers information on molecular mobility, hydrogen bonding differences, and solid crystallinity. Solid-state Nuclear Magnetic Resonance (ssNMR) spectroscopy can analyze cocrystal powders that are difficult to characterize by single crystal X-Ray diffraction analysis (owing to low crystal quality) to acquire a crystal structure.[10] In order to characterize pharmaceutical co-crystals, solid-state nuclear magnetic resonance is frequently used since it can reveal co-crystal structural information. This technique is also employed to differentiate cocrystals and salts since it can detect the degree of proton transfer.[52]

Thermal Analysis: Thermal analysis entails a variety of techniques that record the physical or chemical changes in the sample's thermal properties over time and in a controlled environment via programmed temperature change (e.g., cooling, heating, alternating, or keeping at a constant temperature). Mass, heat or heat flow, enthalpy, and other properties can be assessed.[29]

i. **Differential scanning calorimetry (DSC):** DSC is the widely employed analytical technique in the pharmaceutical industry for characterizing cocrystals. Pure drug, cocrystal former, physical mixture, and cocrystals were weighed out in aluminium pans and heated at rates ranging from 5 to 30 degrees Celsius, with an empty pan used as a reference. The nitrogen gas flow rate of 50 ml/min kept the atmosphere inert. Cocrystal formation can be predicted by the existence of exothermic peak and endothermic peak on the thermogram and cocrystals show a different exothermic peak from that of the pure drug and coformer. DSC can be used to assess the melting point, heat of fusion, glass transition temperature, polymorphic character, and endothermic or exothermic behavior of cocrystals.[14]

ii. **Thermal Gravimetric Analysis (TGA):** TGA is an appropriate technique for determining the hydrates/solvates forms of cocrystals or the presence of volatile components, as well as the temperature of decomposition or sublimation. TGA analysis can predict thermal stability, compatibility, and cocrystal purity. The weight loss of sample mass during TGA analysis is a sign of volatile component loss or cocrystal decomposition.[81,82]

iii. **Hot-stage microscopy (HSM) :** HSM is a technique that combines microscopy with thermal analysis to investigate the physical properties of solid materials as a function of temperature and time. , HSM can be utilized to determine the phase transition and thermal behavior of solid-phase substances.[83] When the drug crystals are heated, they undergo modifications that can be observed immediately and easily under a microscope. Thermal changes such as melting point, melting range, crystal development, crystalline transformations, etc. can be illustrated in this technique.[29]

Field emission Scanning Electron Microscopy (FESEM): FESEM is employed for the microscopic investigation of solid-phase characteristics, such as crystal shape, size, and surface properties.[83] Micrographs of constituents and co-crystals generated from FESEM experiments were used for comparison. Heat energy is not used in the field emission electron microscope; instead, a so-called "cold" source is used. A high electric field is used to emit electrons from the conductor's surface. As a cathode, a tungsten filament with a thin and sharp needle (tip diameter 10- 100 nm) is used. The field emission source is coupled to a scanning electron microscope for the recording of co-crystal micrographs.[52]

MULTIDRUG CO-CRYSTALLIZATION (MDCs)

The combination of multiple active pharmaceutical agents into unit doses has become a prominent drug development approach, because in the management of many chronic disorders, such as infectious diseases, AIDS, cancer, diabetes, and cardiovascular disease, monotherapy is no longer considered effective.[84] The benefit of this was shown in patient adherence and reduced product development costs. These and other advantages can be acquired by combining APIs in pharmaceutical co-crystals.[61] MDCs are crystalline solids composed of two or more active ingredients in a stoichiometric ratio. They are also termed as drug-drug cocrystals. It is a modern technique for drug development.[67] Thipparaboina *et al.* extended co-crystal definitions to MDC systems, proposing that MDCs be defined as ‘dissociable solid crystalline supramolecular complexes comprising two or more therapeutically effective components in a stoichiometric ratio within the same crystal lattice, wherein the components may predominantly interact via nonionic interactions and rarely through hybrid interactions (a combination of ionic and nonionic interactions involving partial proton transfer and hydrogen bonding) with or without the presence of solvate molecules’.[84]

MDC may have benefits over pure APIs, including as improved solubility and dissolution of at least one element, greater bioavailability, improved stability of unstable APIs through intermolecular interactions, and improved mechanical strength and flowability.[17] MDCs are produced in the same way as standard single drug co-crystals, and the processes employed are identical. Solvent evaporation, cooling crystallization, co-grinding, and solvent drop grinding, slurry crystallization, melting, and sonic crystallization are some of the classic techniques for co-crystal formation that are also used in MDC synthesis. The effective application of these approaches to MDCs has been supported by an increasing number of these hybrids in literary works.[61] Grobelny *et al.* reported two drug-drug co-crystals of the anti-tuberculosis drugs isoniazid (INH), pyrazinamide (PYR) and 4-aminosalicylic acid (PAS). The first is the 1 : 1 molecular complex of INH and PAS; another is the monohydrate of the 1 : 1 complex of PYR and PAS.[85] The co-crystallization of meloxicam, a nonsteroidal anti-inflammatory, with aspirin leads in a co-crystal with a lesser duration required to achieve the human therapeutic concentration in comparison to the parent drug meloxicam.[86]

REGULATORY ASPECTS OF PHARMACEUTICAL COCRYSTALS

Pharmaceutical cocrystals development and quality control strategies primarily based on the regulation of cocrystals by regulatory authorities. USFDA classified pharmaceutical cocrystals for the first time in April 2011. In that report, cocrystals were classified as 'Drug Product Intermediates (DPIs)' by the FDA Center for Drug Evaluation and Research (CDER), and were defined as "solids that are crystalline materials consisting of two or more molecules in the same crystal lattice."[2] This classification was unacceptable to industry since recognizing cocrystals as DPIs would have different regulatory reporting requirements than polymorphs or salts.[83] The FDA revised the definition of cocrystal several times, most recently in February 2018, describing pharmaceutical cocrystals as “crystalline materials composed of two or more different molecules, typically an active pharmaceutical ingredient (API) and cocrystal formers (“coformers”), in the same crystal lattice.”[20] A latest guidance by the FDA in February 2018 describes cocrystals as a polymorph, because the solvates are of the initial drug substance.[15] With this guidance, the pharmaceutical industries can manufacture cocrystals at existing formulation facilities using APIs and coformers. When filling new drug applications (NDAs) and abbreviated NDAs (ANDAs) consisting a cocrystal form, pharmaceutical manufacturers are required to provide relevant data that support the structure of the cocrystals and illustrate that no ionic interactions, such as salt and substantial dissociation of the API from its cocrystal form, occur prior to actually reaching the site of pharmacological action.[83]

From a regulatory perspective, drug products that are designed to contain a new co-crystal are considered analogous to a new polymorph of the API. A crystal made up of two or more APIs (with or without the addition of a coformer) will be recognized as a drug product with a fixed-dose combination and not a single new API.[87] In 2015, EMA also published a reflection paper on the use of cocrystal from active ingredients in medicinal products. According to EMA, cocrystals are “homogeneous (single phase) crystalline structures comprising two or more components in a specific stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)”.[2] In contrast to the FDA, EMA considers cocrystals primarily as APIs and applies to various formulations if the drug maker can provide evidence of different efficacy or safety levels. EMA may include the co-crystals in the category of ‘new active substances’ and ‘new active substances’ stated as “The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy”.[88] Moreover, the European Medicines Agency's adoption of the term "cocrystals" as "drug substances or APIs" instead of "DPIs" has complicated this concept. It will now be difficult for pharmaceutical scientists to conceptualize the cocrystal strategy while still adhering to the regulatory requirements set forth by the FDA and EMA.[74]

CONCLUSIONS AND FUTURE OUTLOOK

Over the past decade, cocrystal engineering has emerged as an efficient strategy for enhancing the efficacy of pharmaceutical compounds by changing their undesirable physicochemical characteristics. Researchers from a variety of disciplines, including the pharmaceutical industry, chemical science, crystallography, materials science, and drug regulatory agencies, are still showing a keen interest in pharmaceutical cocrystals. In this review, we covered in depth a wide range of methodologies used for screening, and manufacture of pharmaceutical cocrystals in an attempt to improve undesirable physical characteristics of APIs. This review also provides insight into regulatory aspects of cocrystals, as well as a standard description of several techniques that can be used in co-crystal characterization. The solubility, bioavailability, stability, and other physicochemical qualities of active substances have an impact on their therapeutic application. The creation of pharmaceutical cocrystals of active components can enhance the physical and chemical characteristics of the medicine while retaining its efficacy. The type of coformer used determines the physicochemical characteristics of cocrystals. To prevent unexpected outcomes, it is necessary to do the screening of the coformers and prediction of cocrystal formation prior to the manufacture of co-crystals. Pharmaceutical cocrystals are now a novel field in the manufacturing of pharmaceutical formulations. The industry is becoming more interested in drug cocrystals since the creation of drug cocrystals can improve drug benefits and minimize drug development period. The regulatory approval and market performance for pharmaceutical cocrystals are favorable. There is also the potential to create bioequivalent cocrystals for usage in generic products. The FDA and EMA have different regulatory frameworks for pharmaceutical cocrystals; hence, there is a need for clearer and more rational guidelines to increase opportunities for future cocrystals market.

REFERENCES

1. Buddhadev SS, Garala KC. Pharmaceutical cocrystals—a review. Multidisciplinary Digital Publishing Institute Proceedings. 2021; 62(1):14.

2. Garg U, Azim Y. Challenges and opportunities of pharmaceutical cocrystals: a focused review on non-steroidal anti-inflammatory drugs. RSC medicinal chemistry. 2021; 12(5):705-21.

3. Fukte SR, Wagh MP, Rawat S. Coformer selection: An important tool in cocrystal formation. Int. J. Pharm. Pharm. Sci. 2014; 6(7):9-14.

4. Yadav AV, Shete AS, Dabke AP, Kulkarni PV, Sakhare SS. Co-crystals: a novel approach to modify physicochemical properties of active pharmaceutical ingredients. Indian journal of pharmaceutical sciences. 2009; 71(4):359.

5. Pepinsky R. Crystal engineering-new concept in crystallography. InPhysical Review 1955 Jan 1 (Vol. 100, No. 3, pp. 971-971). ONE PHYSICS ELLIPSE, COLLEGE PK, MD 20740-3844 USA: AMERICAN PHYSICAL SOC.

6. Schmidt GM. Photodimerization in the solid state. Pure and Applied Chemistry. 1971 Jan 1; 27(4):647-78.

7. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research. 1995 Mar; 12:413-20.

8. Thakuria R, Delori A, Jones W, Lipert MP, Roy L, Rodríguez-Hornedo N. Pharmaceutical cocrystals and poorly soluble drugs. International journal of pharmaceutics. 2013 Aug 30; 453(1):101-25.

9. Wöhler F. Untersuchungen über das Chinon. 1844.

10. Sathisaran I, Dalvi SV. Engineering cocrystals of poorly water-soluble drugs to enhance dissolution in aqueous medium. Pharmaceutics. 2018 Jul 31; 10(3):108.

11. Etter MC. Encoding and decoding hydrogen-bond patterns of organic compounds. Accounts of Chemical Research. 1990 Apr 1; 23(4):120-6.

12. Etter MC. Hydrogen bonds as design elements in organic chemistry. The Journal of Physical Chemistry. 1991 Jun; 95(12):4601-10.

13. Desiraju GR. Supramolecular synthons in crystal engineering—a new organic synthesis. Angewandte Chemie International Edition in English. 1995 Nov 17; 34(21):2311-27.

14. Kumar S. Pharmaceutical cocrystals: an overview. Indian Journal of Pharmaceutical Sciences. 2018 Jan 15; 79(6):858-71.

15. https://www.fda.gov/files/drugs/published/Regulatory-Classification-of-Pharmaceutical-Co-Crystals.pdf

16. Panzade P, Shendarkar G, Shaikh S, Rathi PB. Pharmaceutical cocrystal of piroxicam: design, formulation and evaluation. Advanced pharmaceutical bulletin. 2017 Sep; 7(3):399.

17. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. Crystal Growth & Design. 2018 Aug 10; 18(10):6370-87.

18. Seddon KR, Zaworotko M, editors. Crystal engineering: the design and application of functional solids. Springer Science & Business Media; 1999 Sep 30.

19. Ancheria RK, Jain S, Kumar D, Soni SL, Sharma M. An overview of pharmaceutical co-crystal. Asian Journal of Pharmaceutical Research and Development. 2019 Apr 14; 7(2):39-46.

20. Kumar S, Nanda A. Approaches to design of pharmaceutical cocrystals: A review. Molecular Crystals and Liquid Crystals. 2018 May 24; 667(1):54-77.

21. Morissette SL, Almarsson Ö, Peterson ML, Remenar JF, Read MJ, Lemmo AV, Ellis S, Cima MJ, Gardner CR. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Advanced drug delivery reviews. 2004 Feb 23; 56(3):275-300.

22. Kavanagh ON, Croker DM, Walker GM, Zaworotko MJ. Pharmaceutical cocrystals: from serendipity to design to application. Drug Discovery Today. 2019 Mar 1; 24(3):796-804.

23. Babu NJ, Reddy LS, Aitipamula S, Nangia A. Polymorphs and polymorphic cocrystals of temozolomide. Chemistry–An Asian Journal. 2008 Jul 7; 3(7):1122-33.

24. Sarma B, Reddy LS, Nangia A. The role of π-stacking in the composition of phloroglucinol and phenazine cocrystals. Crystal Growth and Design. 2008 Dec 3; 8(12):4546-52.

25. Patole T, Deshpande A. Co-crystallization-a technique for solubility enhancement. International journal of pharmaceutical sciences and research. 2014 Sep 1; 5(9):3566.

26. Garg U, Azim Y. Challenges and opportunities of pharmaceutical cocrystals: a focused review on non-steroidal anti-inflammatory drugs. RSC medicinal chemistry. 2021; 12(5):705-21.

27. Childs SL, Rodríguez-Hornedo N, Reddy LS, Jayasankar A, Maheshwari C, McCausland L, Shipplett R, Stahly BC. Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. CrystEngComm. 2008; 10(7):856-64.

28. Bhogala BR, Basavoju S, Nangia A. Tape and layer structures in cocrystals of some di-and tricarboxylic acids with 4, 4′-bipyridines and isonicotinamide. From binary to ternary cocrystals. CrystEngComm. 2005 Aug 17; 7(90):551-62.

29. Karagianni A, Malamatari M, Kachrimanis K. Pharmaceutical cocrystals: New solid phase modification approaches for the formulation of APIs. Pharmaceutics. 2018 Jan 25; 10(1):18.

30. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: an overview. International journal of pharmaceutics. 2011 Oct 31; 419(1-2):1-1.

31. Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. Acta Pharmaceutica Sinica B. 2021 Aug 1; 11(8):2537-64.

32. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Crystal growth and design. 2009 Jun 3; 9(6):2950-67.

33. Vemuri VD, Lankalapalli S. Insight into concept and progress on pharmaceutical co-crystals: an overview. Indian J. Pharm. Educ. Res. 2019 Oct 1; 53(4):s522-38.

34. Guzmán HR, Tawa M, Zhang Z, Ratanabanangkoon P, Shaw P, Gardner CR, Chen H, Moreau JP, Almarsson Ö, Remenar JF. Combined use of crystalline salt forms and precipitation inhibitors to improve oral absorption of celecoxib from solid oral formulations. Journal of pharmaceutical sciences. 2007 Oct 1; 96(10):2686-702.

35. Jayram P, Sudheer P. Pharmaceutical Co-crystals: A Systematic Review. International Journal of Pharmaceutical Investigation. 2020 Jul 1; 10(3).

36. Sugandha K, Kaity S, Mukherjee S, Isaac J, Ghosh A. Solubility enhancement of ezetimibe by a cocrystal engineering technique. Crystal Growth & Design. 2014 Sep 3; 14(9):4475-86.

37. Wang JR, Yu X, Zhou C, Lin Y, Chen C, Pan G, Mei X. Improving the dissolution and bioavailability of 6-mercaptopurine via co-crystallization with isonicotinamide. Bioorganic & medicinal chemistry letters. 2015 Mar 1; 25(5):1036-9.

38. Chaudhari S, Nikam SA, Khatri N, Wakde S, Co-crystals: a review, Journal of Drug Delivery and Therapeutics 2018; 8(6-s):350-358

39. Jung MS, Kim JS, Kim MS, Alhalaweh A, Cho W, Hwang SJ, Velaga SP. Bioavailability of indomethacin-saccharin cocrystals. Journal of pharmacy and pharmacology. 2010 Nov; 62(11):1560-8.

40. Chaudhari S, Nikam SA, Khatri N, Wakde S. Co-crystals: a review. Journal of Drug Delivery and Therapeutics. 2018 Dec 15;8(6-s):350-8.

41. Zhou Z, Li W, Sun WJ, Lu T, Tong HH, Sun CC, Zheng Y. Resveratrol cocrystals with enhanced solubility and tabletability. International journal of pharmaceutics. 2016 Jul 25; 509(1-2):391-9.

42. Shaikh R, Singh R, Walker GM, Croker DM. Pharmaceutical cocrystal drug products: an outlook on product development. Trends in pharmacological sciences. 2018 Dec 1; 39(12):1033-48.

43. Remenar JF, Peterson ML, Stephens PW, Zhang Z, Zimenkov Y, Hickey MB. Celecoxib: nicotinamide dissociation: using excipients to capture the cocrystal's potential. Molecular pharmaceutics. 2007 Jun 4; 4(3):386-400.

44. Emami S, Siahi-Shadbad M, Adibkia K, Barzegar-Jalali M. Recent advances in improving oral drug bioavailability by cocrystals. BioImpacts: BI. 2018; 8(4):305.

45. Sanphui P, Devi VK, Clara D, Malviya N, Ganguly S, Desiraju GR. Cocrystals of hydrochlorothiazide: solubility and diffusion/permeability enhancements through drug–coformer interactions. Molecular pharmaceutics. 2015 May 4; 12(5):1615-22.

46. Arigo A, Jawahar N, Nikhitha K, Jubie S. Effect of Hygroscopicity on pharmaceutical ingredients, methods to determine and overcome: An Overview. Journal of Pharmaceutical Sciences and Research. 2019; 11(1):6-10.

47. Qi MH, Li H, Zhu B, Hong M, Ren GB. Cocrystals of Oxymatrine: Reducing Hygroscopicity and Affecting the Dissolution Rate. Crystal Growth & Design. 2021 May 27; 21(7):3874-88.

48. Patel DJ, Puranik PK. Pharmaceutical Co-crystal: An Emerging Technique to enhance Physicochemical properties of drugs. Int. J. ChemTech Res. 2020; 13:283-90.

49. Corey EJ. General methods for the construction of complex molecules. Pure and Applied chemistry. 1967 Jan 1;14(1):19-38.

50. Desiraju GR. Supramolecular synthons in crystal engineering—a new organic synthesis. Angewandte Chemie International Edition in English. 1995 Nov 17; 34(21):2311-27.

51. Sopyan IY, Alvin B, Insan Sunan KS, Megantara SA. Systematic review: co-crystal as efforts to improve physicochemical and bioavailability properties of oral solid dosage form. Int. J. Appl. Pharm. 2021 Jan 7; 13(1):43-52.

52. Thayyil AR, Juturu T, Nayak S, Kamath S. Pharmaceutical co-crystallization: Regulatory aspects, design, characterization, and applications. Advanced Pharmaceutical Bulletin. 2020 Jun; 10(2):203.

53. Kumar A, Nanda A. In-silico methods of cocrystal screening: A review on tools for rational design of pharmaceutical cocrystals. Journal of Drug Delivery Science and Technology. 2021 Jun 1; 63:102527.

54. Cruz-Cabeza AJ. Acid–base crystalline complexes and the p K a rule. CrystEngComm. 2012; 14(20):6362-5.

55. Mohammad MA, Alhalaweh A, Velaga SP. Hansen solubility parameter as a tool to predict cocrystal formation. International journal of pharmaceutics. 2011 Apr 4; 407(1-2):63-71.

56. Wood PA, Feeder N, Furlow M, Galek PT, Groom CR, Pidcock E. Knowledge-based approaches to co-crystal design. CrystEngComm. 2014; 16(26):5839-48.

57. Fábián L. Cambridge structural database analysis of molecular complementarity in cocrystals. Crystal Growth and Design. 2009 Mar 4; 9(3):1436-43.

58. Karki S, Friščić T, Fábián L, Jones W. New solid forms of artemisinin obtained through cocrystallisation. CrystEngComm. 2010; 12(12):4038-41.

59. Chiarella RA, Davey RJ, Peterson ML. Making co-crystals the utility of ternary phase diagrams. Crystal growth & design. 2007 Jul 3; 7(7):1223-6.

60. Sun X, Yin Q, Ding S, Shen Z, Bao Y, Gong J, Hou B, Hao H, Wang Y, Wang J, Xie C. Solid–liquid phase equilibrium and ternary phase diagrams of ibuprofen–nicotinamide cocrystals in ethanol and ethanol/water mixtures at (298.15 and 313.15) K. Journal of Chemical & Engineering Data. 2015 Apr 9; 60(4):1166-72.

61. Ngilirabanga JB, Samsodien H. Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy. Nano Select. 2021 Mar; 2(3):512-26.

62. Panzade PS, Shendarkar GR. Pharmaceutical cocrystal: a game changing approach for the administration of old drugs in new crystalline form. Drug development and industrial pharmacy. 2020 Oct 2; 46(10):1559-68.

63. MacFhionnghaile P, Crowley CM, McArdle P, Erxleben A. Spontaneous solid-state cocrystallization of caffeine and urea. Crystal Growth & Design. 2020 Jan 9; 20(2):736-45.

64. Jones W, Motherwell WS, Trask AV. Pharmaceutical cocrystals: An emerging approach to physical property enhancement. MRS bulletin. 2006 Nov; 31(11):875-9.

65. Thenge RR, Patond VB, Ajmire PV, Barde LN, Mahajan NM, Tekade NP. Preparation and characterization of co-crystals of diacerein. Indonesian journal of Pharmacy. 2017 Mar 7; 28(1):34.

66. Daurio D, Medina C, Saw R, Nagapudi K, Alvarez-Núñez F. Application of twin screw extrusion in the manufacture of cocrystals, part I: four case studies. Pharmaceutics. 2011 Aug 31; 3(3):582-600.

67. Yadav BK, Khursheed AT, Singh RD. Cocrystals: A complete review on conventional and novel methods of its formation and its evaluation. Asian J. Pharm. Clin. Res. 2019; 12(7):68-74.

68. Boksa K, Otte A, Pinal R. Matrix-assisted cocrystallization (MAC) simultaneous production and formulation of pharmaceutical cocrystals by hot-melt extrusion. Journal of pharmaceutical sciences. 2014 Sep 1; 103(9):2904-10.

69. Basavoju S, Boström D, Velaga SP. Pharmaceutical cocrystal and salts of norfloxacin. Crystal growth & design. 2006 Dec 6; 6(12):2699-708.

70. Sheikh AY, Abd Rahim S, Hammond RB, Roberts KJ. Scalable solution cocrystallization: case of carbamazepine-nicotinamide I. CrystEngComm. 2009; 11(3):501-9.

71. Rodríguez-Hornedo N, Nehm SJ, Seefeldt KF, Pagan-Torres Y, Falkiewicz CJ. Reaction crystallization of pharmaceutical molecular complexes. Molecular pharmaceutics. 2006 Jun 5; 3(3):362-7.

72. Pawar N, Saha A, Nandan N, Parambil JV. Solution cocrystallization: A scalable approach for cocrystal production. Crystals. 2021 Mar 18; 11(3):303.

73. Thakor P, Yadav B, Modani S, Shastri NR. Preparation and optimization of nano-sized cocrystals using a quality by design approach. CrystEngComm. 2020; 22(13):2304-14.

74. Douroumis D, Ross SA, Nokhodchi A. Advanced methodologies for cocrystal synthesis. Advanced drug delivery reviews. 2017 Aug 1; 117:178-95.

75. Rodrigues M, Lopes J, Guedes A, Sarraguça J, Sarraguça M. Considerations on high-throughput cocrystals screening by ultrasound assisted cocrystallization and vibrational spectroscopy. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2020 Mar 15; 229:117876.

76. Alhalaweh A, Kaialy W, Buckton G, Gill H, Nokhodchi A, Velaga SP. Theophylline cocrystals prepared by spray drying: physicochemical properties and aerosolization performance. Aaps Pharmscitech. 2013 Mar; 14:265-76.

77. Eddleston MD, Patel B, Day GM, Jones W. Cocrystallization by freeze-drying: preparation of novel multicomponent crystal forms. Crystal growth & design. 2013 Oct 2; 13(10):4599-606.

78. Padrela L, de Azevedo EG, Velaga SP. Powder X-ray diffraction method for the quantification of cocrystals in the crystallization mixture. Drug development and industrial pharmacy. 2012 Aug 1; 38(8):923-9.

79. Aakeröy CB, Salmon DJ, Smith MM, Desper J. Cyanophenyloximes: reliable and versatile tools for hydrogen-bond directed supramolecular synthesis of cocrystals. Crystal growth & design. 2006 Apr 5; 6(4):1033-42.

80. Parrott EP, Zeitler JA, Friscic T, Pepper M, Jones W, Day GM, Gladden LF. Testing the sensitivity of terahertz spectroscopy to changes in molecular and supramolecular structure: a study of structurally similar cocrystals. Crystal Growth and Design. 2009 Mar 4; 9(3):1452-60.

81. Steed JW. The role of co-crystals in pharmaceutical design. Trends in pharmacological sciences. 2013 Mar 1; 34(3):185-93.

82. Jiang L, Huang Y, Zhang Q, He H, Xu Y, Mei X. Preparation and solid-state characterization of dapsone drug–drug co-crystals. Crystal Growth & Design. 2014 Sep 3; 14(9):4562-73.

83. Shaikh R, Singh R, Walker GM, Croker DM. Pharmaceutical cocrystal drug products: an outlook on product development. Trends in pharmacological sciences. 2018 Dec 1; 39(12):1033-48.

84. Thipparaboina R, Kumar D, Chavan RB, Shastri NR. Multidrug co-crystals: towards the development of effective therapeutic hybrids. Drug Discovery Today. 2016 Mar 1; 21(3):481-90.

85. Grobelny P, Mukherjee A, Desiraju GR. Drug-drug co-crystals: Temperature-dependent proton mobility in the molecular complex of isoniazid with 4-aminosalicylic acid. CrystEngComm. 2011; 13(13):4358-64.

86. Cheney ML, Weyna DR, Shan N, Hanna M, Wojtas L, Zaworotko MJ. Coformer selection in pharmaceutical cocrystal development: a case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics. Journal of pharmaceutical sciences. 2011 Jun 1; 100(6):2172-81.

87. Sopyan IY, Alvin B, Insan Sunan KS, Megantara SA. Systematic review: co-crystal as efforts to improve physicochemical and bioavailability properties of oral solid dosage form. Int. J. Appl. Pharm. 2021 Jan 7; 13(1):43-52.

88. European Medicines Agency. Reflection paper on the use of cocrystals of active substances in medicinal products.