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Review Article

Pharmaceutical cocrystal-a deft technique for solubility enhancement

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ABSTRACT

Solubility enhancement of active pharmaceutical ingredients is a challenging field in the pharmaceutical industry. Several methods and excipients are employed in the solubility improvement process of poorly soluble drugs. Crystal engineering is one of the novel strategies to alter the physicochemical properties of the molecule without causing significant changes in its structural integrity. Cocrystals are single-phase or homogeneous crystalline structures composed of two or more compounds bound noncovalently with the active pharmaceutical ingredient in a definite stoichiometric ratio. The cocrystallization technique is effective not only in improving the problems associated with solubility, and bioavailability, in addition, it enhances permeability, stability, hygroscopicity, flowability, and processability of the materials. This review represents the concept, characterization, and application of cocrystals in a systematic way. The review focuses on the requisite and mechanism of cocrystal formation, different preparation methods of cocrystals, and stages of screening. The growing interest in this technique has led the regulatory bodies to implement the guidelines, hence, a brief on regulatory perspectives is discussed here. The cocrystallization method establishes its potential in the pharmaceutical field through an increasing number of patents and market approvals.

Keywords:
Cocrystal, Co-former, Cocrystallization method, Solubility enhancement, Cocrystal Evaluation

1. INTRODUCTION

Design and development of a new pharmaceutical dosage form include a censorious evaluative process of strategic study, descriptive research, screening of drug candidates, exploratory research, and overall development. The physicochemical properties and chemical stability of an active pharmaceutical ingredient are related to its solid-state characteristics which influence the biopharmaceutical properties and manufacturability of the dosage form. Drugs in their crystalline forms are associated with the advantages of enhanced stability and easy purification, but the main drawback is their low solubility. Amorphous forms possess high free Gibbs energy and more mobility of the molecules, resulting in increased solubility but are less stable with a tendency to recrystallize over time[1]. Hence the molecular form of the drug plays a major role in solubility, oral bioavailability, and stability. In addition, poor solubility and bioavailability are associated with the drugs belonging to the Biopharmaceutical Classification System (BCS) II or IV category[2].

To overcome the challenges related to solubility and bioavailability, formulation scientists use different approaches like micronization, nanonization, solid dispersion, complexation, salt formation, micellar solubilization, cosolvency, etc,[3]. Among these various approaches, one of the unique approaches is co-crystallization-a multicomponent system consisting of drug and counter molecules, bound together with non-covalent interaction in a definite stoichiometric ratio. The supramolecular structure in association with two more chemical species with noncovalent interaction results in the formation of cocrystals. Several types of interactions like hydrogen bonding, pi-stacking, and Vander Waals forces are responsible for the construction of cocrystal. The drug gets entrapped in the crystal lattice of the counter molecule while retaining its pharmacological characteristics with an improved solubility, and bioavailability. The cocrystal thus formed fine-tunes

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certain physicochemical properties of the drug molecules like reduction in melting point, improvement in flowability, stability, and permeability[4-5]. USFDA defined cocrystals as "dissociable API-excipient molecular complexes (with the neutral guest compound being the excipient called co-formers) wherein both API and excipients are present in the same crystal lattice"[6-7]. EMA describes cocrystals as homogeneous single-phase crystalline structures of two or more chemical components held together with a formation of non-covalent bonds[8]. As per USFDA guidelines, the proton transfer potential of the API and counter molecule should be less to be classified as cocrystal. Hence the difference in pKa of both the components should be less than 1 to oppose the formation of salt[9].

2. REQUISITE AND MECHANISM FOR COCRYSTAL FORMATION

Cocrystals are neutral crystalline single-phase solid materials, consisting of two or more different molecular or ionic compounds that are combined in a particular stoichiometric ratio. The presence of functional groups, nature of solvents used, processing temperature and methods play a vital role in the formation of cocrystal.

The first step of cocrystal formation is the screening of co-formers or the counter molecules. The co-formers should be able to provide supramolecular synthon with the drug by the formation of non-covalent bonds. Mostly H-bonds formation between the drug and co-former is required for the creation of this supramolecular synthon. The Cambridge Structural Database (CSD) reveals that the H bond is the predominant form of interaction between co-formers and the drug[10]. The supramolecular synthons get created between the molecules of good proton donors and good proton acceptors. Strong hydrogen bonds thus created are between N-H . . . O, O-H . . . O, N-H . . . N, and O-H . . . N[11]. The supramolecular structures thus formed are of two types, a combination of similar structures of drug and co-formers are referred as homosynthons, and presence of different but complementary functional groups between drug and co-formers held together by noncovalent bond creates heterosynthons[1].

Computational crystal structure prediction and molecular electrostatic potential surfaces studies thus help to identify the thermodynamically stable crystal and molecular complementarity between drug and co-formers for specific interaction points on the molecular surfaces respectively[12].

The second step of cocrystal formation is the experimental screening through ternary phase diagram, estimation of lattice energy through thermal studies, and determination of Hansen solubility parameters. The three coordinates for the Hansen parameter are the energy from dispersion forces, dipolar intermolecular, and H-bond between molecules.

The entire process of cocrystal formation is a series of various mechanisms between drug and co-formers namely molecular diffusion, eutectic formation, and amorphization,[13] and mostly depends on the type of reactants as shown in Figure 1. If the vapour pressure of the reactants in the solid-state is high, cocrystal formation takes place via molecular diffusion. This type of cocrystals is formed by the grinding method where the mechanical force breaks the intermolecular bonds of the reactants. In eutectic formation reactants in contact with their surfaces converts into liquid and that leads to nucleation and cocrystal formation[14]. Amorphization through cocrystallization takes place when strong intermolecular interactions between reactants lead to the formulation of H bond. This can be achieved by grinding the reactants below the glass transition temperature of the reactants.

3. PREPARATION OF COCRYSTAL

Cocrystallization is a method for joining two or more molecules (API and co-formers) via non-covalent interactions during the crystallization process. When choosing a cocrystallization process, several factors like co-formers solubility, API and co-former compatibility, their stability, and susceptibility to form polymorphs, solvates, or amorphous are strictly considered[1].

Solvent-based cocrystallization and solvent-free cocrystallization are two of the most extensively utilized cocrystal creation techniques[7].

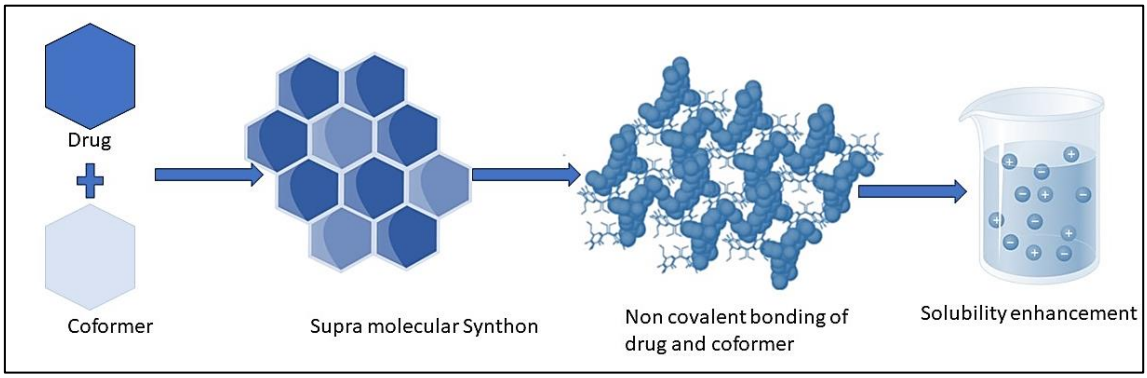

Figure 1. Cocrystal to enhance the solubility of drug.

3.1. Solvent-based cocrystallization

Solvent-based approaches are most often employed, particularly at the laboratory scale, because of their simplicity, ability to trace the process, and manage end product parameters[1]. The selection of a solvent is the critical parameter for this process as it interferes with the practical yield, particle size and shape, crystal forms, purity, and other solvate forms of the product that directly influence the solubility. Solvents that are commonly employed are ethanol, methanol, acetone, iso propanolol, and methyl ethyl ketone. Solvent selection is based on drug and co-formers solubility in it. A ternary phase diagram of drug, co-former, and solvent should be generated to locate the thermodynamically stable phase of the cocrystals and to estimate the degree of supersaturation of drug and co-formers in the solvent[15].

3.1.1. Solvent evaporation

The most frequently used method for preparing cocrystals is solvent evaporation. This method is typically used for synthesizing high-quality single-crystal cocrystals, where the drug and the co-formers should be congruently soluble in the selected solvent. The formed cocrystals are characterized for structural analysis using single-crystal X-ray diffraction[7]. This approach entails dissolving the co-formers in a suitable solvent and then evaporating the solvent. Supersaturation is created as evaporation progress, resulting in cocrystal nucleation and growth[15]. During the dissolving process, the functional moiety of the dtug and co-former interact with each other to build new hydrogen bonds[16]. The cocrystal is anticipated to be thermodynamically favorable because of the formation of hydrogen bonds between complementary functional groups present between the drug and co-former[17]. Due to its simplicity and efficacy, this is a widely used experimental screening method for cocrystal formation[15].

3.1.2. Slurry cocrystallization

Slurry crystallization is one of the alternative approaches for the formation of cocrystal where various solvents are used to make a suspension of drugs and co-formers. The mixture is stirred at room temperature. The solvent is removed by decantation followed by drying under a flow of nitrogen[18]. The nucleation of the drug in the co-former is dependent on the concentration of the drug and the slurry conversion rate which is driven by the solubility of the drug and co-former in the solvent system.

3.1.3. Ultrasound-assisted cocrystallization

Sonication has been investigated as a process intensifier in the preparation of cocrystal by solution-based or slurry cocrystallization process[1]. Sonication causes cavitational energy to develop, and leads to the formation of cavity bubbles inside the solution, to support nucleation. Sonication minimizes induction time and prevents agglomeration[19]. Ultrasound-assisted slurry cocrystallization of caffeine and maleic acid in an aqueous system was studied by Apshingekar et al. The effect of sonication on the ternary phase diagram was significant and resulted in transformation to pure cocrystals. The enhancement of solubility and stability of caffeine and maleic acid cocrystal was correlated with the effect of sonication on the phase diagram[20]. Process parameters that are considered critical for the formation of cocrystal by ultrasonication techniques are the type of solvent used, the duration of sonication, the concentrations of the active pharmaceutical ingredients (APIs), and the co-former.

3.1.4. Supercritical fluid technology

In recent years, supercritical fluid cocrystallization has been employed as a green approach to producing high-purity cocrystals. In this technology carbon dioxide is pressurized, and heated above its critical point to reach the supercritical phase. At this state, it possesses good diffusivity and solvating properties and is used as an antisolvent, solvent, or cosolvent[15].

In supercritical solvent technique, the dissolution of active substance and the co-formers in supercritical CO_2 are carried inside a stainless-steel vessel followed by depressurization to yield cocrystals. The key parameter of this process is the solubility of the components in supercritical CO_2. The process enables to select varieties of green solvents, eliminates extra drying step, and step for removal of residual solvent. This is a continuous process and produces a small particle size with a narrow particle size distribution.

In supercritical antisolvent technique, supercritical CO_2 is used as an anti-solvent for a solution of drug and co-former. The supercritical CO_2 is added dropwise through a nozzle to the solution of drug and co-formers in the primary organic solvent in a closed chamber. The supercritical CO_2 decreases the dissolving power of the primary solvent and leads to nucleation and supersaturation of the drug and co-formers in it which leads to the formation of cocrystals. Itraconazole and succinic acid cocrystals were prepared by this method[21]. The primary advantages of this process are the production of high purity crystal, one-step process, control over polymorphism, minimal use of organic solvents, and environment-friendly method[22]. Both the processes are expensive and requires a sophisticated setup compared to other processes.

3.1.5. Spray drying

Spray drying is a continuous one-step procedure for solidifying solutions, suspensions, and slurries of

drugs and excipients. It is a regulated process of various optimized process parameters and is successfully used in the formulation of amorphous solid dispersion and the synthesis of cocrystals[17]. Spray drying provides flexibility in terms of solvent selection. It also allows adequate control of the solid-state and particle characteristics at the same time[23].

3.1.6. High-pressure homogenization

This process uses mechanical energy for the fragmentation of suspended particles in a solvent system at high pressure. The applied mechanical energy is the driving force for the transition kinetics in the formation of cocrystals. During the process of homogenization, the suspension generates turbulence due to high velocity, and that results in cavitation and thereby cocrystal formation. Cocrystallization of theophylline and saccharine at 1:1 was carried out by Fernandez-Ronco et al to improve the physical stability of theophylline[1,24].

3.2. Solvent-Free Cocrystallization

These methods utilize little or no solvents in the preparation of cocrystal. They are environmentally friendly. Spontaneous development of cocrystal occurs by direct contact or grinding. They are preferable to solution-based cocrystallization procedures in controlling environmental pollution due to the avoidance of organic solvents[7].

3.2.1. Solid-state grinding (Mechanochemical method)

Solid-state grinding, often known as milling, is a scalable, continuous, polymer-assisted cocrystallization method. This can be achieved by two processes- dry grinding and liquid-assisted grinding. Dry grinding involves the trituration of drug and co-formers in mortar and pestle or mixing using a ball mill. The heat evolved during the mixing process is monitored. Cocrystal of sulphathiazole and carboxylic acid were made using Retsch mixer mill at a 25 Hz and the temperature was maintained at 37°C[25]. Dry grinding requires exact stoichiometric proportions of drug and co-formers, else leads to the failure of cocrystal formation, and defects in the crystal structure.

Liquid-assisted grinding requires the addition of solvent to a meagre quantity to the powder mixture of drug and co-formers to assist milling. The solvent plays a catalytic role during the grinding process. This process is more efficient than the dry grinding methods, Trask et al. (2005) used this technique to make cocrystal of caffeine and dicarboxylic acid[13], Cocrystal of piracetam, was produced employing tartaric acid and citric acid as co-formers in both dry and liquid assisted grinding procedures[26]. It was reported that the liquid assisted grinding method was faster than the dry grinding method and screening of the cocrystals was more effective than dry grinding[26-27].

3.2.2. Hot-melt extrusion

Hot-melt extrusion method is a continuous, solvent-free, scalable, and industrially approachable technique for the preparation of cocrystal[28]. It is a process in which the drug is embedded in the molten polymeric matrix of thermoplastic polymers, sugar alcohols, starches, and low-melting waxes. These carrier systems are screened for their desirable features of stability and solubility. To achieve successful processing, the physical state, molecular weight of API, melting point, and polymer play an important role[29]. Fernandes et al. utilized this method for the mechanochemical synthesis of carvedilol cocrystals[30].

The success of this process depends on the setting of temperature, screw configuration, type, size, and speed. Temperature is the most critical parameter for this process as it affects the mass transfer in the molten mass of high viscous materials. Mixing at low temperature leads to poor mixing because of the generation of high torque in highly viscous molten mass. This problem can be overcome by melting the mixture at a high temperature but can lead to degradation of the drug.

It was reported that twin-screw type affects proper mixing and formation of cocrystal than single screw extruder. Screw speed affects particle size. The process is economical and doesn't require solvent usage and drying. It is considered the most efficient scalable method to produce high-quality cocrystal[1].

3.2.3. Microwave-assisted cocrystallization

Microwave radiation enhances molecular mobility due to molecular excitation created in the rotations of dipoles of the molecules. This causes nucleation and assists cocrystal formation[1]. It is a rapid eco-friendly process[31]. Drug and co-formers in a suitable equimolecular ratio are subjected to microwave radiation. The critical process parameters of this process are the frequency of radiation and time of exposure[32].

4. CHARACTERIZATION OF CO-CRYSTALS

4.1. X-ray diffraction (XRD) studies- single crystalline and powder XRD

Cocrystals can be completely characterized by powder X-ray crystallography. The changes in the diffraction patterns help to detect the changes in the crystal lattice of the drug in the co-formers[33]. Single-crystal XRD and Powder XRD are used to study the structure and quantification of cocrystal respectively. They can be used to characterize and quantify the percentage formation of cocrystal and quantify the remaining components in the mixture during the manufacturing of cocrystal as an in-process assessment[17,34].

4.2. Differential scanning calorimetry

Differential scanning calorimetry is commonly employed in the pharmaceutical industry to characterize cocrystals for a screening study, detection of impurities, and formation of the eutectic mixture. A reduction in melting point, enthalpy and heat capacity are the indications for the change in the degree of crystallinity. The shift, new appearance, or change in intensities of the endothermic peak helps to understand the compatibility between co-former and drugs[35]. As the melting point of the cocrystal differs from the individual compounds a new sharp endothermic peak appears in the thermogram to ensure the formation of cocrystal[36].

4.3. Hot stage microscopy

Hot stage microscopy is a combining method of microscopy and thermal analysis to study the physical properties of solid materials as a function of temperature and time. The change in drug crystal on controlled heating is observed under a microscope. This method can be used to detect the melting point, melting range, crystal development, crystalline transformations, and other thermal changes. Therefore, it can be used to study the crystal lattice of the cocrystals of drugs[36].

4.4. Scanning electron microscopy (SEM)

The surface morphology and properties of the cocrystals can be studied using a scanning electron microscope (SEM)[37]. The samples are sputtered with gold at ambient temperature in an argon environment. The samples are pelletized and mounted to an aluminium stub using double-sided adhesive gold tape in this procedure. After that, they are placed in a vacuum to improve their conductivity. An electronic beam is used to scan the samples. The photographs obtained were gathered to observe the surface property[30].

4.5. Spectroscopic studies

There are two types of spectroscopic approaches that can be used to characterize cocrystals: vibrational spectroscopy and nuclear magnetic resonance (NMR). Vibrational spectroscopy includes Fourier-Transform Infrared Spectroscopy (FTIR) or Raman spectroscopy.

FTIR is widely used for predicting and evaluating chemical conformation, intermolecular interactions, elucidation of structure, and detection of cocrystal formation.

Raman spectroscopy is used to monitor the crystallization process and helps to detect the polymorphic forms. Fourier transform Raman spectra give a quantitative analysis of the polymorphic forms and cocrystals,

NMR is a strong characterization method for organic pharmaceutical cocrystals and complexes, providing extensive information on their structure[36].

Solid-state NMR (SSNMR) can provide extensive structural information. SSNMR is a non-destructive approach for analyzing small volumes of powdered material that produces results with a higher information level than vibrational spectroscopy or powder X-ray diffraction.

Hence these spectroscopic analyses can be used in the process to study the structural and quantitative analysis of cocrystal[38].

4.6. Mathematical model of solubility studies

The technique of cocrystallization is typically used to improve the solubility of the API. The solubility of cocrystal can be determined by the mathematical model described by Nehm et al[39]. As per this model, a 1:1 ratio of API (A) and co-former (B) when undergoes dissolution, the equilibrium reaction of solution can be described by the following equation,

$$AB \overset{Ksp}{\rightleftarrows} Asol + Bsol \qquad \ldots..1$$

$$Asol + Bsol \overset{K11}{\rightleftarrows} ABsol \qquad \ldots..2$$

Hence Ksp (Solubility product constant) and K_{11} (complexation constant in solution phase) can be determined from the equilibrium equation, where,

$$Ksp = [A][B]$$

and

$$K_{11} = \frac{[AB]}{[A][B]} = \frac{[AB]}{Ksp}$$

The following mass balance equations describes the total solubility of both drug and co-formers, and can be described as follows

$$[A_T] = [A] + [AB]$$

and

$$[B_T] = [B] + [AB]$$

Therefore,

$$[A_T] = \frac{Ksp}{[B]} + Ksp.K_{11}$$

Hence the above equation establishes the fact that with an increase in co-formers concentration, the solubility of cocrystal decreases Therefore it can be concluded that the cocrystal solubility is greatly influenced by the solubility of the co-formers in the cocrystallization process.

5. PHYSIOCOCHEMICAL PROPERTIES

The physicochemical properties of the cocrystals should be considered to estimate their applicability in

product development. The most important physicochemical characteristics that should be evaluated on a priority basis start from determining the thermal behavior of the cocrystal, physical and chemical stability, solubility, and the rate of dissolution.

5.1. Melting point

The melting point of a solid is a physical property that influences the purity of a substance and provides a correlation to aqueous solubility and vapour pressure[40]. Hence the determination of the melting point can indicate the solubility of the cocrystal. A suitable stoichiometric ratio of drug and co-formers can be used to predict the solubility of the cocrystal from the preliminary estimation of the melting point. Choice of co-formers plays an important role. The molecular arrangement, molecular symmetry, and intermolecular interactions between the drug and co-former are the critical factors that affect the melting point of the cocrystals.

Choosing a co-former with a higher melting point can increase the thermal stability of an API[41]. For thermolabile pharmaceuticals, high melting point co-formers were found to be useful. The thermal stability of the cocrystals is attributed to the stable crystal packing of the drug in the co-former at a suitable stoichiometric ratio. Therefore, selection of the right co-formers to adopt the isostructural crystal packing has high significance[42-43]. During the development phase, the most prevalent methods for determining melting point and thermal analysis are carried out using differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA).

5.2. Stability

The importance of stability testing during the creation of a novel dosage formulation cannot be overstated. In the development phase of pharmaceutical cocrystals, several stability studies such as chemical stability, relative humidity studies, solution stability, thermal stability, and photostability should be carried out. Automated water sorption/desorption tests are carried out under relative humidity stress to assess the influence of water on the formulation[4,44]. The humidity stress test helps to investigate the formation of hydrates of cocrystals which may affect the overall solubility. It also helps to evaluate the effect of moisture exposure on the flowability of the cocrystals.

Thermal stress helps to detect any thermal degradation or change of form of the cocrystal. It also detects the loss of co-formers during thermal stress. These observations are needed to set up the guidance for the drying step to form robust formulation and development of processes. The chemical stability of the cocrystals can be studied at various temperatures and at ambient humidity to understand the processing factors during the development phase. Solution stability study of the cocrystal should be carried out as a measurement of the accountability on solubility, pH effect, ionization, dissociation, recrystallization, etc.

5.3. Solubility

Solubility estimation is of immense importance in the development of pharmaceuticals. The research on cocrystal is carried out mainly to improve the solubility of poorly soluble drugs. The determination of equilibrium solubility of the cocrystals gives a better prediction of drug residence time in GIT[45]. A long dissolution time is an indication of poor absorption. This equilibrium dissolution can be modified by controlling the particle size of the cocrystals. The intrinsic solubility of the drug should be high to bring the spring and parachute effect[46].

The sudden increase in solubility (Spring effect) leads to the supersaturation of the amorphized drug, followed by maintenance of the solubility for a significant period. During this period the amorphous form changes to its metastable polymorph and eventually to a stable polymorph due to Ostwald ripening. This transition constitutes the parachute effect, but by the time the drug transforms to its stable polymorph absorption would have been completed. This parachute effect on solubility can be extended by the addition of polymers or other excipients in the formulation[36].

The solubility of cocrystals should be studied in a variety of media like water, 0.1N HCl, Phosphate buffers, and simulated gastric and intestinal fluid. The dose solubility ratio is indicative of mean dissolution time and drug supersaturation-precipitation. A dose solubility ratio less than 1 indicates dissolution of the drug, whereas >1 predicts the solubility is not enough to dissolve the dose. Hence, a high dose solubility ratio is an indication of a long dissolution time and can be the reason for low absorption[47]. Therefore, determination of dose solubility ratio is a measure of enhancement of solubility of drug and the level of supersaturation.

5.4. Hygroscopicity

Hygroscopicity of a pharmaceutical ingredient should be extensively assessed since it might alter the physicochemical parameters like stability, dissolution rate, solubility, bioavailability, and mechanical characteristics[7]. A systematic sorption/desorption study should be carried out using an appropriate humidity chamber to estimate the moisture uptake of the cocrystals. A powder X-ray diffraction study should be followed to identify the final form.

The physical stability of theophylline anhydrate was improved by the formation of cocrystal with oxalic, malonic, maleic, and glutaric acids. The cocrystals were subjected to relative humidity challenges. After being stored at high relative humidity, none of the cocrystals in

this study changed into a hydrated cocrystal. Theophylline- oxalic acid cocrystal was found to be the most stable among others as reported[48.] The researchers reported that the crystal packing features with H-bond in the cocrystals were responsible for the improvement of this property.

The crystal engineering approach was applied for solubility improvement of indomethacin with the co-formers saccharine. A dynamic vapor sorption study revealed that the 1:1 synthon of the combination gained less than 0.05% in weight at 98%RH and that proved the non-hygroscopicity of the cocrystal[49]. Improvement in caffeine hygroscopicity was observed in 2:1 caffeine/ oxalic acid cocrystal, which was reported to be more stable than pure caffeine[50].

5.5. Bioavailability

The rate and extent to which a pure drug reaches systemic circulation are known as bioavailability. APIs with low oral bioavailability are the obstacle to the development of novel formulations. Pharmaceutical cocrystals with increased water solubility and oral bioavailability are designed and synthesized through crystal engineering.

Ketoconazole, an antifungal agent with a broad range of activity, has a low water solubility and bioavailability. Ketoconazole P-aminobenzoic acid cocrystal demonstrated a 6.7-fold greater oral bioavailability and a 10-fold higher water solubility than crystalline ketoconazole[51].

Apigenin (APG), is a bioflavonoid that has anti-inflammatory, antibacterial, and anticarcinogenic effects. APG's medicinal potential is restricted, due to its poor solubility and bioavailability. The cocrystal of APG and 4,40-bipyridine showed a bioavailability of 3.9 times that of the parent drugs[52].

In a pharmacokinetics investigation in beagle dogs, the oral bioavailability of apixaban-oxalic acid cocrystals was shown to be 2.7 times higher than that of the pure drug[53].

5.6. Permeability

The permeability of the dug through the biological membrane, is another important factor for effective oral absorption. The permeability determines the absorption and distribution of the drug. The influence of cocrystal on drug permeability has not been studied as much as the effect of cocrystal on solubility and dissolving rate. Drug permeability is primarily determined by the n-octanol/water partition coefficient, which may be calculated using log P and (C log P) for the unmodified form of the drug[43].

The antineoplastic drug 5-fluorouracil permeability through the skin was significantly enhanced with the co-formers such as 3-hydroxybenzoic acid, 4-aminobenzoic acid, and cinnamic acid[54].

The permeability of hydrochlorothiazide cocrystal (HCT) with co-formers nicotinic acid, nicotinamide, 4-aminobenzoic acid, succinimide, and resorcinol was examined using the Franz cell diffusion method by Sanphui and coworkers. Except for HCT-succinamide, the quantity of drug flux detected in practically all cocrystals is greater than that of the pure drug. The cocrystals generated from succinimide co-former are an exception. This suggests that permeability and solubility may be mutually exclusive in the study of making cocrystals of drug[55].

5.7. Compressibility and flowability

The formation of cocrystal improves the drug's tablet-ability. The ability of a substance to convert into tablet form is known as tablet-ability. Compaction, crystal packaging, tablet-ability are some of the principal parameters of preformulation studies, and these properties can be altered with the aid of cocrystallization by using suitable co-formers[56].

Latif et al. prepared paracetamol cocrystals with caffeine as co-formers and reported that the compaction power and mechanical properties of paracetamol were enhanced significantly[57].

The cocrystals of resveratrol with the co-formers isoniazid and 4-aminobenzamide exhibited improved tablet ability of the cocrystals of the drug compared to the pure drug[58].

6. REGULATION OF PHARMACEUTICAL COCRYSTALS

The regulation of pharmaceutical cocrystals is stringently based on its development and quality control procedures[59].

This is an emerging topic for the formulation scientist as evidenced by regulatory documents and recommendations from the US Food and Drug Administration (USFDA) and the European Medicines Agency (EMA).

United States Food and Drug Administration was the first to issue guidelines on the regulatory classification of pharmaceutical cocrystal, which is defined as "crystalline material consisting of two or more molecules inside the same crystalline lattice[60]".

Crystal engineering of the drug molecules shows changes in the solution behavior, dissolution, solid-state properties, etc. Hence the guidelines specified the conditions to support the formation of cocrystal for NDA and ANDA submission. USFDA recommends supportive evidence on the following facts.

- API and co-formerss existence in a unit cell.
- The difference between the pKa of API and co-formers should be less than 1[9].

According to EMA, due to conceptual similarities, the approach adopted for documenting the formation of cocrystal and salts, are similar. Additional documentation may be necessary with scientific proof if there are any

Table 1. Regulatory definitions of cocrystal by USFDA and EMA.

Co-crystal Parameter	USFDA	EMA
Definition	"Crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ("coformers"), in the same crystal lattice"	"Homogenous crystalline structures made up of two or more components in a definite stoi-chiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds"[60].
Regulatory category	Drug product intermediate	New active substance
Regulatory considerations	Similar to polymorph of the same API	Similar to salts of the same API
Coformers definition	Neutral guest compound	Non-active components/ Reagents
Chemical interactions	Non-ionic	Non-ionic
Documentation status	Not feasible in US-Drug master files (DMF)	Feasible in EMA-Active substance master file (ASMF)
Applicable Good manufacturing practice (GMP) regulation/guide	CGMP for drug product	Part II of EU GMP Guide (active substances) and ICH Q7

Table 2. List of recent patents and marketed products on cocrystal.

Marketed/ Patented cocrystals	Combination	Purpose
Suglat® (2014)	Ipragliflozin+l-proline	Improvement of stability[27]
Entresto (2015)	Valsartan+sacubitril	Improvement of bioavailability[61]
EP3240575 A1 (8 Nov, 2017)	carfilzomib+maleic acid	To improve solubility[41]
WO2017144598 A1 (31 Aug, 2017)	Lorcaserin hydrochloride+organic diacid	Improvement of stability[62]
SEGLENTIS® (October 15th, 2021)	Celecoxib+racemic tramadol hydrochloride	To improve physicochemical properties, bioavailability and stability[63]

Table 3. Use of artificial intelligence on detection of polymorphism and cocrystal.

Field	Application
Polymorphism	Polymorphism prediction
	Crystal structure analysis
	Crystal property prediction
Cocrystal	CCF screening
	Prediction of cocrystal composition
	Cocrystal formation prediction

special techniques employed[59]. A comparative discussion on regulation by USFDA and EMA is presented in Table 1.

A collection of recent marketed patents and marketed products are presented in the Table 2.

7. COCRYSTAL PREDICTION USING ARTIFICIAL NEURAL NETWORKS

A remarkable recognition has been drawn by the pharmaceutical industry and research scientists towards the design of co-crystal for its unique potential in improving solubility, stability, and bioavailability. But problems arise in searching for the adequate combinations of molecules (or co-formers) to form cocrystals. Hence artificial intelligence and deep learning have shown promising data-driven prediction in the selection of co-formers, cocrystal composition prediction, etc. Artificial neural networks can be used to identify physicochemical characteristics, identification of polymorphism, and prediction of crystal properties[64]. This cutting-edge technology used a special algorithm for various predictions and is listed in Table 3.

The various software used to predict the properties of co-formers are hydrogen-bond propensities, molecular descriptors, electrostatic potential maps, crystal structure prediction, COSMO-RS, molecular dynamics, or PIXEL calculations and Hirshfeld surface analysis[64].

8. CONCLUSION AND FUTURE STANCE OF CO-CRYSTAL

Pharmaceutical cocrystal has been proven a highly potential technique for the improvement of drug solubility, stability, and bioavailability. Several scalable methods are available for their formulation. The physicochemical characterization can be done through sophisticated technologies. The rising interest in the field of crystal engineering is evidenced by the enormous research work by the formulation scientist and the pharmaceutical industry with a high growth curve in CSD database. It is also evidenced by the increase in the number of patent filing in Europe and USA. Despite their promising attributes, the approval of drugs in the market is in a limited number due to a lack of clear regulatory guidance. A detailed insight into the evaluation parameters by the regulatory bodies may bring more optimistic results in the marketability of cocrystal of drugs.

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ABBREVIATIONS

ANDA: Abbreviated New Drug Application; API: Active Pharmaceutical Ingredients; BCS: Biopharmaceutics Classification System; CSD: Cambridge Structural Database; DSC: Differential scanning calorimetry; EMA: European Medicinal Agency; FTIR: Fourier-transform infrared spectroscopy; NDA: New Drug Application; NMR: Nuclear Magnetic Resonance; PXRD: Powder X-ray diffraction analysis; SEM: Scanning Electron Microscope; USFDA: United State Food and Drug Administration.

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