EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 8
213-221
Year: 2022

A REVIEW ON NOVEL APPROACHES TO DEVELOP CO-CRYSTALS FOR ELEGANT PRODUCT

Paul George*, Viresh K. Chandur and A. R. Shabaraya

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India – 574143.

***Corresponding Author: Paul George**
Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India – 574143.

Article Received on 16/06/2022 **Article Revised on 06/07/2022** **Article Accepted on 26/07/2022**

ABSTRACT
The major constraints during the development of a new product are poor aqueous solubility and low oral bioavailability of an active pharmaceutical ingredient. Several approaches have been used to improve the solubility of poorly aqueous soluble drugs, but their success is dependent on the physical and chemical nature of the molecules being developed. Cocrystallization of drug substances allows for the development of new drug products with improved physicochemical properties such as melting point, tabletability, solubility, stability, bioavailability, and permeability while maintaining the active pharmaceutical ingredient's pharmacological properties. Cocrystals are multicomponent systems in which two components, an active medicinal ingredient and a conformer are present in a stoichiometric ratio in the crystal lattice and are linked together by non-covalent interactions. This review article presents a systematic overview of pharmaceutical cocrystals. The theoretical parameters influencing coformer selection and cocrystal screening have been outlined, with several cocrystal creation and evaluation methodologies have been explained.

KEYWORDS: Co-crystals, Coformers, Hansen Solubility Parameter, cocrystallization.

INTRODUCTION
Around 60-70 percent of newly found large numbers of pharmaceutical drugs belongs to BCS Class II and cause difficulties with dissolution, solubility, stability, therapeutic efficacy, and other factors. The need of today's era is to reduce problems associated with drug solubility and permeability using various methods.[1] Researchers have described a number of methods for improving API solubility, including the use of prodrugs, solid dispersions, size reduction, inclusion complexes with cyclodextrins, salt formation, self-emulsifying formulations, surfactants, polymorphs, nanoparticles, and multicomponent molecular crystals. All of the approaches listed above have advantages and disadvantages, but the rate of success will always be determined by the APIs' and polymers' individual physicochemical features. Solvates, hydrates, cocrystals, and salts are multi-component crystals that play an important role in the design of new solids, particularly in the pharmaceutical industry. To improve their solubility, weakly water-soluble drugs can be prepared as amorphous forms, crystalline solid formulations, or lipid formulations. Co-crystallization, by means of crystal engineering, is a propitious method for addressing drug-related issues.[2]

Pharmaceutical co-crystallization is a unique technology for obtaining salts, solvates, and polymorphs as alternatives for API modification throughout the dosage form formulation process.[3] Cocrystals are multicomponent molecular crystals where all components are at a stoichiometric ratio and comprise of two or more chemically different molecules includes modification of drugs to alter physical properties of a drug, especially a drug's solubility without altering its pharmacology effect. A pharmaceutical cocrystal is considered to be composed of an active pharmaceutical ingredient (API) and an appropriate conformer.[4]

Crystal engineering can be used to create a pharmaceutical cocrystal with the goal of improving the solid-state properties of an API without changing its inherent structure. Crystal engineering is the application of supramolecular chemistry concepts to the solid state, with a focus on the notion that crystalline solids are actual instances of self-assembly. Crystal engineering is the process of modifying the intermolecular interactions that control the breaking and creation of non-covalent bonds, such as hydrogen bonding, van der Waals force, $\pi \cdots \pi$ stacking, electrostatic interactions, and halogen bonding, to alter the crystal packing of a solid material.[5]

Solvent and solid-based methods can be used to make co-crystals. Slurry conversion, solvent evaporation, cooling crystallisation, and precipitation are all solvent-based techniques. Net grinding, solvent-assisted

grinding, and sonication are examples of solid-based processes.[6]

Selection of coformers

The drug compatibility of the coformer should be researched prior to the construction of pharmaceutical co-crystals, and these are the primary hurdles to be overcome. The tool which is used to choose the coformer that can be formed as a co-crystal with the drug is called coformer screening. Before being developed into a viable dosage form, the optimal candidate is examined for its physicochemical and pharmacological qualities. There is a long list of coformers that can be utilised, but the ones with a group capable of creating molecular synthons with the API are the most important. Coformers should be classified as generally regarded as safe (GRAS), which indicates that they must meet pharmaceutical safety and quality standards.[7]

The mechanism of cocrystals has been explained using several theoretical approaches such as hydrogen bonding propensity, Cambridge Structure Database, supramolecular synthon, pKa values, and Hansen solubility parameters. The application of chemical element bonding principles, synthons, and graph sets to the style and analysis of cocrystal systems should be beneficial. Normal prediction of whether or not cocrystallization will occur is not possible, thus empirical observation will have to suffice for the time being.[8]

Supramolecular synthon approach

Coformer selection is typically based on the "synthon" technique which creates a supermolecule within the cocrystal by using certain molecular fragments to generate "supramolecular synthons." According to the synthon approach, specific functional groups present on the drug and the coformer will play an essential role in the production of cocrystals, and coformers with complementary functional groups to those of the drug should be employed for successful cocrystallization. Supramolecular synthons are further classified as supramolecular homosynthons or supramolecular heterosynthons. The former are functional groups that are identical, such as two carboxylic acid groups, whereas the latter are functional groups that are distinct, such as carboxylic acid and amide groups.[9]

However, one problem of the synthon technique is that it is not quantifiable in the sense that, while supermolecule formation may be favourable, the supermolecule itself may be unable to pack into an ordered crystalline structure. In addition, the approach does not consider factors such as competition among the different functional groups present within the API or the coformer nor the steric density around the donor and acceptor.[10]

PKa based model

The phenomenon of proton transfer happens in the case of salts. pKa=[pKa(base) - pKa(acid)] is the equation used to predict the development of cocrystals. If the difference in pKa values is more than 3, proton transfer can be noticed. If the pKa value is less than zero, co-crystals may form, while a larger value of more than 3 leads to the development of salts. If the pKa value is between 0 and 3, either co-crystal or salt is likely. Succinic acid (pKa 4.2) forms a co-crystal with urea base (pKa 0.1), whereas the salt is made with L-lysine base (pKa 9.5).[11]

Cambridge structural database

The Cambridge Structure Database (CSD) is a useful tool for determining crystal intermolecular interactions. In structural chemistry, material sciences, and life sciences, including drug discovery and development, the Cambridge Structure Database (CSD) is critical. The CSD can be used to forecast stable hydrogen bonding motifs, with the goal of keeping the most stable motifs intact throughout a family of related structures. This provides details on the sort of intermolecular interaction, geometrical preferences, directional properties, and supramolecular synthon types involved.[12]

Understanding intermolecular interactions is required for supramolecular synthon synthesis. The study of hydrogen bond patterns in crystalline solids can lead to the development of potential synthons. The systematic examination of vast numbers of connected structures is a strong research process, capable of producing results that could not be acquired by any other method, according to CSD. It is mostly based on the shape and polarity of cocrystal formers. The CSD database contains information on the common functional groups involved in supramolecular synthon production. The model's potential flaw is that it was trained on cocrystal observations from the CSD database, neglecting probable failures in realistic cocrystal screenings.[13]

Hansen Solubility Parameter (HSP)

The Hansen solubility parameter (HSP) used to predict cocrystal formation was reported by Mohammad MA, et al. Hansen C.M. initially presented this concept for estimating polymer solubility in paints. The overall energy of vaporisation of a liquid, which is made up of multiple distinct component forces, is the basis of these so-called HSPs. For the purpose of cocrystal formation prediction, the difference in total solubility parameters ($\Delta\delta t$) of the API and conformer is determined. ($\Delta\delta t$) values less than $7MaP^{0.5}$ suggest a high likelihood of cocrystal formation, whereas values more than 10 $MP^{0.5}$ indicate a low likelihood of cocrystal formation. Only a few coformers created cocrystals, despite the fact that ($\Delta\delta t$) was less than $7MPa^{0.5}$ in the study, indicating that this technique has limited use in cocrystal prediction.[14]

Using HSP, it is feasible to predict the miscibility of a drug and its coformer, as well as the production of cocrystals. The group contribution method is often used to calculate the HSP because it only requires the compound's structure. In the computation of HSP, the

Fedors technique, Hoy's approach, and Van Krevelen's method are the most commonly used group contribution methods. The physicists Krevelen and Greenhalgh propose a theoretical prediction or potential for the co-crystal formulation. If the partners' solubility parameter values differ by more than 5MPa1/2, co-crystals may form, according to Krevelen. If the difference is less than 7 MPa1/2, Greenhalgh predicts the production of co-crystals.[15]

Hydrogen bonding

Cocrystals can be designed based on empirical understanding of hydrogen-bond patterns, which can be determined using Etter M.C and Donohue J. recommendations [16]. These rules are:

(a) all acidic hydrogen present in a molecule will be used in hydrogen bonding in the crystal structure of that compound, (b) when hydrogen-bond donors are available, all good acceptors will be used in hydrogen-bonding, and (c) hydrogen bonds will be formed preferentially between the best hydrogen-bond donor and the best hydrogen-bond acceptor.

According to numerous research, the hydrogen bond donors and acceptors of the partners must form hydrogen bonds. Furthermore, the best hydrogen bond donors and acceptors interact within the crystal structure, resulting in co-crystal formation. FTIR spectroscopy can confirm the production of hydrogen bonds.[17]

Fabian's method

The molecular descriptors (single atom, bond and group counts, hydrogen bond donor and acceptor counts, size and shape, surface area) were estimated for each molecule using different sets of valid cocrystal forming structures derived from the CSD. The database described pairs of chemicals that might form cocrystals based on computed molecular characteristics. The shape and polarity of cocrystal formers had the highest descriptive connection.[18]

Cosmo-Rs

COSMO-therm software, based on the COSMO-RS fluid phase thermodynamic technique, was used to describe the miscibility of coformers in super cooled liquid (melt) phase for the purpose of screening acceptable coformers for an API. When comparing pure components to API and coformer mixtures, the excess enthalpy, Hex (a crucial determinant for H-bonding interactions) represents the tendency of those two chemicals to cocrystallize. Solvents with the highest value of H_{ex} with an API, which had the least chance of forming solid solvates, were chosen in the same way as suitable coformers for cocrystallization were discovered. This method was used to select different coformers for itraconazole and solvents for Axitinib (tyrosine kinase inhibitor) in order to avoid the production of hydrates and solvents.[19]

Virtual cocrystal screening

The creation of cocrystals, according to Musumeci et al., is due to all conceivable intermolecular interaction sites present on the surface of molecules. The strength of a hydrogen bond is determined by the H-bond donors and acceptors; the strongest hydrogen bond is formed when the best H-bond donor and best H-bond interact, then the next best H-bond acceptor interacts with the next H-bond donor, and so on, until all sites are fulfilled. When the ΔE difference between cocrystals and two pure solids is greater than 11 kJ/mol, the probability of cocrystal formation is increased by 50%. This method was tested with roughly 1000 compounds from the literature for APIs (caffeine and carbamazepine), and the ΔE parameter was determined to be a useful and quick screening tool.[20]

Cocktail cocrystal method

For screening of cocrystal formation, a new "cocrystal cocktail method" was devised in which four coformers were processed simultaneously with API in a ball mill. This method reduced the workload by 50%, making it more convenient and time-consuming than traditional single-time-consuming methods. The chemical moieties in the coformers and the drug interacted and synthons (homosynthons or heterosynthons) were generated between the drug and the coformers.[21] This approach was used to make itraconazole cocrystals with succinic acid and serine, and the findings demonstrated the best in vitro solubility and dissolution rate when compared to all other formulations.[22]

Preparation of cocrystals

Cocrystal preparation methods such as solid-state grinding, solution reaction crystallisation, solvent evaporation, slurry conversion, and hot melt extrusion have all been recorded to date. The choice of a suitable cocrystallization process, on the other hand, is purely empirical. The most extensively utilised cocrystal formation methods can be divided into two categories: solution-based methods and solid-based methods. Recently, various new cocrystal creation procedures have emerged, including area unit ultrasound aided methodology, critical fluid atomization technique spray-drying technique, and hot soften extrusion technique. The lack of uniformity and knowledge makes it difficult to duplicate or compare cocrystal preparation procedures, which will certainly confuse beginners to the field.

Solution-based methods

In these procedures there are ternary phases in the solution (API, coformer, and solvent), and the ideal state is for the cocrystal to be supersaturated while the reactants (API and coformer) are saturated or undersaturated under the experimental conditions. As a result, the degree of supersaturation with regard to the cocrystal in solution is a significant parameter for cocrystallization, which can be changed by adjusting the API and coformer concentrations.[23] The solubility of the reactants determines the placement of

thermodynamically stable cocrystal phase zones.[24] The ternary phase diagrams show how to supersaturate cocrystals when the reactants are in a saturated or unsaturated condition, depending on the solubilities of the reactants.[25]

Solvent evaporation method

The most common method for preparing cocrystals is solvent evaporation, which is commonly used to synthesise high-quality single-crystal cocrystals appropriate for structural study by single-crystal X-ray diffraction. The ingredients of the cocrystal are entirely dissolved in a suitable solvent at an adequate stoichiometric ratio, and the solvent is then evaporated to obtain the cocrystal.[26] Cocrystallization is influenced by the solvent used, which can have an impact on the reactants' solubility. The cocrystal components should all be soluble in the same solvent. When two incompatible soluble components cocrystallize, the less soluble component precipitates preferentially, resulting in a solid mixture of cocrystal and cocrystal components or a failure to form cocrystals. Many cocrystals have been successfully synthesised using this method[27,28] Slow evaporation of acetonitrile at room temperature for 365 days produced a block-shaped single crystal of a 1:1 febuxostat-piroxicam cocrystal that interacted via a carboxylic acideazole synthon. The cocrystal that resulted had a higher solubility and tabletability than the individual components. Solvent evaporation was used to generate nebivolol hydrochloride nicotinamide cocrystals with a faster dissolving rate.[29]

Antisolvent method

Antisolvent method, also known as vapour diffusion, is a method for producing high-quality cocrystals by using antisolvent. In this procedure, a solvent that is less soluble for the molecule is frequently added to another solution, allowing the solids to precipitate. Supersaturation is achieved by adding a second liquid, which is miscible with the solvent and in which the cocrystals are insoluble or sparingly soluble, to a solution of the drug-conformer to be crystallised. The resultant suspension is filtered, and the solid obtained by XRPD can be identified.[30] The methodology for determining the appropriate concentration (e.g., ratio of solvent to antisolvent) for the production of cocrystals in this research must need the creation of phase solubility diagrams. In most situations, however, a coformer solution is added to the drug organic solution to aid cocrystallization. This phenomenon is very useful for precipitation or recrystallization of the cocrystal's former and active medicinal ingredients.[31]

Cooling crystallisation

Cooling crystallisation is a common technique for producing large-scale, pure crystals. The local supersaturation, which is determined by process parameters such as mass and heat transformation, determines the crystal properties of distribution size, purity, morphology, and crystal polymorphism in this method. [32] As a result, in the cocrystal preparation process, these variables must be accurately controlled according to multiple solid-liquid equilibria. The operational region in the crystallisation process is depends on the cocrystal's stoichiometry as well as its thermodynamic stability zone at the start and end temperatures.[33,34] A continuous oscillatory baffled crystallizer (Fig. 5) produced α-Lipoic acid-nicotinamide cocrystals yields, 99 percent purity, and consistent particle sizes at a rate of 330 g/h. A 10% w/w seeding suspension was fed into the crystallizer for 10 seconds at 10°C to induce cocrystal nucleation.[35]

Reaction cocrystallisation

When the cocrystal components have various solubilities, reaction cocrystallization is appropriate; reactants with nonstoichiometric concentrations are combined to produce cocrystal supersaturated solutions, resulting in cocrystal precipitation. The ability of reactants to reduce cocrystal solubility controls the nucleation and development of cocrystals in this approach.[36] Reaction cocrystallisation methods have been used to produce meloxicam-salicylic cocrystals,[37] carbamazepine-saccharin cocrystals, and indomethacin-saccharin cocrystals.[38]

Slurry conversion

The slurry conversion method is a solution-mediated phase transition procedure that necessitates the addition of excess cocrystal components to the solvent. Each component gradually dissolves and creates a complex in the slurry, promoting cocrystal nucleation and development. The concentrations of the reactants decrease as cocrystals form, resulting in undersaturation (relative to the reactants) and the inability to dissolve the cocrystal components.[39] The ternary phase diagram, which governs cocrystal supersaturation production, controls the operational range of the component's concentration and temperature. Huang et al.[40] discovered that the initial concentration of the components and the operating temperature had a substantial impact on the rate of theophylline-benzoic acid cocrystal formation, as measured by in-line Raman spectroscopy.

Solid state methods

Solid-state crystallisation methods for cocrystal production are successful and environmentally benign since they require little or no solvent; the cocrystal forms spontaneously by direct contact or grinding with increased energy inputs. They are suitable alternatives to solution-based cocrystallization procedures, which can be hazardous to the environment due to the enormous amount of solvent used. Numerous pharmaceutical cocrystals have been synthesized by solid-based methods.

Contact cocrystallization

The creation of cocrystals spontaneously by mixing pure API and coformer in a controlled atmospheric

environment has already been discussed. During cocrystallization, no mechanical forces are utilised in this approach. A quick grinding of the pure components—individually, before mixing—has been carried out in some situations. The rate of cocrystallization of premilled reactants was found to be significantly faster than that of unmilled reactants. Furthermore, regardless of mechanical activation, larger cocrystallization rates have been recorded for the same system at higher temperatures and relative humidity. [41] Caffeine-urea cocrystals were created in 3 days by mixing separately premilling raw ingredients at room temperature and 30% relative humidity, according to MacFhionnghaile et al.[42] The authors discovered that the solids' interparticle surface contact was the most important component in the development of caffeine urea cocrystals.

Solid state grinding

Cocrystal powder samples are frequently generated using solid state grinding processes. There are two types of grinding: neat (dry) grinding and liquid-assisted grinding.

Neat grinding

Previous research has shown that the probable pathways for molecular cocrystal production by neat grinding includes molecular cocrystal diffusion, eutectic formation, and/or transient formation of amorphous intermediate. Grinding molecular diffusion is a method that involves grinding a dynamic solid surface, which results in vaporisation or energy transfer. As a result, in the neat grinding process, a high vapour pressure of the solid-state components (at least one of the components) is required; thus, cocrystals could develop on the crystal surface due to gas phase diffusion.[43] During the creation of diphenylamine and benzophenone cocrystals, Chadwick et al.[44] noticed a liquid eutectic phase on the solid-liquid border using a microsce.

Liquid-assisted grinding

Compared to neat grinding, the liquid-assisted grinding (LAG) approach is effective at producing cocrystal products with high yields and crystallinity. Furthermore, this method is appropriate for quick cocrystal screening, regardless of the raw materials' solubility. The addition of a little amount of liquid, which acts as a catalyst for increasing cocrystal formation, can achieve enhanced molecular diffusion.[45] The amount and type of liquid used in the mechanochemical process influence the production of various solid products as well as the quality of crystals. Fischer et al.[46] evaluated the effect of solvent characteristics on 1:1 caffeine-anthranilic acid cocrystal polymorphs and discovered that form I emerged in the majority of them. Only solvents with strong dipole moments of carbonyl or nitrile groups showed Form II.

Melting crystallization

For the manufacture of pharmaceutical cocrystals, melting crystallization offers an alternative solution. Although no solvents are used in this method, the drug and coformer's thermal stability should be carefully evaluated before use. [47] Rodr'guez-Hornedo and colleagues [48] explored how the carbamazepine-nicotinamide cocrystal crystallises from the melt when heated. Individual cocrystal components crystallised initially, then were melted, and the stable form of the cocrystal emerged from the melt.

Characterization of co-crystals

FTIR spectroscopy

FTIR spectroscopy is used to predict intermolecular interactions and to investigate drug-coformer compatibility. This method is extensively used to predict a compound's chemical conformation.[49] By analysing the carboxylic acid role in hydrogen bond formation, Aakeroy et al.[50] employed FTIR to identify cocrystals from salts. In the range of 400-4000 cm-1, FTIR is used to analyse pure drug, coformer, physical mixture, and cocrystals. For the screening of cocrystals, FTIR is employed in conjunction with other techniques such as DSC or XRD.

Differential scanning calorimetry

Cocrystal formation has been screened using DSC. The presence of an exothermic peak followed by an endothermic peak in DSC spectra can be used to screen for cocrystal formation. The presence of these peaks in the physical mixing of components indicates that cocrystals could develop. Pure drug, coformer, physical mixture, and cocrystals were weighed out (1.5-2.5 mg) in aluminium pans and analysed at heating rate of 5-30° with an identical empty pan as a control. The inert atmosphere was maintained by nitrogen gas at a flow rate of 50 ml/min. DSC can be used to determine melting point, glass transition temperature, polymorphic nature, heat of fusion, and endothermic or exothermic behaviour.[51,52,53]

Thermal analysis

Thermal analysis as a function of increasing temperature or time is used to identify the physical and chemical properties of solids. TGA is an effective method for determining the hydrates/solvates forms of cocrystals, the presence of volatile components, and the temperature of decomposition or sublimation. TGA analysis can predict the thermal stability, compatibility, and purity of cocrystals. The decrease of sample mass during TGA analysis indicates the loss of a volatile component or cocrystal breakdown.[54,55]

Powder X-ray diffraction studies

This analytical method is used to determine the phase identification of unit cells that are connected with the co-crystal. Single and powder X-ray crystallography can provide complete structural information about co-crystals. PXRD is extensively used for cocrystal structure screening and determination. For the purpose of analysing the structure of cocrystals, the PXRD patterns generated from the diffractometer were compared to each

other. Cocrystal formation is indicated by the distinct PXRD patterns of cocrystals compared to their constituents.[56,26]

Powder XRD is frequently used to identify various co-crystals by detecting changes in the crystal lattice because different characteristic peaks are associated with different co-crystals, whereas single crystal XRD is primarily used for structural recognition using software like 'DIFFRAC.SUITE TOPAS.' [57] The most significant issue with single crystal XRD is the difficulty of obtaining a single crystal. The material is triturated to provide a homogeneous fine powder for powder XRD. For analysis, the sample should follow Bragg's law ($n\lambda = 2d \sin\theta$).[58]

Terahertz Time-Domain spectroscopy

For the characterization of cocrystals, terahertz time-domain spectroscopy (THz-TDS) is used as an alternative to PXRD. Terahertz spectroscopy can discriminate between chiral and racemic molecular and supramolecular structures. Terahertz spectroscopy was used to differentiate between theophylline cocrystals with different coformers (such as malic acid and tartaric acid) that were present in chiral and racemic forms.[59]

Solid-state NMR

Solid-state NMR (SSNMR) is a technique for identifying solid phases that cannot be examined using SXRD. By analyzing the degree of proton transfer, SSNMR was utilised to explore the nature of complexes. Thus, SSNMR is a crucial technique for determining if a substance is cocrystal or salt. By estimating hydrogen bonding and local conformation changes caused by couplings, SSNMR can also be employed to examine the cocrystal structure.[60,61]

Vibrational spectroscopy

In vibrational spectroscopy (infrared and Raman), the energy absorbed or dispersed by chemical bonds in co-crystals differs from that of pure components, allowing structural behaviour of co-crystals to be identified. Cocrystals have a distinct spectrum of bands in infrared spectroscopy than pure drugs and coformers due to hydrogen bonding between them. The bands of functional groups that have undergone hydrogen bonding show a distinct variation.[62,63]

Field emission scanning electron microscopy

The surface morphology of co-crystals is studied using FESEM or topography. The comparison is based on micrographs of components and co-crystals acquired from FESEM experiments. Heat energy is not used in the field emission electron microscope; instead, a "cold" source is used. The electrons are emitted from the conductor's surface using a strong electric field. As a cathode, a tungsten filament with a thin and sharp needle (tip diameter 10– 100 nm) is used. A scanning electron microscope is connected to the field emission source to obtain micrographs of co-crystals.[64,65]

Hot stage microscopy

The hot stage microscopy study uses a combination of microscopy and heat analysis. A solid form's physicochemical properties are investigated as a function of temperature and time. Under the microscope, the changes that happened when heating the co-crystal sample on a glass slide are clearly observed for measuring changes such as melting point, melting range, and crystalline transformation. [66]

Table 1: Some reported co-crystals with their Coformers and Method of preparation.[67]

Drug	Coformer	Methos of preparation
Acyclovir	Tartaric acid, malonic acid, adipic acid	Solvent evaporation
Indomethacin	Saccharin	
Aceclofenac	Nicotinamide	Neat grinding
Chloral hydrate	Betain	Cooling crystallization
Gliclazide	Sebacic acid, α-hydroxyacetic acid	Liquid-assisted grinding
Piroxicam	Sodium acetate, saccharin sodium, urea, nicotinamide, resorcinol	Dry grinding
Isoniazide	Vanillic acid, ferulic acid, caffeic acid, resorcinol	Slurry crystallization
P-coumaric acid	Nicotinamide	
Mefenamic acid	Nicotinamide	Co-milling
Quercetin	Caffeine, nicotinamide	Electrospray technique
Baicalein	Nicotinamide	High-pressure homogenization
Caffeine	Oxalic acid, glutaric acid	Spray congealing
Fenofibrate	Nicotinamide	Solvent drop grinding

CONCLUSION

Cocrystal engineering has emerged as a viable method for improving the performance of pharmaceutical compounds by changing their undesirable physicochemical characteristics throughout the last decade. There have been numerous reports of pharmaceutical cocrystals, with some of them having been approved by the FDA or being tested in clinical studies. Developing cocrystals into commercial pharmaceutical formulations, however, still poses significant difficulties. The choice of a good coformer is crucial when creating a pharmaceutical cocrystal. The

selection of coformers, on the other hand, has generally relied on trial and error, which is time-consuming and labor-intensive. A range of computer-assisted technologies have recently emerged as appealing tools for speeding up the screening process for cocrystals. The rational design of cocrystals with defined functions and performances requires a better understanding of the structure-based physicochemical features. In addition, while constructing a cocrystal formulation, compatibility with other excipients, pharmacokinetic profiles, therapeutic efficacy, and toxicity problems should all be carefully considered.

REFERENCES

1. Fong SYK, Ibisogly A, Bauer-Brandl A. Solubility enhancement of BCS class-II drug by solid phospholipid dispersions: Spray drying versus freeze-drying. Int J Pharm, 2015; 496: 382-91.
2. Shan, N, Zaworotko, M.J. The role of cocrystals in pharmaceutical science. Drug Discov. Today, 2008; 13: 440-46.
3. Butler, J.M, Dressman J.B. The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development. J. Pharm. Sci, 2010; 99: 4940-54.
4. Bagde S.A, Upadhye K.P, Dixit G.R, Bakhle S.S. Formulation and Evaluation of Cocrystals of poorly water-soluble Drug. Int. J. Pharm. Res, 2016; 7: 4988-97.
5. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev, 2007; 59(7): 617-30.
6. Morissette SL, Almarsson O, Peterson ML, Remenar JF, Read MJ, Lemmo AV, et al. High-throughput crystallization: polymorphs, salts, cocrystals and solvates of pharmaceutical solids. Adv Drug Deliv Rev, 2004; 56: 275-300.
7. Jones W, Motherwell WDS, Trask AV. Pharmaceutical cocrystals: An Emerging approach to physical property enhancement. MRS Bull, 2006; 31: 875-79.
8. Lange L, Lehmkemper K, Sadowski G. Predicting the aqueous solubility of pharmaceutical cocrystals as a function of pH and temperature. Cryst Growth Des, 2016; 16(5): 2726- 40.
9. Savjani JK, Pathak C. Improvement of physicochemical parameters of acyclovir using cocrystallization approach. Braz J Pharm Sci, 2016; 52(4): 727-40.
10. Douroumis D, Ross SA, Nokhodchi A. Advanced methodologies for cocrystal synthesis. Adv Drug Deliv Rev, 2017; 117: 178-95.
11. Ghadi R, Ghuge A, Ghumre S, Waghmare N, Kadam VJ. Co-crystals: emerging approach in pharmaceutical design. Indo Am J Pharm Res, 2014; 4(7): 3881-93.
12. Trask, A.V. An overview of pharmaceutical cocrystals as intellectual property. Mol. Pharmaceut, 2007; 4: 301–09.
13. Hilfiker R. Polymorphism: In the Pharmaceutical Industry. Wiley-VCH, 2014; 6: 81-93.
14. Blagden N, Berry DJ, Parkin A, Javed H, Ibrahim A, Gavan PT, et al. Current directions in co-crystal growth. New J Chem, 2008; 32: 1659-72.
15. Bond AD. "Pharmaceutical Satls and Cocrystals," ed. by Wouters J., Quere L., Royal Society of Chemistry, Cambridge, 2012; 9–28.
16. Tiekink, Vittal JJ. Frontiers in Crystal Engineering, John Wiley & Sons, Ltd, Chapter: Crystal Engineering of Pharmaceutical Co-crystals, 2006; 2: 25-50.
17. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals J Pharm Sci, 2006; 95: 499-516.
18. Laszlo F, Cambridge structural database analysis of molecular complementarity in cocrystals. Cryst Growth Des, 2009; 9(3): 1436-43.
19. Abramov YA, Loschen C, Klamt A. Rational coformer or solvent selection for pharmaceutical cocrystallization or desolvation. J Pharm Sci, 2012; 101(10): 3687-97
20. Musumeci D, Hunter CA, Prohens R, Scuderi S, McCabe JF. Virtual cocrystal screening. ChemSci, 2011; 2: 883-90.
21. Yamamoto K, Tsutsumi S, Ikeda Y. Establishment of cocrystal cocktail grinding method for rational screening of pharmaceutical cocrystals. Int J Pharm, 2012; 437: 162-71.
22. Shete A, Murthy S, Korpale S, Yadav A, Sajane S, Sakhare S, et al. Cocrystals of itraconazole with amino acids: screening, synthesis, solid state characterization, in vitro release and antifungal activity. J Drug Delivery SciTechnol, 2015; 28: 46-55.
23. Kuminek G, Cao F, Bahia de Oliveira da Rocha A, Gonc¸alves Cardoso S, Rodrı´guez-Hornedo N. Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5. Adv Drug Deliv Rev, 2016; 101: 143-66.
24. Chiarella RA, Davey RJ, Peterson ML. Making co-crystals the utility of ternary phase diagrams. Cryst Growth Des, 2007; 7: 1223-6.
25. Blagden N, Berry DJ, Parkin A, Javed H, Ibrahim A, Gavan PT, et al. Current directions in co-crystal growth. New J Chem, 2008; 32: 1659-72.
26. Raheem Thayyil A, Juturu T, Nayak S, Kamath S. Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications. Adv Pharm Bull, 2020; 10(2): 203-212.
27. Basavoju S, Bostro¨m D, Velaga SP. Pharmaceutical cocrystal and salts of norfloxacin. Cryst Growth Des, 2006; 6: 2699-708.
28. Chow SF, Chen M, Shi L, Chow AHL, Sun CC. Simultaneously improving the mechanical properties, dissolution performance, and hygroscopicity of ibuprofen and flurbiprofen by cocrystallization with nicotinamide. Pharm Res (N Y), 2012; 29: 1854-65.

29. Modani S, Gunnam A, Yadav B, Nangia AK, Shastri NR. Generation and evaluation of pharmacologically relevant drug–drug cocrystal for gout therapy. Cryst Growth Des, 2020; 20: 3577-83.
30. Nikam VJ, Patil SB. Pharmaceutical cocrystals of nebivolol hydrochloride with enhanced solubility. J Cryst Growth, 2020; 534: 1254-88.
31. Ober, C.A.; Gupta, R.B. Formation of Itraconazole–Succinic Acid Cocrystals by Gas Antisolvent Cocrystallization. AAPS PharmSciTech, 2012; 13: 1396–1406.
32. Wang IC, Lee MJ, Sim SJ, Kim WS, Chun NH, Choi GJ. Anti-solvent co-crystallization of carbamazepine and saccharin. Int J Pharm, 2013; 450: 311-22.
33. Hickey MB, Peterson ML, Scoppettuolo LA, Morrisette SL, Vetter A, Guzma´n H, et al. Performance comparison of a co-crystal of carbamazepine with marketed product. Eur J Pharm Biopharm 2007; 67: 112-9.
34. Yu ZQ, Chow PS, Tan RBH. Operating regions in cooling cocrystallization of caffeine and glutaric acid in acetonitrile. Cryst Growth Des, 2010; 10: 2382-7.
35. Leung DH, Lohani S, Ball RG, Canfield N, Wang Y, Rhodes T, et al. Two novel pharmaceutical cocrystals of a development compound screening, scale-up, and characterization. Cryst Growth Des, 2012; 12: 1254-62.
36. Sheikh AY, Rahim SA, Hammond RB, Roberts KJ. Scalable solution cocrystallization: case of carbamazepine-nicotinamide I. CrystEngComm, 2009; 11: 501-9.
37. Rodrı´guez-Hornedo N, Nehm SJ, Seefeldt KF, Paga´n-Torres Y, Falkiewicz CJ. Reaction crystallization of pharmaceutical molecular complexes. Mol Pharm, 2006; 3: 362-7.
38. Machado TC, Kuminek G, Cardoso SG, Rodrı´guez-Hornedo N. The role of pH and dose/solubility ratio on cocrystal dissolution, drug supersaturation and precipitation. Eur J Pharm Sci, 2020; 152: 1054-22.
39. Cao F, Amidon GL, Rodriguez-Hornedo N, Amidon GE. Mechanistic analysis of cocrystal dissolution as a function of pH and micellar solubilization. Mol Pharm, 2016; 13: 1030-46.
40. Maya P, Lipert Naı´r, Rodrı´guez-Hornedo. Cocrystal transition points: role of cocrystal solubility, drug solubility, and solubilizing agents. Mol Pharm, 2015; 12: 3535-46.
41. Douroumis, D.; Ross, S.A.; Nokhodchi, A. Advanced methodologies for cocrystal synthesis. Adv. Drug Deliv. Rev, 2017; 117: 178–195.
42. Huang Y, Zhou L, Yang W, Li Y, Yin Q. Preparation of theophylline-benzoic acid cocrystal and on-line monitoring of cocrystallization process in solution by Raman spectroscopy. Crystals, 2019; 9: 329-44.
43. Kaupp G. Solid-state molecular syntheses: complete reactions without auxiliaries based on the new solid-state mechanism. Cryst Eng Comm, 2003; 5: 117-33.
44. Macfhionnghaile P, Crowley CM, Mcardle P, Erxleben A. Spontaneous solid-state co-crystallization of caffeine and urea. Cryst Growth Des, 2020; 20: 736-45.
45. Lien Nguyen K, Friscic T, Day GM, Gladden LF, Jones W. Terahertz time-domain spectroscopy and the quantitative monitoring of mechanochemical cocrystal formation. Nat Mater, 2007; 6: 206-220.
46. Chadwick K, Davey R, Cross W. How does grinding produce cocrystals? Insights from the case of benzophenone and diphenylamine. Cryst Eng Comm, 2007; 9: 732-4.
47. Friscic, T.; Jones, W Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. Cryst. Growth Des, 2009; 9: 1621-37.
48. Fischer F, Scholz G, Benemann S, Rademann K, Emmerling F. Evaluation of the formation pathways of cocrystal polymorphs in liquid-assisted syntheses. Cryst Eng Comm, 2014; 16: 8272-8.
49. Yan Y, Chen JM, Lu TB. Thermodynamics and preliminary pharmaceutical characterization of a melatonin-epimelic acid cocrystal prepared by a melt crystallization method. Cryst Eng Comm, 2015; 17: 612-20.
50. Seefeldt K, Miller J, Alvarez-Nu´n˜ez F, Rodrı´guez-Hornedo N. Crystallization pathways and kinetics of carbamazepine-nicotinamide cocrystals from the amorphous state by in situ thermomicroscopy, spectroscopy, and calorimetry studies. J Pharm Sci, 2007; 96: 1147-58.
51. Wu TK, Lin SY, Lin HL, Huang YT. Simultaneous DSCFTIR microspectroscopy used to screen and detect the cocrystal formation in real time. Bioorg Med Chem Lett, 2011; 21: 3148-5.
52. Aakeroy CB, Salmon DJ, Smith MM, Desper J. Cyanophenyloximes: reliable and versatile for hydrogen bond directed supramolecular synthesis of cocrystals. Cryst Growth Des, 2006; 6: 1033-42.
53. Karagianni A, Malamatari M, Kachrimanis K. Pharmaceutical cocrystals: new solid phase modification approaches for the formulation of APIs. Pharmaceutics, 2018; 10(1).
54. Lu E, Rodriguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. CrystEngComm, 2008; 10: 665-68.
55. Yamashita H, Hirakura Y, Yuda M, Terada K. Coformer screening using thermal analysis based on binary phase diagram. Pharm Res, 2014; 31: 1946-57.
56. Steed JW. The role of cocrystals in pharmaceutical design. Trends Pharmacol Sci, 2013; 34(3): 185-93.
57. Jiang L, Huang Y, Zhang Q, He H, Xu Y, Mei X. Preparation and solid state characterization of dapsone drug-drug cocrystals. Cryst Growth Des, 2014; 14: 4562-73.
58. Yadav S, Gupta PC, Sharma N, Kumar J. Co-crystals: An alternative approach to modify

physicochemical properties of drugs. Int J Pharm, 2015; 5(2): 427-36.
59. 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(10): 4630-7.
60. Aitipamula S, Vangala VR. X-ray crystallography and its role in understanding the physicochemical properties of pharmaceutical cocrystals. J Indian Inst Sci, 2017; 97(2): 227- 43.
61. Aakeroy CB, Salmon DJ, Smith MM, Desper J. Cyanophenyloximes: reliable and versatile for hydrogen bond directed supramolecular synthesis of cocrystals. Cryst Growth Des, 2006; 6: 1033-42.
62. Stevens JS, Byard SJ, Schroeder SLM. Salt and cocrystals? Determination of protonation state by X-ray photoelectron spectroscopy (XPS). J Pharm Sci, 2010; 99(11): 4453-7.
63. 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.
64. Blagden N, Berry DJ, Parkin A, Javed H, Ibrahim A, Gavan PT, et al. Current directions in co-crystal growth. New J Chem, 2008; 32: 1659-72.
65. Yao H, Kimura K. Field emission scanning electron microscopy for structural characterization of 3D gold nanoparticle superlattices. In: Méndez-Vilas A, Díaz J, eds. Modern Research and Educational Topics in Microscopy. Formatex, 2007; 568-75.
66. Gnanamoorthy P, Karthikeyan V, Prabu VA. Field Emission Scanning Electron Microscopy (FESEM) characterisation of the porous silica nanoparticulate structure of marine diatoms. J Porous Mater, 2014; 21(2): 225-33.
67. Raheem Thayyil A, Juturu T, Nayak S, Kamath S. Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications. Adv Pharm Bull, 2020; 10(2): 203-212.