Review Article

Role of Coformers in Solubility Enhancement of Poorly Soluble Drugs through Cocrystallization: An Overview

Hema R*, Ganesh N S, Vineeth Chandy
Department of Pharmaceutics, T. John College of Pharmacy, Bangalore - 560083, Karnataka, India.
***Corresponding author's E-mail:** hema.rajanna23@gmail.com

Received: 18-03-2022; **Revised:** 26-05-2022; **Accepted:** 03-06-2022; **Published on:** 15-06-2022.

ABSTRACT

Improving the solubility of poorly soluble pharmaceuticals is a key problem in the pharmaceutical industry, and it can be solved using a range of methods, such as particle size reduction, surface modification, and other procedures. Cocrystallization is a new method for enhancing solubility in the pharmaceutical industry, which can be done with the help of cocrystal former (Coformer). These are water-soluble stoichiometric cocrystals of the active pharmaceutical ingredient (API) with water-soluble small molecule coformers such as ascorbic acid, Nicotinamide etc. Selection of coformer is a principal challenge in evolution of cocrystals, which can be done by various approaches such as trial and error, supra molecular synthon, virtual screening, etc. Hydrogen bonding, halogen bonding, and π-π interactions all play a part in the development of cocrystals. Moisture absorption, cocrystal reactant dissolution, cocrystal nucleation, and growth are all factors that impact crystal formation. Cocrystals can be prepared by various methods such as Solution evaporation method, Solution cooling crystallization, Solid state grinding, Liquid assisted grinding method, Hot melt extrusion, etc. This review complies the various research works on cocrystals.

Keywords: Cocrystal, Coformer, Solubility, Hydrogen bonding, Solvation, Crystal lattice.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2022.v74i02.024

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v74i02.024

INTRODUCTION

One of the most efficient methods for delivering medicine is by oral administration. Clinical efficacy is hampered by limited oral bioavailability. Enhancing oral absorption of low water soluble or low permeable drug is a dynamic field of research.[1] Particle Size Reduction, Nanonization, Cosolvency, Solid Dispersion, Self-Emulsifying or Self-Micro Emulsifying Systems, Hydrotropy, and Liquisolid Methods and Nanotechnologies such as Nano-cocrystal are one of the techniques used to increase the solubility and dissolution rate of water-insoluble actives.[2,3]

Pharmaceutical cocrystals are multicomponent systems kept together by H-bonding and made up of two or more molecules in a stoichiometric ratio. Pharmaceutically authorized coformers and medicinal compounds are combined in the same crystal lattice to create a unique active pharmaceutical component formulation.[3] The pharmaceutical industry pays close attention to cocrystals because they boost an API's (active pharmaceutical ingredient's) total bioavailability.[4] Manufacturing pharmaceutical cocrystals allows for incremental changes to an API's crystalline shape, resulting in an API with changing physiochemical characteristics without compromising its intended biological capabilities. Solvent evaporation, Anti-solvent addition, Melt crystallisation, Solid state grinding and other methods can also be used to make pharmaceutical cocrystal's.[5] Cocrystals can ameliorate the physical / chemical properties of an API like solubility, melting point, bioavailability, stability, dissolution rate without interrupting the covalent bonds.[6]

Coformers are used to make cocrystals, which are deemed safe for human consumption and are included on the US FDA's GRAS (Generally Recognized as Safe Determination) list.[7] Which is defined as a non-volatile component in the crystal lattice that interacts non-ionically with the API and is not a solvent (including water).[8] These are water-soluble stoichiometric cocrystals of the active pharmaceutical ingredient (API) with water-soluble small molecule coformers such as ascorbic acid, Nicotinamide, Saccharin, citric acid, tartaric acid and some amino acids. In this case the API and coformer molecules should interact in such a degree that leads to 3-dimensional ordering into a crystal lattice, which leads to the improvement of dissolution and oral bioavailability of poorly soluble crystalline API.[9]

The majority of coformers are pharmaceutical excipients, although they can also be other active pharmacological components with efficacy. In addition, coformers can indeed be employed as food additives and preservatives. In general, the API to coformer ratio is 1:1, 1:2, or vice versa. Acidic, alkaline, or neutral APIs and coformers exist. The coformer is typically a tiny organic acid molecule that can create hydrogen bonds with the target API. Carboxylic acid, amide, and alcohol are three common coformer groups. In a cocrystal system, these functional groups frequently interact with each other.[10] Other important

features of APIs improved by pharmaceutical cocrystals include flowability, chemical stability, compressibility, and hygroscopicity.[11]

Need of Cocrystals

1) The physical and chemical properties of an API like solubility, melting point, bioavailability, stability, dissolution rate can be enhanced by cocrystals without breaking or making the covalent bonds.

2) One of the technique to improve solubility is salt formation which requires acidic, basic and ionisable site, whereas, cocrystals can be prepared even in the absence of acidic, basic or ionisable group in an API.[6,12]

SELECTION OF COCRYSTAL FORMER

One of the most difficult aspects of cocrystal evolution is choosing the right coformers which is suitable with API. A fundamental technique such as "tactless" cocrystal screening for coformer selection is utilized to set out cocrystallization using a specified library of pharmaceutically accepted/approved chemicals. The screened cocrystal with improved physicochemical and pharmacological qualities and compatibility with the cocrystal former can then be produced into a dosage form. One of the most popular technique of cofomer selection in cocrystal formation is trial and error.

Other approaches are as follows

I. The supramolecular synthon technique utilizes the Cambridge structural data

II. Hansen solubility parameter

III. Understanding of hydrogen bonding between coformer and API

IV. Acid dissociation constant (P^{Ka}) based method

V. Virtual screening method[11,13]

Supramolecular synthon approach

Supramolecular synthons will hold a cocrystal containing two or more components together (structural units formed with intermolecular interactions). Functional groups which is able to form supramolecular hetero or homosynthons must be present in the API and coformer in order to obtain cocrystals.

The following is the procedure for developing Cocrystals using a supramolecular synthon approach:

1. Selecting the target molecule (API)

2. Complementary functional groups capable of forming a hydrogen bond are investigated.

3. Methods of preparation

Supramolecular synthons are patterns that are made up of both molecular and supramolecular elements. Such a network of contacts is known as a supramolecular synthon since it repeats itself. Supra molecular synthons are further categorized into:

a) Supramolecular homosynthon: Composed of identical self-complementary functionalities.

b) Supramolecular heterosynthons: Composed of different but complementary functionalities.[11]

Cambridge structural database

Small-molecule crystal structures are included in the Cambridge structural database (CSD). Researchers can modify the crystal structure of a molecule using single-crystal x-ray crystallography. When a structure is solved, the information about it is kept in CSD. Variety of software is used to visualize the structure such as atoms, powder cell etc. This is extremely important for analytical purpose because it facilitates the recognition of phases present in a crystalline powder mixture without the need of growing crystals.[11]

CSD can be used to assess the intermolecular hydrogen bonding potential of different substances.[5] Supramolecular synthons are commonly used in the rational design of cocrystals. To overcome the method's limitations, cocrystal screening, a trial-and-error approach, is commonly utilized.

Hansen solubility parameter

The miscibility of a drug and a coformer suggests that a cocrystal will form; Hansen Solubility Parameters can assist predict this factor, which aids in the selection of acceptable coformers prior to cocrystal screening. The HSP model is based on Hildebrand and Scott's discovery of dividing total cohesive energy into different components (Hydrogen bonding). It's also utilized in tablet pre-formulation and formulation development to anticipate the physicochemical qualities (solubility, melting point, etc.) and compatibility of pharmaceutical components.[11]

The researchers of Krevelen have suggested a theoretical prediction or potential for a cocrystal formulation. Cocrystals might be formed in between the partners if the deviation in solubility parameter value is <5$MPa^{1/2}$. According to Greenhalgh, Cocrystals will form if the difference is ≤7 $MPa^{1/2}$. Salem *et al.*, have recently achieved a more dependable cut-off value of 8.18 $MPa^{1/2}$, which is the outcome of the relaxation of the value compared to previous values.[5]

Hydrogen bond

As proven by the utilization of hydrogen-bonded supramolecular synthons. Hydrogen bonds are essential for the production of cocrystals.[11] It has been proven that hydrogen bonds are the strongest chemical interactions in crystal engineering after coordination bonds with metals and ionic interactions (e.g., dipole-dipole). Hydrogen bonds are important in pharmaceutical cocrystals because they allow an API and a coformer molecule to recognize one another. The analytical instrument for confirming the production of hydrogen bonds is FTIR spectroscopy.[5]

pKa model

All of the proposed coformers were extracted from the GRAS, and each item was added to the EAFUS ("Everything" Added to Food in the United States) list of foods.[11] For selecting potential coformers ΔpKa value was used. In case of salts, proton transfer is a phenomenon. The equation which is concerned in the prediction of cocrystal formation is ΔpKa = [pKa (base) – pKa (acid)]. If the difference in the P^{Ka} value is more than 3, it indicates the transfer of proton. Cocrystals might be formed, if the ΔpKa value is less than zero and salt formation will take place if the value is more than 3. Either cocrystal or salt can be anticipated if the ΔpKa value is in between 0-3. For example, Succinic acid which is having ΔpKa value as 4.2 forms salt by using L-lysine base (P^{Ka} 9.5) whereas cocrystal is formed by using urea base (ΔpKa).[5]

Virtual screening method

The COSMO-RS (conductor-like screening model for real solvents) methodology was used to optimize all candidate coformers that were chosen using the pKa method.[13] The enthalpy, dispersion energy and hydrogen bond of the API and coformer complex was calculated for all the molecules. Apart from the pure components, the excess heat production of the API-coformer complex reveals the possibility of cocrystal formation. Abramov and coworkers used COSMOtherm software to implement the COSMO-RS theory for the screening of coformers.[5]

Contribution of Systematic Coformer to Cocrystal Stabilization

The energy of cocrystal packing is dominated by the intermolecular connection between the coformer and its molecular partner. A thorough understanding of the molecular partner's feasible supramolecular affinity is required to construct the cocrystal. In order to successfully change the final properties of the material, there has to be a relevant molecular interaction between the molecular partner and coformers. Paolo P. Mazzeo and coworkers investigated on series of phenol-derivates to examine the contribution of self-interactions of these coformers to the packing energy in cocrystals. They worked on two recently synthesized cocrystals, that is (Acridine: Thymol) in 1:1 ratio and (Acridine: Carvacrol) in 1:2 ratio. Acridine is used as coformer in both the crystals, natural essential oils like Thymol and Carvacrol is used as two isomeric components which is extracted from thyme and oregano. The crystal structures of newly found cocrystals are solved via SCXRD analysis. Dimers are built up by assembling (Acridine and Thymol in 1:1) and (Acridine and Carvacrol in 1:2) molecules with two sets of hydrogen bonds created by inversion centers between two polycyclic molecules. Acridine-acridine dispersive π-π interactions inside dimers contribute to total cocrystal stabilisation in both cocrystals, in addition to hydrogen bond interactions.[14]

Cocrystals Chemistry

Cocrystals are created utilising a crystal engineering approach to improve an API's solid-state characteristics while keeping its structure intact. Intermolecular interactions that influence the breaking and creation of non-covalent bonds are used to affect the pattern of crystal packing in crystal engineering.[6]

Halogen bonding

The non-covalent interaction halogen bonding (XB) can be employed to cocrystallize. In numerous ways, it's analogous to hydrogen bonding (HB). In HB, one atom, group, or molecule "donates" a hydrogen atom to another atom, group, or molecule that receives it. In XB, a donor atom (D) and acceptor atom (A) share a halogen atom (X) (A).[15]

π-π interactions

Cocrystals exhibit two distinct types of interactions: The first interaction utilises hydrogen bonding to produce substructures, whereas the second involves combining substructures and weak forces to construct a supramolecular framework.[16]

PROPERTIES OF COCRYSTALS

Chemical stability, hygroscopicity, dissolution and solubility of pharmaceutical materials are among the physico-chemical properties that can be changed due to cocrystallization. For a few API cocrystals, this has been demonstrated.[17]

1. Hygroscopicity and hydrate formation

Cocrystals can alter the hygroscopicity of the API.[17] Caffeine cocrystals, a nonstoichiometric crystalline hydrate of Caffeine containing roughly 0.8 moles of water per mole of Caffeine, confirmed this. Caffeine hydrate was made by converting anhydrous or Caffeine crystalline powder to Caffeine hydrate at a high relative humidity (98 %). Caffeine hydrate, on the other hand, loses its hydration water and changes to Caffeine when the relative humidity is low. Only one pharmaceutically acceptable salt form of Caffeine was identified during CSD's research: a hydrochloride dihydrate.[18]

2. Melting point

Molecular interactions cause the melting values of individual crystals to differ from those of cocrystals.[17] The Indomethacin-Saccharin cocrystal demonstrated this. The melting point of IND–SAC cocrystals is around 184°C. This is the temperature range in which Indomethacin (162°C) and Saccharin (225–227°C) melt. The distinctive melting point of IND–SAC cocrystals indicates the formation of a new crystalline phase. The lack of any unbound or absorbed solvent or water, as well as the phase's stability until melting point, are demonstrated by a single endothermic transition in the IND–SAC cocrystals.[19]

3. Chemical stability

Cocrystallization can help an API's chemical stability.[17] As shown, Carbamazepine cocrystals containing Nicotinamide and Saccharin CBZ: NCT in (1:1) crystallised from organic solvents using solvothermal techniques, enhanced chemical stability following photoirradiation and better physical stability after prolonged exposure to relative humidities of 75% at 22° C.[20] The molecular interactions and packing arrangement of CBZ molecules are altered when it is cocrystallized with coformers such as Saccharin (SAC) or Nicotinamide (NCT). As a result, these cocrystals exhibit greater stability against hydration and degradation.[17]

4. Dissolution rates and solubility

The solubility and rate of dissolution of crystalline drugs are affected by cocrystals. As illustrated, benzoic acid, Succinic acid, and fumaric acid were used to make antidepressant Fluoxetine hydrochloride cocrystals. The cocrystals dissolved quickly in water at 20°C, according to powder dissolution experiments. The intrinsic dissolution rate studies were used to compare the dissolving rates of cocrystals and crystalline salt. The 2:1 Fluoxetine-fumaric acid cocrystal dissolved at the same rate as pure crystalline Fluoxetine hydrochloride, whereas the Fluoxetine-benzoic acid 1:1 cocrystal dissolved at half the rate. The dissolving rate of the Fluoxetine hydrochloride-Succinic acid 2:1 cocrystal was about three times greater, although the rate was so quick that an accurate number was impossible to determine. As a result, tailoring drug dissolution rates is possible using cocrystal synthesis with various ligands.[21]

Mechanism Which is Involved in Synthesis of Cocrystal

According to new study, the dissolution profile of Celecoxib/Nicotinamide cocrystals might be altered by the dissolution media or pharmaceutical additives. This study revealed that before pharmacokinetic testing, it is imperative to examine how the cocrystal converts in aqueous media. Dependent on the strength of the buffer in the aqueous medium, ionised Indomethacin/Saccharin cocrystals dissolve differentially. API forms, such as cocrystals, have an influence on dissolution and absorption based on particle size, which is an adjustable parameter.[22]

A study was conducted to see how deliquescent circumstances might cause moisture to form cocrystals from solid particles of cocrystal reactants. Carbamazepine, Caffeine, and Theophylline are among the APIs found in crystal form. When solid mixes containing cocrystal reactants deliquesce, Carbamazepine-Nicotinamide, Carbamazepine-Saccharin, and Caffeine or Theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid) produce cocrystals as a result of moisture absorption. Cocrystal reactant dissolution, moisture absorption, cocrystal nucleation, and growth are all processes that cause cocrystal formation.[23]

In the case of Carbamazepine-Nicotinamide Cocrystallization, the ability of the Cocrystal components to reduce the solubility of the molecular complex to be crystallised controlled nucleation and growth. Cocrystal hydrate formation and stability in aqueous solutions are likewise governed by the concentration of coformer.[24] Cocrystals are produced when Carbamazepine is ground with Saccharin or Nicotinamide. Crystallization is mediated by the amorphous phase, and temperature, moisture, and hydrated form of the reactant are all factors that influence crystallization. Higher cogrinding temperatures and water in the crystal lattice or vapor phase enhance cocrystallization.[17]

METHODS TO PREPARE COCRYSTALS

Cocrystals can be prepared using the techniques listed below

Solution evaporation method, Solution cooling crystallization, Solid state grinding, Liquid assisted grinding method, Slurry conversion, Antisolvent addition, Melting method, Supercritical fluid technology, Ultrasound assisted solution crystallization, Hot melt extrusion, High shear granulation and Freeze drying.[6]

1. Solution evaporation method

The solvent evaporation technique is a simple approach to manufacturing cocrystals using a coformer and a suitable solvent. Between the two chemicals, hydrogen bonds are formed during the cocrystallization process.[6] To make single crystals, the evaporative crystallisation method is commonly utilised. This method uses a solution of both coformers in a solvent to nucleate and grow a crystal, with supersaturation attained by solvent evaporation. Slow evaporation is preferred since it results in the formation of a few bigger crystals rather than a huge number of smaller ones.[25] This also makes it easier for hydrogen bonds to develop between the components.[26] This approach involves dissolving the API and coformer separately in the same solvent at an acceptable stoichiometric ratio. Both solutions are combined and then evaporated entirely. To remove solvent residue, a vacuum oven set to 30°C for 48 hours is employed.[27] Setyawan *et al*., worked on Quercetin-Succinic acid cocrystals, which was prepared in 1:1 molar ratio using solvent evaporation. To investigate on physicochemical properties and dissolution profile. The researchers have found that forming Quercetin and Succinic acid cocrystals using solvent evaporation improved the physicochemical characteristics and dissolution rate of Quercetin (87.25%). This could be caused by formation of a new crystal lattice and the decrease in enthalpy energy.[26]

2. Solution cooling crystallization

An equimolar proportion of an API and a suitable coformer is dissolved in an organic solvent by heating at 65°C for one hour while continuously stirring. When the solution cools to room temperature, it forms cocrystals in the reaction vessel. The cocrystals are filtered, then washed twice in solvent and dried for 48 hours in a vacuum oven at 30°C.[6] Carbamazepine-Nicotinamide cocrystals were studied in

solution. Slow evaporation is the most popular method for separating cocrystals. Additionally, solution crystallization can be used to purify the solution and control particle sizes and shapes.[25]

3. Hot melt extrusion

Cocrystal production by Hot melt extrusion (HME) is a continuous, single-step, expandable, industrially achievable and solvent free process. Due to its solvent-free nature, HME offers numerous benefits such as rapid processing and environmental benefits. A continuous HME process involves feeding materials into a die at a constant screw speed at high temperatures in order to obtain uniform pellets". Enhanced surface contact between drug and coformers occurs due to efficient mixing and material packing, which promotes the solvent-free formation of cocrystals. Cocrystal nucleation in HME involves synchronized melting and mixing of the drug and cocrystal former.[6] A study was conducted on Carvedilol cocrystals by using hot melt extrusion technique to improve the solubility of the API by adjusting the barrel temperature and screw speed parameters, they were able to make Carvedilol and Nicotinamide crystals via hot melt extrusion (HME). The cocrystals produced are 4.79 times more soluble than pure Carvedilol. The maximal release profile of pure Carvedilol was 18.35% in 60 minutes. After 60 minutes, the cocrystals had discharged 88% of their contents. This might be caused by hydrogen bonds forming between the Nicotinamide amide functional group and the carboxyl group.[28]

4. Liquid assisted grinding method

Kneading, solvent-drop, and wet cogrinding are all terms used to describe this process. To accelerate the cocrystallization process, a little quantity of appropriate solvent is introduced. Solvent-drop grinding (SDG) regulates polymorphism cocrystallisation results in addition to enhancing cocrystallisation rate. The choice of solvent is an important aspect of grinding, and one of the criteria is that it should be able to dissolve at least some of the original components. SDG uses less solvent than slow evaporation cocrystallisation, which appears to be a more cost-effective and ecologically friendly way of preparation.[29] A study was undertaken on the liquid assisted grinding process for manufacturing Zaltoprofen-Nicotinamide cocrystals. Which were prepared in 1:1 and 1:2 molar ratio of drug and coformer, As compared to the pure drug, ZFN-Nicotinamide cocrystals were significantly more soluble. ZFN-Nicotinamide 1:1 cocrystals showed higher solubility (3.28±0.336 mg/ml) than 1:2 cocrystals (1.372±0.875 mg/ml). This improved solubility could be a result of interaction between the oxygen atom of the drug and the hydrogen atom of the Nicotinamide.[30]

Mechanisms by Which Cocrystals Enhance Solubility

Solubility is governed by two different factors i.e, crystal lattice strength and solvation of cocrystal components. Solubility can be improved by lowering lattice energy or increasing solvent affinity.[31] Cocrystal and co-former solubilities (for cocrystals of the same drug) must be around 10-fold greater than the API in order to increase cocrystal solubility relative to the drug.[32]

Solubility Enhancement by Cocrystallization

Cocrystals are crystalline structures that are composed up of two or more compounds with weak intermolecular interactions like hydrogen bonding and π-π stacking. Molecular interactions and constitution of pharmaceutical materials is modified by cocrystallization and it is considered as a better substitute to improve drug properties.

The latter can be any additional excipient or API that when used together decreases the dose as well as the negative effects. As a result, even if the API remains the same, altering the coformer will alter the pharmacological characteristics (chemical stability, bioavailability, solubility, melting point, moisture uptake, dissolution, etc.). "Multicomponent crystal that is created between two substances that are solids under ambient circumstances, where at least one component is an acceptable ion or molecule," according to a more precise definition of a cocrystal. Cocrystals are a preferable option for APIs that cannot be transformed into salt form, it's due to the absence of an ionic charge.[33]

Pros and Cons of Cocrystal

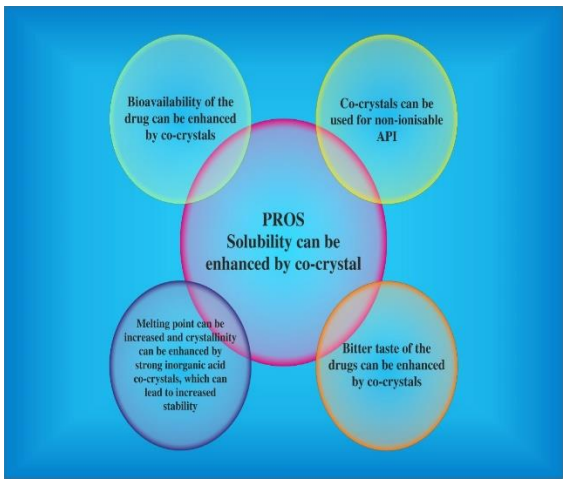

Figure 1: Pros of Cocrystal[31,34,35,36]

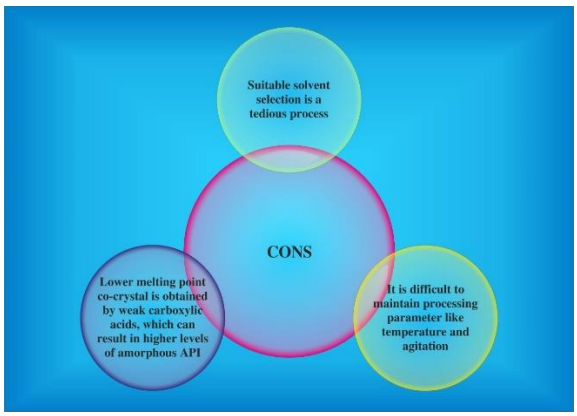

Figure 2: Cons of Cocrystal[31,34,35,36]

APPLICATIONS OF COCRYSTAL

1) Cocrystallization can be used in process of taste masking for increasing palatability of formulations.

2) When compared to other solid-state modification approaches, cocrystal production appears to be a more beneficial option for drug discovery (new chemical synthesis, nutraceutical cocrystals) and drug delivery (solubility, bioavailability). [6,31,35]

Different Works on Cocrystals to Enhance the Solubility of Poorly Soluble Drugs

1. *Felodipine Cocrystal*

Felodipine, a dihydropyridine calcium channel blocking antihypertensive contender, was chosen as the medication candidate in this investigation due to its low bioavailability and poor solubility. The sugar substitute xylitol (xylo-Pentane-1,2,3,4,5-pentol) is utilised as a coformer for Felodipine cocrystals. Which can enhance the dissolution of the API, as well as the ability to inhibit the growth of cariogenic Streptococcus mutans bacteria, which can prevent the formation of dental caries. Crystals deposited from methanolic solutions containing Felodipine and increasing quantities of xylitol were wet cogrinded to accomplish cocrystallization (1:1, 1:2, and 1:3). Felodipine is crystallized with xylitol, producing a material that dissolves faster than the pure Felodipine. With just 16.6% dissolving efficiency, pure Felodipine was found to be exceedingly sluggish. The drug was cocrystalized with xylitol at a 1:1 molar ratio, which increased the solubility rate to 67.6%. Dissolution increased to 79.8% when xylitol molar ratio was increased to 2. Due to formation of new crystalline structure.[37]

2. *Curcumin cocrystals*

Curcumin is the active ingredient in turmeric, an Indian spice (1, diferuloylmethane). Which possesses anti-inflammatory, antioxidant, antiproliferative, antiangiogenic, and anticancer characteristics. Due to its delayed absorption and metabolism, it has a low solubility and bioavailability. New Curcumin cocrystals were made employing phenolic coformers such as resorcinol and pyrogallol using a 1:1 ratio liquid-assisted grinding technique. Curcumin has a very low solubility in water (8.7 mg/L). It was found that cocrystals of Curcumin- pyrogallol (1:1) and Curcumin-resorcinol (1:1), they dissolved ~12 and ~5 times faster than Curcumin in 40% EtOH-water, which improved the bioavailability of pure drug. The cocrystals preserve their 1:1 stoichiometry thanks to a hydrogen connection between the Curcumin's carbonyl OH groups and the coformers' phenolic OH groups.[7]

3. *Favipiravir cocrystals*

Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide) is an antiviral medication that inhibits the RNA-dependent RNA polymerase of RNA viruses (RdRP). SARS-CoV-2 infections are treated with this medication. P-aminobenzoic acid (PABA), 4-hydroxybenzoic acid (4HBA), gallic acid (GA), and ferulic acid (FRA), as well as the phosphodiesterase inhibitor Theophylline, were chosen as GRAS coformers. The drug's physicochemical properties were improved by adding cocrystals to it. Favipiravir along with all other coformers were prepared in 1:1 molar ratio by liquid-assisted grinding method. Cocrystal with different shapes were obtained using different coformers. Using distilled water and pH 7 phosphate buffer in equilibrium, all synthesized cocrystals are soluble in the following way: Fav-anhydrous (7.83), Fav-PABA (8.47), Fav-4HBA (7.1), Fav-Theo (11.52) Fav-GA (14.12) and Fav-FRA (5.57). Low solubility of FRA is due to formation of cocrystal dihydrate. The cocrystals associated with coformers with higher solubility became more soluble. Furthermore, a decline in the solubility of Fav-FRA is caused by the low solubility of FRA.[38]

Table 1: Correlation between coformers and solubility of Favipiravir[38]

Drug	Coformer	Shape of crystal	Solubility
Favipiravir	Theophylline	Needle shaped single crystal	11.52
	PABA	Lath shaped single crystal	8.47
	4-hydroxybenzoic acid	Block shaped single crystal	7.1
	Gallic acid	Block shaped single crystal	14.12
	Ferulic acid	Thin needle shaped single crystal	5.57

4. *Diclofenac-proline nano-cocrystal*

Diclofenac is a non-steroidal anti-inflammatory medicine (NSAID) that is used to treat arthritis and soft tissue injuries, as well as functioning as a local anti-inflammatory and pain relief. It's a low-solubility, high-permeability class II medication. L-proline was used as a coformer to prepare nano-cocrystal in 1:1 ratio. Top-down approaches included wet milling and tidy grinding, whereas the bottom-up strategy relied on rapid evaporation assisted microwaving. Diclofenac-proline solubility was increased by 7.6 folds. It was concluded that Nano-Diclofenac-proline-cocrystal showed the highest dissolution and diffusion profile than conventional Diclofenac-proline cocrystal, due to large surface area of nano-sized particles which can increase the solubility of insoluble drugs and can enhance their solubility by improving their dissolution rate. Due to the nano-cocrystal's higher saturation solubility, the percentage of drugs dissolving with DPC (Diclofenac-

proline cocrystal) was lower than with NDPC (Nano-Diclofenac-proline-cocrystal).[39]

Table 2: Comparison between the drug release rate of DPC and NDPC (percentage of drug release after 60 min in medium)[39]

Sample	pH 1.2 buffer	pH 6.8 buffer	pH 7.4 buffer
DPC	3.08 ± 0.58	85.09 ± 0.16	42.55 ± 0.25
NDPC	4.09± 0.68	97.0± 0.25	100.57± 0.10

5. Furosemide cocrystals

Hypertension and edema are treated with the loop diuretic Furosemide (Lasix). For a BCS class IV medicine, its solubility and permeability (6 mg/L in water) are inadequate (log Pow 1.4). Several coformers with the functional groups CONH and COOH were cocrystallized in order to generate Furosemide cocrystals. Which are as following: (i) Furosemide –caffeine (FUROS–CAF), (ii) Furosemide –urea (FUROS–UREA), (iii) Furosemide-p-aminobenzoic acid (FUROS–PABA), (iv) Furosemide–acetamide (FUROS–ACT), (v) Furosemide –nicotinamide (FUROS–NIC), (vi) Furosemide-Isonicotinamide (FUROS–INIC), (vii) Furosemide –adenine (FUROS–ADEN), and (viii) Furosemide –cytosine (FUROS–CYT). Furosemide cocrystals were made to improve the drug's physicochemical qualities, such as solubility and stability. Liquid aided grinding was used to make them in a 1:1 ratio. Furosemide dissolves twice as quickly as the pure medication because it is a cocrystal. Furosemide dissolves the most readily with cytosine, adenine, and Caffeine among the stable forms, with solubilities around 11, 7, and 6-fold greater than Furosemide. As a result of their crystal structure, cocrystals are more stable than metastable polymorphs or amorphous drug forms. As a result, cocrystals can provide increased solubility and stability for more effective drug delivery.[40]

6. Glimepiride (GLMP) cocrystals

Glimepiride is a sulfonylurea drug that belongs to the third generation and is used to treat type 2 diabetes. GLMP is classified as a class II medicine in the biopharmaceutical classification system due to its low water solubility and high permeability (BCS). Bioavailability is limited and varies due to poor solubility and dissolution rate. GLMP was used to test three possible coformers: citric acid, tartaric acid, and oxalic acid dihydrate. A total of 6 formulations containing, respectively, 1:1 and 1:2 molar ratios of Glimepiride: coformer were prepared using the solvent evaporation method. It is possible that the remarkable increase in dissolution rate could be due to a change in the crystal habit, where molecules might be arranged in less packed crystalline arrays due to weaker intermolecular bonds compared to the parent drug molecules. Another possibility for the faster dissolving rate is that the coformers utilised in this study are highly soluble in aqueous solutions, leading in dissociation of the cocrystals to their constituents and hence faster dissolution.[41]

Table 3: Percentage of drug release of Glimepiride with different coformers[41]

Drug	Coformer	Ratio (1:1)	Ratio (1:2)
Glimepiride	Citric acid	67.59	81.01
	Tartaric acid	63.35	99.92
	Oxalic acid dihydrate	50-60	40-50

7. Hydrochlorothiazide Cocrystals

Hydrochlorothiazide is a diuretic that works by preventing the kidneys from retaining water. It is designated as a BCS class IV medicine because of its low aqueous solubility (0.7 g/L) and permeability. Coformers used to generate cocrystals included nicotinic acid (NIC), nicotinamide (NCT), 4-aminobenzoic acid (PABA), succinamide (SAM), and resorcinol (RES). Which were created utilising a variety of coformer ratios and liquid-assisted grinding techniques. The solubility of the majority of cocrystals is greater (except NIC and SAM crystals). It is explained by the increase in polarity caused by cocrystallization. All cocrystals, with the exception of HCT-SAM, exhibit greater permeability values than the parent drug. SAM crystals, however, showed poor solubility and flux. The fundamental sulfonamide dimer synthon in SAM cocrystals is identical to that in HCT polymorphs, which might explain its strange behaviour.[42]

Table 4: Correlation between different coformers and it's ratio on solublitiy and permeability of Hydrochlorothiazide[42]

Drug	Coformer	Ratio of drug and coformer	Shape of crystal	Solubility	Permeability
Hydrochlorothiazide	Nicotinic acid	1:1	Needle shaped	Low	2
	Nicotinamide	1:1	Plate shaped	1..3 fold	1..8 fold
	4-aminobenzoic acid	1:2	Rod shaped	2.4	1.3
	Succinamide	1:0.5	Block shaped	Low	Low
	Resorcinol	1:1	No single crystals	Low	Low

8. Agomelatine cocrystals

Valdoxan and Melitor are two brand names for Agomelatine, which is an antidepressant. It's a medication that's used to help people who are depressed. Cocrystals were created to boost its solubility in water (1.1 mg/ml). The evaporation process was used to produce Agomelatine cocrystals in a 1:1 stoichiometry from urea (1), glycolic acid (2), isoNicotinamide (3), and methyl 4-hydroxybenzoate (4). It has a far higher solubility than pure Agomelatine, with solubility values of 2.2, 2.9, 4.7, and 3.5 times those of pure Agomelatine in phosphate buffer at pH 6.8.[43]

Table 5: Correlation between different coformers and dissolution rate of Agomelatine[43]

Drug	Coformer	Shape of crystal	Dissolution rate
Agomelatine	Urea	Column shaped	2.2 times > than pure Agomelatine
	Glycolic acid	Block shaped	2.9
	IsoNicotinamide	Block shaped	4.7
	Methyl 4-hydroxybenzoate	Column shaped	3.5

Reported Studies of Cocrystals

Table 6: Reported studies of different Cocrystals[7,37-43]

Drug	Coformer	Method of preparation	Dissolution rate	Reason for solubility enhancement
Felodipine (Antihypertensive agent)	Xylitol	Wet co-grinding	Pure Felodipine (16.6%) Felodipine Cocrystal in 1:1 ratio (67.6%) In 1:2 ratio (79.8%)	Due to formation of new crystalline nature
Curcumin (Antioxidant, anticancer, anti-inflammatory, etc,)	Resorcinol and Pyrogallol	Liquid assisted grinding	Curcumin. Cocrystals improved the solubility of Curcumin by 12 and 5 times, significantly, compared pure	Since the hydrogen link between the drug and the coformer is maintained
Favipiravir (Antiviral drug)	Theophylline, PABA, 4-hydroxybenzoic acid, Gallic acid, Ferulic acid	Liquid assisted grinding	Pure Favipiravir (7.83%) Dissolution of cocrystals, which are as following: 11.52%, 8.47%, 7.1%, 14.12%, 5.57%	When compared to pure drug, a coformer with a higher solubility becomes ever more soluble.
Diclofenac (NSAIDS)	Proline	Wet milling and neat grinding	In comparison to pure drug, cocrystal solubility increased by 7.6 times. (97.00±0.25 in pH 6.8 buffer)	Nano-Cocrystals have a large surface area and a greater saturation solubility.
Furosemide (Loop diuretic)	Caffeine, Urea, PABA, Acetamide, Nicotinamide, IsoNicotinamide, Adenine, Cytosine	Liquid assisted grinding	As compared to the pure drug, Furosemide Cocrystals dissolve 2 times faster.	Because of the new crystalline structure and stability
Glimepiride (Antidiabetic)	Citric acid, Tartaric acid and Oxalic acid dihydrate	Solvent evaporation method	Drug and coformer in 1:1 ratio (67.59%, 63.35%, 50-60%) In 1:2 ratio (81.01%, 99.92%, 40-50%)	Due in change in the crystal habit (In less packed crystalline array) and high solubility of Cocrystals
Hydrochlorothiazide (Diuretic)	Nicotinic acid, Nicotinamide, 4-aminobenzoic acid, Succinamide and Resorcinol	Liquid assisted grinding	Nicotinamide and 4-aminobenzoic acid Cocrystals increased their solubility by 1.3 and 2.4 times, significantly.	Due to the higher polarity caused by cocrystallization
Agomelatine (Antidepressant)	Urea, Glycolic acid, IsoNicotinamide and Methyl 4-hydroxy benzoate	Solvent evaporation	Dissolution of Cocrystal are as following: 2.2, 2.9, 4.7, 3.5 times greater than pure Agomelatine	Because coformer in a Cocrystal has a higher solubility.

CONCLUSION

Nowadays, Cocrystal is most promising approach to enhance the solubility of poorly soluble drugs. This review is an attempt to discuss about the role of coformers on poorly soluble drugs and the mechanism involved in synthesis of Cocrystal. Prior to preparation screening the Cocrystal play important role to avoid the unexpected results, which are done using various screening techniques. Hydrogen bonding, π-π interactions play significant role in structural assembly. Solubility and intrinsic dissolution rate experiments demonstrated that there was a significant increase in solubility. These results indicate that it is possible to alter the physiochemical properties. Wide range of options exist to prepare Cocrystals like solution evaporation, solution cooling crystallization, etc. This review offers the example of various Cocrystals and their preparation methods, studies show that Cocrystals solubility was better compared to that of pure drug. Commercially available cocrystals in recent days are Suglat®, Entresto®, and Steglatro®. Challenges which are faced during developing the cocrystals are selecting the suitable coformer, dissociation of the cocrystal in the formulation and lack of in vitro–in vivo correlation. It is anticipated that Cocrystal will become more projecting routine in pharmaceutical development in coming years.

REFERENCES

1. Emami S, Siahi-Shadbad M, Adibkia K, Barzegar-Jalali M. Recent advances in improving oral drug bioavailability by cocrystals. Bioimpacts 2018; 8(4): 305–320. DOI: 10.15171/bi.2018.33; PMID: 30397585.
2. Kumar S, Singh P. Various techniques for solubility enhancement: An overview. The Pharma Innovation. 2016;5(1, Part A):23-28.
3. Pi J, Wang S, Li W, Kebebe D, Zhang Y, Zhang B, Qi D, Guo P, Li N, Liu Z. A nano-cocrystal strategy to improve the dissolution rate and oral biovailability of baicalein. Asian journal of pharmaceutical sciences. 2019; 14(2): 154-64. DOI: 10.1016/j.ajps.2018.04.009; PMID: 32104447.
4. Cuadra IA, Cabañas A, Cheda JA, Türk M, Pando C. Cocrystallization of the anticancer drug 5-fluorouracil and coformers urea, thiourea or pyrazinamide using supercritical CO2 as an antisolvent (SAS) and as a solvent (CSS). The Journal of Supercritical Fluids. 2020; 160: 104813. Doi.org/10.1016/j.supflu.2020.104813.
5. Thayyil AR, Juturu T, Nayak S, Kamath S. Pharmaceutical Cocrystallization: regulatory aspects, design, characterization, and applications. Advanced Pharmaceutical Bulletin. 2020; 10(2): 203-212. DOI: 10.34172/apb.2020.024; PMID: 32373488.
6. Patil S, Mhatre K, Shirode A, Kadam V. Pharmaceutical Cocrystals: An Emerging Approach for Enhancement of Solubility and Bioavailability of a Drug. American Journal of Pharmtech Research. 2019; 9(05): 1-21. DOI:10.46624/ajptr.2019.v9.i5.001.
7. Sanphui P, Goud NR, Khandavilli UR, Nangia A. Fast dissolving Curcumin cocrystals. Crystal Growth & Design. 2011; 11(9): 4135-4145. Doi.org/10.1021/cg200704s
8. Regulatory classification of pharmaceutical Cocrystals guidance for industry. U.S department of Health and Human sciences. Food and Drug Administration. Centre for drug Evaluation and Research: Pharmaceutical Quality/CMC; February 2018 Revision 1.
9. Newman A, Reutzel-Edens SM, Zografi G. Coamorphous active pharmaceutical ingredient–small molecule mixtures: considerations in the choice of coformers for enhancing dissolution and oral bioavailability. Journal of pharmaceutical sciences. 2018; 107(1): 5-17. DOI: 10.1016/j.xphs.2017.09.024; PMID: 28989014.
10. Sopyan I, Alvin B, k.S Insan Sunan, H.S Cikra Ikhda. Systematic review: cocrystal as efforts to improve physicochemical and bioavailability properties of oral solid dosage form. International Journal of Applied pharmaceutics. 2021k; 13(1): 43-52. Doi:10.22159/ijap.2021v13i1.39594.
11. Fukte SR, Wagh MP, Rawat S. Coformer selection: An important tool in cocrystal formation. International Journal of Pharmacy and Pharmaceutical Sciences. 2014; 6(7): 9-14
12. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Crystal growth and design. 2009; 9(6): 2950-2967. doi: 10.1021/cg900129f; PMID: 19503732.
13. Kumar S, Gupta A, MISHRA C, Singh S. Synthesis, Characterization and Performance Evaluation of Aceclofenac-Urea Cocrystals. Indian Journal of Pharmaceutical Sciences. 2020; 82(5): 881-890. DOI: 10.36468/pharmaceutical-sciences.717.
14. Mazzeo PP, Canossa S, Carraro C, Pelagatti P, Bacchi A. Systematic coformer contribution to cocrystal stabilization: energy and packing trends. CrystEngComm. 2020; 22(43): 1-9. Doi: 10.1039/d0ce00291g.
15. Aakeröy CB, Chopade PD. Cocrystals: synthesis, structure, and applications. Supramolecular Chemistry: From Molecules to Nanomaterials. 2012 Mar 15. Doi.org/10.1002/9780470661345.smc113.
16. Seth SK, Das NK, Aich K, Sen D, Fun HK, Goswami S. Exploring contribution of intermolecular interactions in supramolecular layered assembly of naphthyridine Cocrystals: Insights from Hirshfeld surface analysis of their crystalline states. Journal of Molecular Structure. 2013; 1048: 157-165. Doi: 10.1016/j.molstruc.2013.05.048.
17. Jayasankar A. Understanding the mechanisms, thermodynamics and kinetics of cocrystallization to control phase transformations (Doctoral dissertation, University of Michigan).
18. Trask AV, Motherwell WS, Jones W. Pharmaceutical cocrystallization: engineering a remedy for Caffeine hydration. Crystal Growth & Design. 2005; 5(3): 1013-1021. Doi.org/10.1021/cg0496540.
19. Basavoju S, Boström D, Velaga SP. Indomethacin–Saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization. Pharmaceutical research. 2008; 25(3): 530-541. DOI: 10.1007/s11095-007-9394-1; PMID: 17703346
20. Spong BR. Enhancing the pharmaceutical behavior of poorly soluble drugs through the formation of cocrystals and mesophases. University of Michigan; 2005.
21. Childs SL, Chyall LJ, Dunlap JT, Smolenskaya VN, Stahly BC, Stahly GP. Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic acids. Molecular complexes of Fluoxetine hydrochloride with benzoic, succinic, and fumaric acids. Journal of the American Chemical Society. 2004; 126(41): 13335-13342. DOI: 10.1021/ja048114o; PMID: 15479089.
22. Shiraki K, Takata N, Takano R, Hayashi Y, Terada K. Dissolution improvement and the mechanism of the improvement from cocrystallization of poorly water-soluble compounds. Pharmaceutical research. 2008; 25(11): 2581-2592. DOI: 10.1007/s11095-008-9676-2; PMID: 18651208.

23. Jayasankar A, Good DJ, Rodríguez-Hornedo N. Mechanisms by which moisture generates cocrystals. Molecular pharmaceutics. 2007; 4(3): 360-372. DOI: 10.1021/mp0700099; PMID: 17488034.

24. Rodríguez-Hornedo N, Nehm SJ, Seefeldt KF, Pagan-Torres Y, Falkiewicz CJ. Reaction crystallization of pharmaceutical molecular complexes. Molecular pharmaceutics. 2006; 3(3): 362-367. DOI: 10.1021/mp050099m; PMID: 16749868.

25. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. Crystal Growth & Design. 2018; 18(10): 6370-6387. Doi.org/10.1021/acs.cgd.8b00933.

26. Setyawan D, Oktavia IP, Farizka R, Sari R. Physicochemical characterization and in vitro dissolution test of Quercetin-Succinic acid Cocrystals prepared using solvent evaporation. Turkish Journal of Pharmaceutical Sciences. 2017; 14(3): 280-284. DOI: 10.4274/tjps.16362; PMCID: PMC7227936.

27. Nurismi E, Rosaini H, Dona Octavia MD. Review: Effect of Different Methods on the Multicomponents Crystal Formation from Medicinal Natural Ingredient Compounds. International Journal of Pharmaceutical Sciences and Medicine. 2021; 6(5): 32-39. Doi: 10.47760/ijpsm.2021.v06i05.004.

28. Fernandes GJ, Rathnanand M, Kulkarni V. Mechanochemical synthesis of Carvedilol cocrystals utilizing hot melt extrusion technology. Journal of Pharmaceutical Innovation. 2019; 14(4): 373-381. Doi: 10.1007/s12247-018-9360-y.

29. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: an overview. International journal of pharmaceutics. 2011; 419(1-2): 1-11. Doi: 10.1016/j.ijpharm.2011.07.037; PMID: 21827842.

30. Panzade P, Shendarkar G. Design and Preparation of Zaltoprofen-Nicotinamide Pharmaceutical Cocrystals via Liquid Assisted Grinding Method. Indian Journal of Pharmaceutical Education and Research 2019; 53(4): S563-S570. Doi: 10.5530/ijper.53.4s.151.

31. Devne SR, kapse VN, Ingale PL. Cocrystal: a review on pharmaceutical corystals design and preparation. World journal of pharmaceutical research. 2019; 8(7): 1936-1950. DOI: 10.20959/wjpr20197-15004.

32. Elder DP, Holm R, De Diego HL. Use of pharmaceutical salts and cocrystals to address the issue of poor solubility. International journal of pharmaceutics. 2013; 453(1): 88-100. DOI: 10.1016/j.ijpharm.2012.11.028; PMID: 23182973.

33. Patole T, Deshpande A. Cocrystallization-a technique for solubility enhancement. International Journal of Pharmaceutical Sciences and Research. 2014; 5(9): 3566-3576. DOI: 10.13040/IJPSR.0975-8232.5(9).3566-76.

34. Nanjwade VK, Manvi FV, Ali MS, Nanjwade BK, Maste MM. New trends in the Cocrystallization of active pharmaceutical ingredients. Journal of Applied Pharmaceutical Science. 2011; 1(08): 01-05.

35. Dhakate CS, Upadhye KP, Dixit GR, Bakhale SS, Umate RM. Taste masking by Cocrystallization: A review. World Journal of Pharmaceutical Research. 2017; 6: 1531-1548. DOI: 10.20959/wjpr20177-8881.

36. Friščić T, Jones W. Benefits of cocrystallisation in pharmaceutical materials science: an update. Journal of Pharmacy and Pharmacology. 2010; 62(11): 1547-1559. DOI: 10.1111/j.2042-7158.2010.01133.x; PMID: 21039540.

37. Arafa MF, El-Gizawy SA, Osman MA, El Maghraby GM. Xylitol as a potential Cocrystal co-former for enhancing dissolution rate of Felodipine: preparation and evaluation of sublingual tablets. Pharmaceutical development and technology. 2018; 23(5): 454-463. DOI: 10.1080/10837450.2016.1242625; PMID: 27681386.

38. Deka P, Gogoi D, Althubeiti K, Rao DR, Thakuria R. Mechanosynthesis, Characterization, and Physicochemical Property Investigation of a Favipiravir Cocrystal with Theophylline and GRAS Coformers. Crystal Growth & Design. 2021; 21(8): 4417-4425. Doi.org/10.1021/acs.cgd.1c00339.

39. Nugrahani I, Auli WN. Diclofenac-proline nano-Cocrystal development, characterization, in vitro dissolution and diffusion study. Heliyon. 2020; 6(9): 1-9. DOI: 10.1016/j.heliyon.2020.e04864; PMID: 32964159.

40. Goud NR, Gangavaram S, Suresh K, Pal S, Manjunatha SG, Nambiar S, Nangia A. Novel Furosemide cocrystals and selection of high solubility drug forms. Journal of pharmaceutical sciences. 2012; 101(2): 664-680. DOI: 10.1002/jps.22805; PMID: 22081478.

41. Jaafar IS, Radhi AA. Preparation and physicochemical characterization of cocrystals for enhancing the dissolution rate of Glimepiride. Journal of Advanced Pharmacy Education & Research. 2020; 10(3): 68-76.

42. 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; 12(5): 1615-1622. DOI: 10.1021/acs.molpharmaceut.5b00020; PMID: 25800383.

43. Yan Y, Chen JM, Geng N, Lu TB. Improving the solubility of Agomelatine via cocrystals. Crystal growth & design. 2012; 12(5): 2226-2233. DOI:10.1021/cg201423q.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.