Review Article

Thai Journal of Pharmaceutical Sciences

A comprehensive review on pharmaceutical cocrystal - a subtle technique for solubility enhancement

Sayani Bhattacharyya, Archana Manjunath

Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, India

Corresponding Author:
Dr. Sayani Bhattacharyya, Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, India.
E-mail: sayanibh@gmail.com

Received: May 23, 2022
Accepted: September 15, 2022
Published: January 16, 2023

ABSTRACT

Solubility enhancement of active pharmaceutical ingredients is a challenging field in the pharmaceutical industry. Poorly soluble drugs lack oral bioavailability. Several methods and excipients are employed in the solubility improvement process. The physical and chemical properties of the developed compound play a key role in solubility enhancement. Crystal engineering is a novel strategy 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 in improving the problems associated with solubility, bioavailability, permeability, stability, hygroscopicity, flowability, and process ability. This review represents the concept, characterization, and application of cocrystal 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 and a brief on regulatory perspectives is discussed here. The cocrystallization method establishes the proof of concept of its potential in the pharmaceutical field through increasing number of patents and market approval.

Keywords: Cocrystal, cocrystallization method, coformer, evaluation of cocrystal, physicochemical properties

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 solid-state of an active pharmaceutical ingredient determines its physicochemical properties and chemical stability, and that influences the biopharmaceutical properties and manufacturability of the dosage form. 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 resulting in increased solubility but are less stable with a tendency to recrystallize over time.[1]

As per the biopharmaceutical classification system drugs with low solubility are grouped in BCS II or BCS IV category and some of the drugs exhibit therapeutic inefficiency because of their poor water solubility.[2]

Formulation scientists use different approaches such as micronization, nanonization, solid dispersion, complexation, salt formation, micellar solubilization, and cosolvency for improving drug solubility, resulting in increased bioavailability.[3]

Among these various approaches, one of the unique approaches is co-crystallization-a multi-component system consisting of drug and coformer, bound together with non-covalent interaction in a definite stoichiometric ratio. The concept of solid-state chemistry to create the supramolecular structure in association with two more chemical species with non-covalent interaction results in the formation of cocrystals. Several types of interactions such as 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 coformer retaining its pharmacological characteristics with an improvement in the solubility, and hence bioavailability. The cocrystal thus formed fine-tunes certain physicochemical properties of the drug molecules such as reduction in melting point, improvement in flowability, stability, and permeability.[4,5]

US food and drug administration (USFDA) defined cocrystals as "dissociable API-excipient molecular complexes (with the neutral guest compound being the excipient called coformers) wherein both API and excipients are present in the same crystal lattice."[6,7]

European medicines agency (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 coformer should be less to be classified as cocrystal. Hence, the difference in pKa of both the components should be <1 to oppose the formation of salt.[9]

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 key role in the formation of cocrystal.

The first step of cocrystal formation is the screening of coformers. The coformers 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 coformer is required for the creation of this supramolecular synthon. The Cambridge Structural database reveals that the H bond is the predominant form of interaction between coformers 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 conformers are referred as homosynthons, and presence of different but complementary functional groups between drug and conformers 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 coformers 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 coformers, namely, molecular diffusion, eutectic formation, and amorphization,[13] and mostly depends on the type of reactants. If the vapor pressure of the reactants in the solid-state is high, cocrystal formation takes place through 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]

Cocrystalllization through amorphization 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.

PREPARATION OF COCRYSTAL

Cocrystallization is a method for joining two or more molecules (API and conformer) via non-covalent interactions during the crystallization process. When choosing a cocrystallization process, several factors such as conformer solubility, API, and coformer 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]

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 ability to 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 propranolol, and methyl ethyl ketone. Solvent selection is based on API and conformers solubility in it. A ternary phase diagram of drug, coformer, and solvent should be generated to locate the thermodynamically stable phase of the cocrystals and to estimate the degree of supersaturation of drug and conformer in the solvent.[15]

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 coformers should be congruently soluble in the selected solvent. The formed cocrystals are characterized for structural analysis using single-crystal X-ray diffraction (XRD).[7]

This approach entails dissolving the coformers 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 API and coformer interact with each other to build new hydrogen bonds.[16] The cocrystal is anticipated to be thermodynamically favorable in this case because of the formation of hydrogen bonds between complementary functional groups present between the drug and coformer.[17]

Due to its simplicity and efficacy, this is a widely used experimental screening method for cocrystal formation.[15]

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 coformers. 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 coformer is dependent on the concentration of the drug and the slurry conversion rate which is driven by the solubility of the drug and conformer in the solvent system.

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 APIs, and the coformer.

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]

Supercritical solvent technique: The dissolution of active substance and the conformer 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.

Supercritical antisolvent technique: In this technique, supercritical CO_2 is used as an anti-solvent for a solution of drug and coformer. The supercritical CO_2 is added dropwise through a nozzle to the solution of drug and conformer 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 conformer 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]

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]

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]

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]

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 conformer in mortar and pestle or mixing using a ball mill. The heat evolved during the mixing process is monitored. Cocrystal of sulfathiazole 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 coformers, else leads to the failure of cocrystal formation, and defects in the crystal structure.

Liquid-assisted grinding requires the addition of solvent to a meager quantity to the powder mixture of drug and coformers 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*. used this technique to make cocrystal of caffeine and dicarboxylic acid,[13] Cocrystal of piracetam, was produced employing tartaric acid and citric acid as coformers 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]

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]

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 conformer 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]

CHARACTERIZATION OF CO-CRYSTALS

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 coformers.[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]

Differential Scanning Calorimetry (DSC)

DSC 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 coformer 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]

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]

Scanning Electron Microscopy (SEM)

The surface morphology of the cocrystals can be studied using a SEM. The surface properties of cocrystals can be studied with a ZEISS Electron Microscope, EVO MA15.[37] The samples are sputtered with gold at ambient temperature in an argon environment. The samples are pelletized and mounted to an aluminum 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]

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 XRD.

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

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 coformer (B) when undergoes dissolution, the equilibrium reaction of solution can be described by the following equation,

$$AB \overset{Ksp}{\rightleftarrows} Asol + Bsol \quad (1)$$

$$Asol + Bsol \overset{K11}{\rightleftarrows} ABsol \quad (2)$$

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

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

and

$$K11 = \frac{[AB]}{[A][B]} = \frac{[AB]}{Ksp}$$

The following mass balance equations describe the total solubility of both drug and conformer and can be described as follows

$$[AT] = [A] + [AB]$$

And

$$[BT] = [B] + [AB]$$

Therefore,

$$[AT] = \frac{Ksp}{[B]} + Ksp.K11$$

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

PHYSICOCHEMICAL 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.

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 vapor pressure.[40] Hence, the determination of the melting point can indicate the solubility of the cocrystal. A suitable stoichiometric ratio of drug and conformer can be used to predict the solubility of the cocrystal from the preliminary estimation of the melting point. Choice of coformers plays an important role. The molecular arrangement, molecular symmetry, and intermolecular interactions between the drug and coformer are the critical factors that affect the melting point of the cocrystals.

Choosing a coformer with a higher melting point can increase the thermal stability of an API.[41] For thermolabile pharmaceuticals, low melting point coformers were found to be useful. Therefore, the melting point of cocrystals varies on the selection of the right coformers in the correct stoichiometric ratio.[42,43] During the development phase, the most prevalent methods for determining melting point and thermal analysis are carried out using DSC and thermal gravimetric analysis.

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 coformers 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.

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. A high dose solubility ratio is an indication of a long dissolution time and can be the reason for low absorption.[47]

Hygroscopicity

Hygroscopicity of a pharmaceutical ingredient should be extensively assessed since it might alter the physicochemical parameters such as 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 XRD study should be followed to identify the final form.

The physical stability of theophylline was improved by the formation of cocrystal with oxalic, malonic, maleic, and glutaric acids. Theophylline-oxalic acid cocrystal was found to be the most stable among others as reported.[48]

The crystal engineering approach was applied for solubility improvement of indomethacin with the conformer saccharine. A dynamic vapor sorption study revealed that the 1:1 synthon of the combination gained <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]

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]

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 coformers such as 3-hydroxybenzoic acid, 4-aminobenzoic acid, and cinnamic acid.[54]

The permeability of hydrochlorothiazide cocrystal (HCT) with coformers 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 coformer are an exception. This suggests that permeability and solubility may be mutually exclusive in the study of making cocrystals of drug.[55]

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, and 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 coformers.[56]

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

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

REGULATION OF PHARMACEUTICAL CO-CRYSTALS

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 USFDA and the 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 conformers existence in a unit cell
- The difference between the pKa of API and conformer should be <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 special techniques employed.[59]

A comparative discussion on regulation by USFDA and EMA is presented in Table 1.

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 stoichiometric 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 □ of EU GMP Guide (active substances) and ICH Q7

USFDA: US food and drug administration, EMA: European medicines agency

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

Marketed/patented cocrystals	Combination	Purpose	Reference
Suglat® (2014)	Ipragliflozin+l-proline	Improvement of stability	[27]
Entresto (2015)	Valsartan+sacubitril	Improvement of bioavailability	[61]
EP3240575 A1 (November 08, 2017)	carfilzomib+maleic acid	To improve solubility	[41]
WO2017144598 A1 (August 31, 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	Algorithm
Polymorphism	Polymorphism prediction Crystal structure analysis crystal property prediction	Random forest artificial neural network logistic regression, support vector machine
Cocrystal	CCF screening prediction of cocrystal composition cocrystal formation prediction	Principal component analysis analyse the principal components cluster analysis multivariate adaptive regression splines

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

COCRYSTAL PREDICTION BY 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 coformers) to form cocrystals. Hence, artificial intelligence and deep learning have shown promising data-driven prediction in the selection of coformers, 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.

CONCLUSION

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.

REFERENCES

1. Rodrigues M, Baptista B, Lopes JA, Sarraguça MC. Pharmaceutical cocrystallization techniques. Advances and challenges. Int J Pharm 2018;547:404-20.
2. Sopyan I, Alvin B, Sunan KS, Ikhda NH, Megantara S. Systematic review: Cocrystal as efforts to improve physicochemical and bioavailability properties of oral solid dosage form. Int J Appl Pharm 2021;13:43-52.
3. Ancheria RK, Jain S, Kumar D, Soni SL, Sharma M. An overview of pharmaceutical co-crystal. Asian J Pharm Res Dev 2019;7:39-46.
4. Kumar S, Nanda A. Pharmaceutical cocrystals: An overview. Indian J Pharm Sci 2017;79:858-71.
5. Athira AS, Anu S, Seeja SR, Thaifa MS. A review on pharmaceutical cocrystals. Int J Pharm Res Sch 2018;7:1-18.
6. Kale DP, Zode SS, Bansal AK. Challenges in translational development of pharmaceutical cocrystals. J Pharm Sci 2017;106:457-70.

7. Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. Acta Pharm Sin B 2021;11:2537-64.
8. Agreed QW, Agreed C, Start C, Adoption QW, Adoption C, Cocrystals K. Reflection Paper on the Use of Cocrystals of Active Substances in Medicinal Products. Amsterdam, Netherlands: European Medicines Agency; 2015. p. 44.
9. Food and Drug Administration. Regulatory Classification of Pharmaceutical Cocrystals, Guidance for Industry. Vol. 2. United States: United States Department of Health and Human Services; 2018. p. 1-4.
10. Haynes DA, Chisholm JA, Jones W, Motherwell WD. Supramolecular synthon competition in organic sulfonates: A CSD survey. CrystEngComm 2004;6:584-8.
11. Martinez JM, Dominguez-Chavez JG, Rivera-Islas J, Hopfl H, Morales-Rojas H, Senosiain JP. A twist in cocrystals of salts : Changes in packing and chloride coordination lead to opposite trends in the biopharmaceutical performance of fluoroquinolone hydrochloride cocrystals. Cryst Growth Des 2014;14:3078-95.
12. Chan HC, Kendrick J, Neumann MA, Leusen FJ. Towards ab initio screening of co-crystal formation through lattice energy calculations and crystal structure prediction of nicotinamide, isonicotinamide, picolinamide and paracetamol multi-component crystals. CrystEngComm 2013;15:3799-807.
13. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. Cryst Growth Des 2018;18:6370-87.
14. Friscic T, Jones W. Recent advances in understanding the mechanism of cocrystal formation via grinding. Cryst Growth Des 2009;9:1621-37.
15. Pawar N, Saha A, Nandan N, Parambil JV. Solution cocrystallization: A scalable approach for cocrystal production. Crystals 2021;11:303-21.
16. Yadav BK, Khursheed A, Singh RD. Cocrystals: A complete review on conventional and novel methods of its formation and its evaluation. Asian J Pharm Clin Res 2019;12:68-74.
17. Burande SR, Gandhi PV, Chakole RD, Charde MS, Burade KB. Preparation and characterization of co-crystals: A review. Int J All Res Educ Sci Methods 2021;9:1755-63.
18. Buddhadev SS, Garala KC. Pharmaceutical cocrystals-a review. Proceedings 2021;62:14.
19. Pawar N, Agrawal S, Methekar R. Modeling, simulation, and influence of operational parameters on crystal size and morphology in semibatch antisolvent crystallization of α-lactose monohydrate. Cryst Growth Des 2018;18:4511-21.
20. Apshingekar PP, Aher S, Kelly AL, Brown EC, Paradkar A. Synthesis of caffeine/maleic acid co-crystal by ultrasound-assisted slurry co-crystallization. J Pharm Sci 2017;106:66-70.
21. Ober CA, Gupta RB. Formation of itraconazole-succinic acid cocrystals by gas antisolvent cocrystallization. AAPS PharmSciTech 2012;13:1396-406.
22. Ribas MM, Sakata GS, Santos AE, Dal Magro C, Aguiar GP, Lanza M, *et al*. Curcumin cocrystals using supercritical fluid technology. J Supercrit Fluids 2019;152:104564.
23. 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;14:265-76.
24. Fernández-Ronco MP, Kluge J, Mazzotti M. High pressure homogenization as a novel approach for the preparation of co-crystals. Cryst Growth Des 2013;13:2013-24.
25. Hu Y, Gniado K, Erxleben A, McArdle P. Mechanochemical reaction of sulfathiazole with carboxylic acids: Formation of a cocrystal, a salt, and coamorphous solids. Cryst Growth Des 2014;14:803-13.
26. Rehder S, Klukkert M, Löbmann KA, Strachan CJ, Sakmann A, Gordon K, *et al*. Investigation of the formation process of two piracetam cocrystals during grinding. Pharmaceutics 2011;3:706-22.
27. Bandaru RK, Rout SR, Kenguva G, Gorain B, Alhakamy NA, Kesharwani P, *et al*. Recent advances in pharmaceutical cocrystals : From bench to market. Front Pharmacol 2021;12:780582.
28. Panzade PS, Shendarkar GR, Kulkarni DA. Hot Melt Extrusion: an Emerging Green Technique for the Synthesis of High-Quality Pharmaceutical Cocrystals. J Pharm Innov 2022;17:283-293.
29. Rajadhyax A, Shinde U, Desai H, Mane S. Hot melt extrusion in engineering of drug cocrystals : A review. Asian J Pharm Clin Res 2021;14:10-9.
30. Fernandes GJ, Rathnanand M, Kulkarni V. Mechanochemical synthesis of carvedilol cocrystals utilizing hot melt extrusion technology. J Pharm Innov 2018;14:373-81.
31. Pagire S, Korde S, Ambardekar R, Deshmukh S, Dash RC, Dhumal R, *et al*. Microwave assisted synthesis of caffeine/maleic acid co-crystals: The role of the dielectric and physicochemical properties of the solvent. CrystEngComm 2013;15:3705-10.
32. Zalte AG, Saudagar RB. Advanced techniques in preparation of cocrystals. Int J Sci Prog Res 2015;12:32-5.
33. Lapidus SH, Stephens PW, Arora KK, Shattock TR, Zaworotko MJ. A comparison of cocrystal structure solutions from powder and single crystal techniques. Cryst Growth Des 2010;10:4630-7.
34. Chandel N, Gupta V, Pandey A, Saxena S, Choudhary S. Co-crystalization of aceclofenac and paracetamol and their characterization. Int J Pharm Life Sci 2011;2:1020-8.
35. Bagde SA, Upadhye KP, Dixit GR, Bakhle SS. Formulation and evaluation of co-crystals of poorly water soluble drug. Int J Pharm Sci Res 2016;7:4988-97.
36. Karagianni A, Malamatari M, Kachrimanis K. Pharmaceutical cocrystals: New solid phase modification approaches for the formulation of APIs. Pharmaceutics 2018;10:18.
37. Jayram P, Sudheer P. Pharmaceutical co-crystals : A systematic review. Int J Pharm Investig 2020;10:246-52.
38. Vogt FG, Clawson JS, Strohmeier M, Edwards AJ, Pham TN, Watson SA. Solid-state NMR analysis of organic cocrystals and complexes. Cryst Growth Des 2009;9:921-37.
39. Nehm SJ, Rodríguez-Spong B, Rodríguez-Hornedo N. Phase solubility diagrams of cocrystals are explained by solubility product and solution complexation. Cryst Growth Des 2006;6:592-600.
40. Abourahma H, Cocuzza DS, Melendez J, Urban JM. Pyrazinamide cocrystals and the search for polymorphs. CrystEngComm 2011;13:6442-50.
41. Kumar A, Kumar S, Nanda A. A review about regulatory status and recent patents of pharmaceutical co-crystals. Adv Pharm Bull 2018;8:355-63.
42. Batisai E, Ayamine A, Ayamine OE, Báthori NB. Melting point-solubility-structure correlations in multicomponent crystals containing fumaric or adipic acid. CrystEngComm 2014;16:9992-8.
43. Ross SA, Lamprou DA, Douroumis D. Engineering and manufacturing of pharmaceutical co-crystals: A review on solvent-free manufacturing technologies. Chem Commun 2016;52:8772-86.
44. Shilpa C, Sarika N, Needu K, Shubham W. Co-crystals: A review. J Drug Deliv Ther 2018;8:350-8.
45. Shekunov B, Montgomery ER. Theoretical analysis of drug dissolution: I. Solubility and intrinsic dissolution rate. J Pharm Sci 2016;105:2685-97.
46. Sun DD, Lee PI. Evolution of supersaturation of amorphous pharmaceuticals: Nonlinear rate of supersaturation generation regulated by matrix diffusion. Mol Pharm 2015;12:1203-15.
47. Rinaki E, Valsami G, Macheras P. Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio. Pharm Res 2003;20:1917-25.
48. Trask AV, Motherwell WD, Jones W. Physical stability enhancement of theophylline via cocrystallization. Int J Pharm

2006;320:114-23.
49. Basavoju S, Boström D, Velaga SP. Indomethacin-saccharin cocrystal: Design, synthesis and preliminary pharmaceutical characterization. Pharm Res 2008;25:530-41.
50. Trask AV, Motherwell WD, Jones W. Pharmaceutical cocrystallization: Engineering a remedy for caffeine hydration. Cryst Growth Des 2005;5:1013-21.
51. Martin F, Pop M, Kacso I, Grosu IG, Miclăuş M, Vodnar D, *et al*. Ketoconazole-p-aminobenzoic acid cocrystal: Revival of an old drug by crystal engineering. Mol Pharm 2020;17:919-32.
52. Ma XQ, Zhuang C, Wang BC, Huang YF, Chen Q, Lin N. Cocrystal of apigenin with higher solubility, enhanced oral bioavailability, and anti-inflammatory effect. Cryst Growth Des 2019;19:5531-7.
53. Chen Y, Li L, Yao J, Ma YY, Chen JM, Lu TB. Improving the solubility and bioavailability of apixaban via apixaban-oxalic acid. Cryst Growth Des 2016;16:2923-30.
54. Dai XL, Li S, Chen JM, Lu TB. Improving the membrane permeability of 5-fluorouracil via cocrystallization. Cryst Growth Des 2016;16:4430-8.
55. Sanphui P, Devi VK, Clara D, Malviya N, Ganguly S, Desiraju GR. Cocrystals of hydrochlorothiazide: Solubility and diffusion/permeability enhancements through drug-coformer interactions. Mol Pharm 2015;12:1615-22.
56. Gawade A, Kuchekar A, Wagh P. Application of co-crystals technology in pharmaceuticals. Indo Am J Pharm Res 2021;11:1552-64.
57. Latif S, Abbas N, Hussain A, Arshad MS, Bukhari NI, Afzal H, *et al*. Development of paracetamol-caffeine co-crystals to improve compressional, formulation and *in vivo* performance. Drug Dev Ind Pharm 2018;44:1099-108.
58. Zhou Z, Li W, Sun WJ, Lu T, Tong HH, Sun CC, *et al*. Resveratrol cocrystals with enhanced solubility and tabletability. Int J Pharm 2016;509:391-9.
59. Thayyil AR, Juturu T, Nayak S, Kamath S. Pharmaceutical co-crystallization o-crystallization co-cryco-cry-cryo-cry-cryco-cryo-cry co-cryilit Adv Pharm Bull 2020;10:203-12.
60. Gadade DD, Pekamwar SS. Pharmaceutical cocrystals: Regulatory and strategic aspects, design and development. Adv Pharm Bull 2016;6:479-94.
61. Emami S, Siahi-Shadbad M, Adibkia K, Barzegar-Jalali M. Recent advances in improving oral drug bioavailability by cocrystals. Bioimpacts 2018;8:305-20.
62. Kumar A, Kumar S, Nanda A. A Review about Regulatory Status and Recent Patents of Pharmaceutical Co-Crystals. Adv Pharm Bull 2018;8:355-363.
63. Almansa C, Mercè R, Tesson N, Farran J, Tomàs J, Plata-Salamán CR. Cocrystal of tramadol hydrochloride-celecoxib: A novel API-API co-crystal for the treatment of pain. Cryst Growth Des 2017;17:1884-92.
64. Devogelaer JJ, Meekes H, Tinnemans P, Vlieg E, de Gelder R. Co-crystal prediction by artificial neural networks. Angew Chem Int Ed Engl 2020;59:21711-8.