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Solubility And Dissolution Enhancement Of Hydrophobic Drug By Co-Crystallization

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Abstract: Pharmaceutical cocrystals are multicomponent systems in which at least one component is an active pharmaceutical ingredient and the others are pharmaceutically acceptable ingredients. Cocrystallization through various methodologies leads to improved physicochemical properties of active pharmaceutical ingredients. This process will most likely result in enhanced bioavailability, flowability, solubility, and tablet ability. Cocrystallization of a drug substance with a conformer is a promising and emerging approach to improve the performance of pharmaceuticals, such as solubility, dissolution profile, pharmacokinetics and stability. This review article presents a comprehensive overview of pharmaceutical crystal's, including preparation methods, physicochemical properties, and applications. Furthermore, some examples of drug crystals are highlighted to illustrate the effect of crystal structures on the various aspects of active pharmaceutical ingredients, such as physical stability, chemical stability, mechanical properties, optical properties, bioavailability, sustained release and therapeutic effect. This review will provide guidance for more efficient design and manufacture of pharmaceutical cocrystals with desired physicochemical properties and applications.

Keywords: Pharmaceutical cocrystal, Cocrystal engineering, Physicochemical properties, Solid dosage forms, Crystallization.

INTRODUCTION

The physicochemical properties, such as the stability, particle size, powder flow ability, taste, hygroscopicity, solubility and compatibility, of active pharmaceutical ingredients (APIs) are critical attributes that impact the therapeutically effectiveness and manufacturing cost of solid dosage forms[1]. In oral drug delivery systems, gastrointestinal absorption significantly depends on the solubility and dissolution rate of drug molecules. However, at present, approximately 90% of new chemical entities and 40% of currently marketed drugs belong to the Biopharmaceutical Classification System (BCS) II and IV

classes, which suffer from the problems of poor water solubility and low bioavailability [2]. As a result, the absorption of drugs in the gastrointestinal tract is limited, and subsequently, the clinical applications of drugs are hindered. Obviously, the physicochemical properties of pharmaceutical solids considerably influence the performance of drug products.

Most of the solid-state active pharmaceutical Ingredients exist mainly in two morphological structures crystalline or amorphous. Among these crystalline material are more preferable due to their high solubility when Compare to the amorphous forms. Crystalline materials are preferred for product development due to their high stability. Even crystal forms are stable reproducible and easily profitable than other types of solidsmajor drawback is its solubility [3].

Co-Crystallization is one of the alternative ways to solve the problems confined with physicochemical properties of the API over the last twenty years a number publications have been shown significant increase in the use Co-crystals and theirpossible an the use in the formulation as optimization strategy for solubility, dissolution rate, physical stability & Bioavailability enhancement of API for oral administration the solubility and dissolution rate of a drug are crucial factors for its sufficient bioavailability.These factors are the main challenge to the formulation scientists for the development and formulation of effective drugs. More than 40% of drugs in the development suffer from bioavailability problems owing to poor solubility'. Alternative strategies have been introduced to enhance solubility, dissolution rate, and bioavailability. These involve salt formation, solid dispersion, cyclodextrins complexion, micro emulsification, Solubilization, micronation etc. Approximately 70%of candidate drugs have problems with the Solubility therefore it is a big challenge in the field of pharmaceutical to developing drug and drug dosage forms to show a good profile of solubility and dissolution rate, especially for oral preparation.[4]

According to Biopharmaceutical Classification System (BCS) the drugs get classified into four major categories depending upon their solubility and gastrointestinal permeability as BCS class I, II, I, IV'. BCS Class II and class IV drug s majority suffer from low aqueous solubility Leading to poor absorption and bioavailability which faces challenges for drug development process. Bio pharmaceutics classification system (BCS) class Il and IV drugs suffer from poor aqueous solubility and hence low bioavailability'. There are various strategies have been well documented to enhance solubility and dissolution of poorly water soluble drug via pro-drug approach, Salt formation, Particle size reduction, Complexation and Solid dispersion. Nowadays, poor solubility, lower bioavailability, and hindered physical, chemical, and biopharmaceutical properties of active pharmaceutical ingredients (APIS) become a very important matter of discussion for pharmaceutical scientists. It is a challenging task for pharmaceutical researchers and industry to develop a suitable formulation with improved physicochemical properties. The process of co-crystallization is long known; however, in the recent times, this approach has gained enormous importance in pharmaceuticals as a relatively new method for enhancement of solubility, bioavailability, stability, thermal properties, permeability, tablet ability, and other related physicochemical properties.[5]

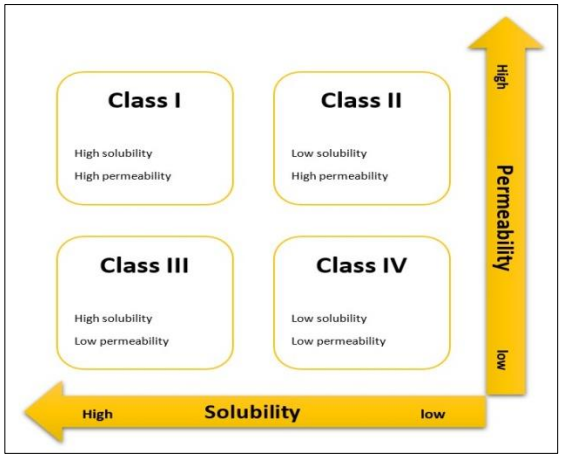

Fig. 1. Biopharmaceutical classification System (BCS) of drugs

Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical cocrystals can enhance other essential properties of the APIs such as Flowability, chemical stability, compressibility and Hygroscopicity Physical property improvement is of particular interest to pharmaceuticals as the vast majority of medicines are delivered as solid forms. The physical properties of the solids contained within a pharmaceutical drug product will have a direct impact on the processing, delivery, and, ultimately, performance of the medicine. [6]

The last few years, an outsized number of medicines are discovered with low aqueous solubility. Among these, about 60-70% of the drugs belong to BCS Class II (low solubility/high permeability) and IV (low solubility/ low permeability) suffers from problems like poor aqueous solubility, poor dissolution profile and poor stability. Many Active Pharmaceutical Ingredients (API) have not been developed in formulations due to low aqueous solubility, which affects the bioavailability and therapeutic effect of drugs. Therefore, co-crystallization comes in such cases which allow using them as neutral molecules along with the co-formers without altering its biological activity. Various approaches have been reported to enhance the solubility of drugs, which leads to an improvement in the bioavailability. Size reduction, solid dispersion, complexation, salt formation, co solvency, self-emulsifying drug delivery system are some approaches used to enhance the solubility of poorly water-soluble drugs. Among all those techniques, co-crystals approach is exclusive, therein it does not affect the pharmacological properties of the drug, but it is going to modify the drugs bioavailability and also improve its physicochemical properties, like physical and chemical stability, dissolution rate and bioavailability. Hence co-crystals have developed a tremendous interest in pharmaceutical research and development because of its potential to customize physicochemical properties of the solid while maintaining the chemical integrity of the drug. Poor dissolution rate, solubility, chemical stability and moisture uptake influence therapeutic efficacy of many pharmaceuticals, and significantly lower the market value of a drug. Multi-component crystals e.g. solvates, hydrates, co-crystals, salts play important role in the design of new solids particularly in the pharmaceutical area. Physical property improvement is of particular interest to pharmaceuticals as the vast majority of medicines are delivered as solid forms. The physical properties of the solids contained within a pharmaceutical drug product will have a direct impact on the processing,

delivery, and, ultimately, performance of the medicine. To provide a classic example, crystal structure directly affects the solubility of a given solid in solution. Drug productsrequire a certain solubility to be bioavailable in the body. It is estimated that 40% of existing drug products and up to 90% of new chemical entities have limited aqueous solubility and hence cannot be delivered to the body using conventional techniques. Cocrystal formation with a suitable co-former offers the potential of improved solubilityvia modification of the underlying crystal structure, thus potentially rendering the compound bioavailable. As cocrystal research has expanded, it has available a range of application areas for physical property manipulation through cocrystal formation. Improvements in solubility, stability, bioavailability, and mechanical properties have been well documented and emerging applications such as taste masking and intellectual property extension are being explored.[7]

CO-CRYSTAL

Cocrystals are solids that are neutral crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.[8] If at least one of the coformers is an API and the other is pharmaceutically acceptable, then it is recognized as a pharmaceutical cocrystal.[9] A cocrystal has a different crystal structure to either of the starting materials and as a result different physicochemical properties. Cocrystals are attractive because the cocrystal solid can be designed to have superior physical properties to either of the pure starting molecules. Physical property improvement via cocrystal formation has been demonstrated for solid explosives, agrochemicals, pigments, and, particularly, pharmaceuticals. [10-11]

According to the definition by the US Food and Drug Administration (FDA), cocrystals are crystalline materials composed of two or more different molecules, typically drug and cocrystal formers (“coformers”), in the same crystal lattice. Pharmaceutical cocrystals have presented opportunities for engineering solid state forms beyond conventional solid-state forms of an active pharmaceutical ingredient (API), such as salts and polymorph. This includes modification of drugs to alter physical properties of a drug, especially a drug’s solubility, without altering its pharmacology effect. The FDA also added that cocrystals can be tailored to enhance drug product bioavailability and stability so enhance the processability of APIs during drug product manufacture. As per literature, the first cocrystal synthesized was quinhydrone, which is a 1:1 cocrystal between benzoquinone and hydroquinone. [12, 13]

CLASSIFICATION OF CO-CRYSTAL[14]

- Cocrystal anhydrates,
- Cocrystal hydrates (solvates),
- Cocrystals of salts (unsolvated, unanhydrates)

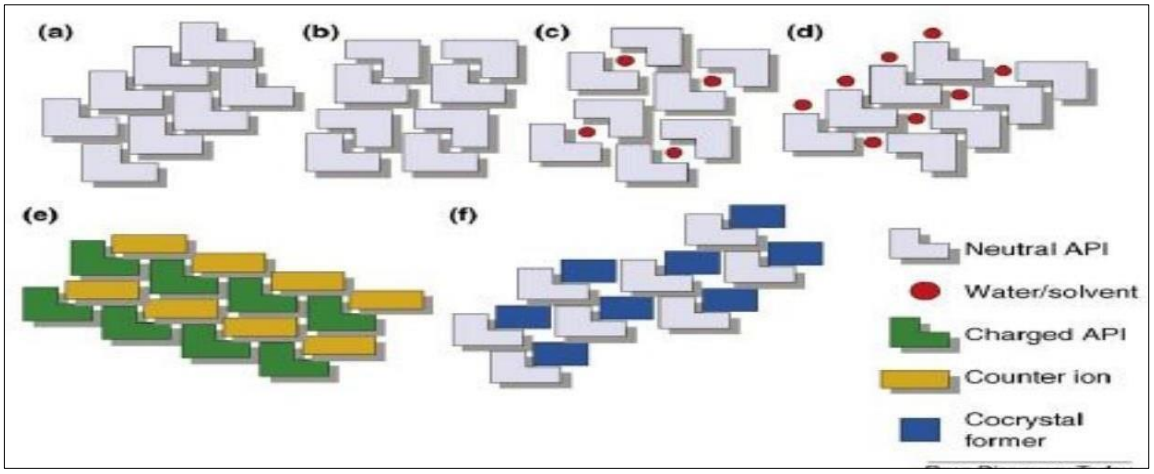

Fig 2: Schematic representation of (a) pure API; (b) polymorphs of API; (c) clathrates solvate/hydrate of API, (d) solvates/hydrates of API, (e) salt of API, (f)pharmaceutical cocrystals of API.

Difference between co-crystals, salt, solvates, and hydrates

Cocrystals and solvates can be differentiated based on their physical state of the components. The compounds which are liquid at room temperature are called as solvates whereas those compounds which are solid at room temperature are called as cocrystals. If the solvates contain water as a solvent in their crystal lattice then they are known as hydrates . Solvates/hydrates are quite unstable, because they lose solvent/water at high temperature and low humidity during storage and the physiochemical properties will be different for hydrated/dehydrated forms. [15]

Advantages of cocrystals [16]

1. Cocrystals exist in stable crystalline form.
2. APIs will benefit of their physicochemical properties enhancements.
3. Cocrystals can be made for non-ionizable APIs as well as for those complex drugs which have sensitive functional groups that may not survive the harsh reaction conditions of strong acids or bases.
4. Cocrystals have the potential to shorten the drug development timeline of APIs.
5. Applicable to wide range of drug
6. Reduce chemical degradation when exposed to light.

Disadvantages of cocrystals [17]

1. Addition of a coformer will contribute to a higher mass of dosage form.
2. Selection of the suitable solvent is tedious process
3. Maintenance of processing parameters is difficult.

Implication of co-crystals [20,21]

Effect of co-crystals on physicochemical properties of API Along with all other aspect's investigations of physicochemical properties plays most important role in developing the new dosage form. These physicochemical properties of the drugs can be adjusted with an increased instability and efficiency of dosage form by using co- crystallization techniques.

Melting point

It is one of the physical properties of solid and used for determination of purity. Pure substances or solid melt at sharp meting point with narrow range. Thermodynamic stability of any API can be governed by its meting point so utility of high melting point co-former for its better stability and also useful in case of thermolabile drugs, so selection of co-former is very important in case of synthesis of cocrystals.

Tablet ability

Tablet ability means ability of substance to get convert in tablet form. Crystal packing, tablet ability, and compaction are important parameters of pre-formulation study with help of co-crystallization we can alter these properties by using suitable co-formers.

Solubility:

As discussed in introduction about 60 to 70 % drugs are belongs to BCS Class II (low solubility/high permeability) and IV (low solubility/ low permeability), so its need to improve solubility of these drugs to develop the various formulations. With development of cocrystal one can increase the solubility of lo soluble drug many researchers have been improved solubility of drug with this technique.

Stability:

It is also imperative study has to be done during the development of new dosage formulation. Different stability studied like chemical stability, thermal stability, solution stability and photostability should be performed during development of pharmaceutical co-crystals.

Bioavailability:

It is defined as the rate and extent of pure drug that reaches into systemic circulation. Low oral bioavailability of APIs is one of the major challenges in development of formulations, with help of co-crystallization one can enhance or improve the bioavailability of drug. Many researchers has been enhanced the bioavailability of different drugs with conversion in cocrystal form .

Relative humidity (RH) stress:

RH stress provides the information about the water content in co-crystals which leads to deterioration of molecules. This in turn helps in determining the best storage condition. Many of the literature concluded that the co-crystals are stable to moisture under normal storage conditions.

Thermal stress:

This is the most important parameter used to determine physical and chemical stability.

Chemical stability:

These studies were normally conducted using accelerated stability conditions such as 40°C/75% RH and 60°C/75% RH to minimize the chemical degradation of the formulation. Only limited research work was done on the chemical stability of co-crystals.

Spring and Parachute effect:

Spring and Parachute phenomenon was explained by Guzman, this concept improves the solubility of hydrophobic drugs by using a supersaturation strategy. This mechanism involves in the origination of supersaturated Metastable state and its maintenance. The weak Bonds (Hydrogen bonds) that connects the drug and the co- former in co-crystals are dissociated, which leads to the release of high water-soluble co- former from the crystal lattice of co-crystal to the biological medium. The Hydrophobic drug has been converted to supersaturation state which is having higher energy than its crystalline molecule called spring. This spring will precipitate to clusters immediately. The maintenance of this super saturated stage for a sufficient period is beneficial for improving the solubility. Using some of the excipients or compounds which intervene with crystal growth may lead to inhibit the precipitate and maintain spring state this referred to as parachute. This state lasts for a long time in the dissolution medium showin high solubility. This stage transformer follows Ostwald's Law of stages.

COCRYSTALLIZATION TECHNIQUES

There are various methods available for the preparation of cocrystals, which could be broadly classified into two categories, namely, solid-state based and solution based. Both methods have their own advantages and disadvantages. Solidstate methods are convenient for the preparation of cocrystals on both laboratory and industrial scale, as these techniques can be considered as a convenient, versatile, sustainable, and eco-friendly method for the preparation of cocrystals.[22] Solution-based methods are mainly confined to and convenient for the preparation of cocrystals on a laboratory scale, as they are simple, easy to process, monitor, and control the final product, but at the same time, one should be careful, as solvent selection affects the characteristics of cocrystal. [23]

There are various types of methods of preparation:

1) Solid-state preparation method

2) Solution-state preparation method

3) Supercritical Fluid method

4) Miscellaneous method

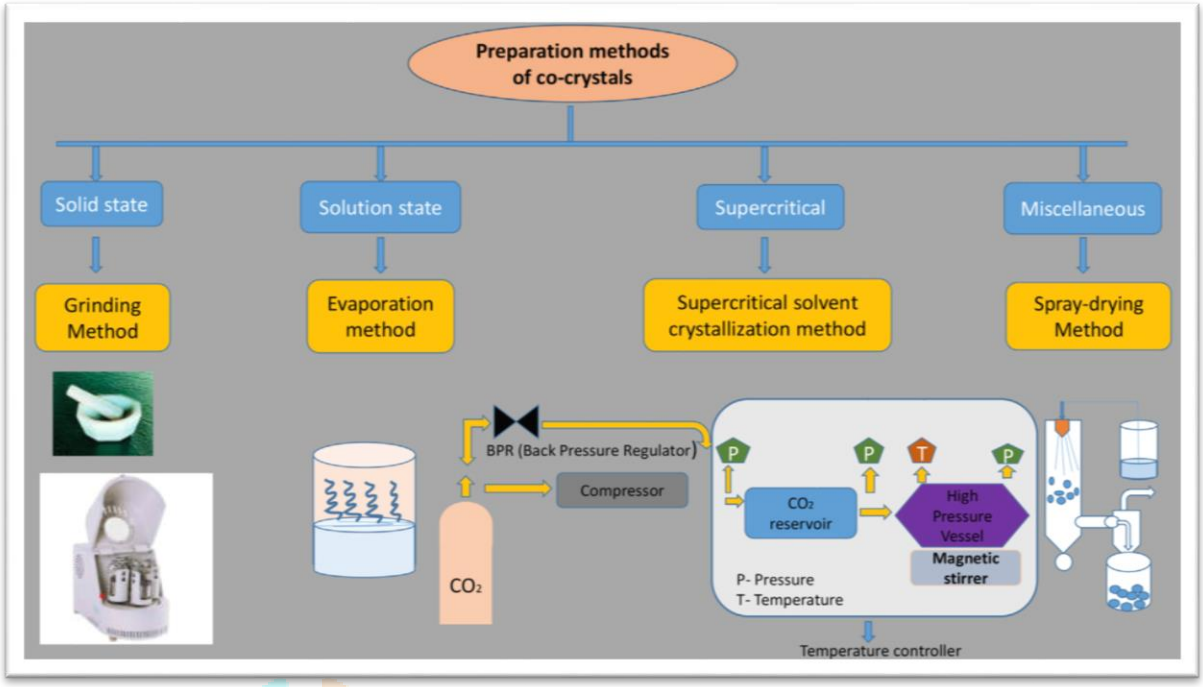

Fig 3: Different types of co-crystallization techniques

1. Solid-State Preparation Methods

Contact Formation Method

The contact formation method involves the concept of decreasing the size of the particle by increasing its crystallization rates. [24] It has also been proven that the crystals that are pre-milled largely contribute toward the spontaneous reaction for the formation of cocrystals.[25] Many cocrystals have been prepared using this method, proving the fact that the smaller sized particles lead to faster cocrystals formation, for example, urea and 2-methoxybenzamide whose surface energetics increases due to reduction in particle size .[26]

Solid-State Grinding Method

Solid-state grinding is another method that has been used for many years in the field of research for the preparation of cocrystals. For example, adopting this methodology, liquidassisted grinding (LAG) in the solid state was used to examine the production of diastereomeric cocrystals of malic and tartaric acids [27] . Primarily, this approach follows two different methods for the preparation of molecular assemblies, such as the neat or dry grinding (DG) method and LAG method.

Dry or Neat Grinding Method

In the DG method, the solid form of the API and conformer get ground together manually using a mortar and pestle or mechanically by using a ball mill. [28,24] Brexpiprazole is a drug that lies in BCS Class II. To improve its solubility, the ball milling technique is used and has been found to be one of the convenient methods to prepare cocrystals with conformers, for example, succinic acid and catechol [29] . The main problem lies with the dry grinding method, that is, one cannot ensure the formation of a stoichiometry

mixing of cocrystals, which requires further an additional step to get a pure cocrystal product.

Liquid-Assisted Grinding Method

The LAG method incurs the addition of a small amount of the solvent (to the mixture) in order to get the desired cocrystal product. This added solvent can act as a catalyst for the formation of cocrystals.[24] followed the LAG to prepare cocrystals of caffeine and dicarboxylic acid, which indicated that there was an acceleration of reaction kinetics by choosing the suitable solvent for the reaction. Another notable example is the cocrystal of piracetam, a nootropic drug, which was prepared by employing both dry and LAG methods using tartaric acid and citric acid as the conformers. Comparing the above methods, it was observed that the LAG method is the faster method than the dry or neat grinding methods. [30] LAG is a more efficient method than the neat grinding method for the screening of cocrystal hydrates. compared the outcomes of LAG and neat grinding for the screening of cocrystal hydrates of theophylline–citric acid and caffeine–citric acid. They found that LAG gives consistent results irrespective of the reactant's nature (hydrated/anhydrous) compared to neat grinding. Hence, LAG is the preferred method for the screening of pharmaceutical cocrystals. There are several research studies regarding the formation of carbamazepine cocrystals with nicotinamide and saccharin in which the use of the solvent drop method has been proved to be convenient for preparing cocrystals. [31] Despite several advantages of LAG and DG methods such asbeing inexpensive, easy to perform, and eco-friendly, when it comes to preparing for large-scale production for industries, hotmelt extrusion (HME) is preferred.[32]

Hot-Melt Extrusion

The HME method is a widely used technique in the pharmaceutical industry. Since the last decade, this method has shown the capability to replace old methods of preparation of cocrystals and be used both in laboratories and commercially. [33] In this technique, both the API and conformer get mixed simultaneously with the aid of heat and pressure above their melting points.[24] The HME method for preparing cocrystals was introduced by where they found that there is an increase in surface contact among the molecules, and homogeneous mixing can significantly assist the production of cocrystals. The proper selection of extruders is highly essential in the case of the HME method. Especially for pharmaceutical cocrystal preparation, a twin-screw extruder could be used to ensure a proper homogeneous mixture of components. [32] The temperature is an important factor when the HME method is considered. reported the formation of cocrystal with ibuprofen and nicotinamide; here, they observed that raising the temperature above the eutectic point improves mixing and increases the dissolution rate, and further eliminates the size reduction step. Screw configuration also affects the quality of the cocrystals. [34] Low screw rotational speed is required to get high-quality cocrystals, as high rotational speed may degrade the product . HME can be used in a variety of ways; for example, it can act as a reaction vessel to produce cocrystals to enhance the bioavailability of poorly water-soluble APIs. Hence, HME is a reliable method used widely to accept the changing regulatory demands, is solvent free, and is a single-step method that can replace the other old methods.

High Shear Wet Granulation

The high shear wet granulation (HSG) method includes assembling the powder components in a liquid medium which could be performed in a high shear granulator. [24] HSG can also be considered a suitable method for the formation of cocrystal components on the batch scale. Granules formation is quite dependent upon the impeller speed, excipient used, and time of exposure of the granules. [35] Proper selection of a liquid media for the granulate in order to get the desired product is absolutely necessary. Veronika et al. successfully prepared cocrystals of ivabradine hydrochloride with the conformer S-mandelic acid in situ by the wet granulation method. They studied the influence of excipients on the stability of cocrystals during the wet granulation process and found that excipients do not have an influence on the

production of ivabradine–mandelic acid cocrystals. [36] The HSG method is convenient for many samples, but it is not appropriate for drugs which are thermally labile and have a complex process. Hence, depending upon the kind of sample and retaining the quality of cocrystal needed to be formed, the desired technique needs to be selected.

2. Solution-Based Preparation Methods

The solution-based method is another category of preparation method for cocrystals, which includes evaporative cocrystallization, cooling crystallization, reaction cocrystallization, and isothermal slurry conversion. [24] The cocrystal operating range is the best tool to create cocrystals from the solution. This range can be found using eutectic points from the solution containing a cocrystal mixture and conformer. This range is explained by the ternary phase diagram, [37] and it also explains the stability.

Evaporative Cocrystallization

In this technique, a solution of cocrystal components (API and conformer) is prepared in a volatile solvent. The solution is kept at room temperature. Due to the slow evaporation of the solvent, the solute components reach their supersaturation concentration which leads to nucleation and crystal growth. [38] This technique is suitable for preparing pharmaceutical cocrystals. used this method for the preparation of ibuprofen–nicotinamide cocrystals in ethanol solvent. The advantages of this technique are that it is easy to handle, it has high potency while screening, and the process is simple. The limitations of the technique are the excess consumption of precious organic solvents which is harmful to the environment, scale-up is difficult, and there is the possibility of formation of solvates. [39]

Cooling Crystallization

In crystallization, temperature plays a key role. For some of the compounds, increasing the temperature leads to an increase in solubility, and for some others like supersaturated solutions, allowing to cool leads to the formation of cocrystals as precipitates. The main lead in this technique is the formation of the most uniform cocrystal size with energy efficiency. Latent heat is taken out by heating the solution, and the remaining are allowed to cool. In this system, the warm solution is circulated and cooled at time intervals using pressure as a function, and it is also combined with the evaporative system in some of the other instruments. [40, 24] By using this preparative method, cocrystals of caffeine and glutaric acid in acetonitrile are prepared. [40] Methods like vacuum cooling crystallizer, continuous cooling crystallizer, and scraped

surface cooling crystallizer are the various techniques under this method.

Reaction Crystallization

The cocrystals under this method were formed by using a solution containing reactants. Upon addition to another solution and stirred in a vessel, the concentration overcomes the solubility

in the mixture that leads to the formation of the crystals. Mostly, in this type of technique, reactions are done very quickly and mixing conditions influence the crystal size. [41, 24] Nucleation growth depends on the mixing at the microstate level that gives supersaturation and reduces solubility. It allows nucleation and leads to crystal formation. By using this technique, carbamazepine forms cocrystals with nicotinamide . This technique can inhibit the formation of a single component crystal, whereas the major drawback of this technique is that it ishazardous to the environment (solvents), solvates in the yields, and is difficult to scale. [39]

Isothermal Slurry Conversion

This is the most efficient screening and scale-up method for cocrystallization. [42, 24] In this method, the conformer and API aredissolved in different solutions at a suitable temperature and allowed to stir for the required time. Then the concentration of constituents exceeds the critical activity of the conformer that allows the nucleation growth that results in the crystal formation. [43, 39, 23] The presence of a stable form of theophylline–aspirincrystal in isopropyl alcohol was observed by isothermal slurry conversion. It is an easy way to prepare cocrystals because it involves the use of less apparatus and halts the development of a single component crystal, but its limitations involve being not eco-friendly, as hazardous solvents are employed, and the scale up being challenging. [23]

3. Supercritical Fluid Methods

Morphology and size reduction can be altered by using this technique [23], where we can achieve single-step particle formation. This is the most advantageous technique for cocrystallization where we can get the highest quality of crystals. [23,43] The most commonly used supercritical fluid is CO_2; the advantages of using this fluid is to reduce the processing steps, being eco-friendly solvent, well-finished products (without solvent), a greater tendency for solubility, and mainly product degradation that is less because of the lower temperatures (31°C, 7.39 MPa). [44, 45, 46]

Rapid Expansion of Supercritical Solution

The rapid expansion of the supercritical solution is one of the techniques used to produce fine microparticle crystals. The conformer and API solution are depressurized under atmospheric conditions in supercritical fluid CO_2, then the solvent fluid drops gradually to supersaturation in the supercritical CO_2. The supersaturation leads to nucleation growth, finally forming the crystals. The solubility of letrozole was improved 7.1 times by this method . The drawback of this technique is that only some of the pairs of conformer–drug combinations are soluble in CO_2, and it also gives low yields. [46]

Supercritical Solvent Crystallization

In the supercritical solvent crystallization technique, CO_2 works as a solvent, so there is no need to add any other organic solvents. In this method, the solvent causes intermolecular interactions that lead to the

nucleation growth and formation of crystals. The benefit of this technique is that it can be performed by eliminating the drying steps. [47] Solubility can be altered by adjusting the temperature and pressure conditions (of CO_2). Crystals of carbamazepine with saccharin, theophylline, and indomethacin were obtained with high product yield . The advantage of this technique is that it prevents the formation of solvates and hydrates in the crystals because of the absence of water in this method. It is limited to single-component crystal formation. [39]

Supercritical Anti-Solvent Method

In the supercritical anti-solvent method, CO_2 acts as an antisolvent because of its low solvent power toward the conformerd and API, also greater miscibility toward the organic solvents. Ethanol or acetone is a polar organic solvent which dissolves the API and conformer in it. By inducing the solution containing the API and conformer into the high-pressure vessel containing supercritical CO_2 fluid or using other methods by spraying the solution into the precipitation chamber, the fluid expands the volume and decreases the solubility and leads to supersaturation forms of the cocrystals.[48,49,24] For example, naproxen–nicotinamide microcrystalline ensemble was prepared by using CO_2 as an antisolvent. It is also a single-step process and the drawback of the technique includes the use of hazardous solvents and many special condition processes are needed for the solvents. [23]

Supercritical Assisted Spray Drying Method

Other supercritical processes are atomization and supercritical fluid–enhanced atomization , and both these methods work in a similar way. When the solution gets depressurized (cocrystal components along with supercritical CO_2), the following liquid splits (using coaxial nozzle) into the form of fine droplets, which are sprayed into a drying chamber under atmospheric pressure in the atomization method and into other chambers at required pressures. Crystals need to be collected which are deposited on the walls of the chamber. In both the methods, CO_2 acts as an anti-solvent, while in the secondary stream, CO_2 can be replaced by N2 gas ; Crystals of itraconazole with L-malic acid were prepared by atomization and anti-solvent crystallizationmethods. In the final crystals, tetrahydrofuran was removed by flushing and dried with more supercritical CO_2. Similarly, supercritical fluid–enhanced crystallization gave the pure form of theophylline crystals by using different conformers. [23, 24, 48, 49]

4. Miscellaneous Methods

Besides the abovementioned popular methods, there are various methods used for getting the desired cocrystals.

Laser Irradiation

The laser irradiation method provides a new way to prepare cocrystals as in this technique, high-power CO_2 laser is used by varying the raster speed along with the power of the laser which stimulates recrystallization to a cocrystal framework by using the powder form of the conformer. Cocrystals of caffeine with oxalic acid and cocrystals of caffeine with malonic acid were prepared by using this technique. Electrospray Technology The electrospray cocrystallization of carbamazepine and itraconazole , developed with the desired conformer, revealed that the electrospray technique is a unique technique which is a single-step, selective method for the synthesis of cocrystals, which leaves the traditional

techniques far behind. This technique involves the occurrence of droplets and charging at the same time. [50]

Electrospray Technology

The electrospray cocrystallization of carbamazepine and itraconazole , developed with the desired conformer, revealed that the electrospray technique is a unique technique which is a single-step, selective method for the synthesis of cocrystals, which leaves the traditional techniques far behind. This technique involves the occurrence of droplets and charging at the same time by providing an electric field,which leads to the formation of elongated solution.[51]

Spray Drying Technique

Spray drying is a unique single-step method that has the capability to transfer solutions, emulsions, or suspensions to solid form (e.g., powder form or agglomerate). This concept has been used many decades back but has been recently used in pharmaceutical industries as the product at the end ensures proper quality standards in particle size and shape, moisture content of particles, and manages the bulk density. Carbamazepine and nicotinamide cocrystals are prepared using the spray drying method more conveniently and a similar quality crystal obtained as formed by the LAG method . Hence, spray drying is a reliable method for the production of cocrystals on an industrial scale. Besides, this method has bulky and expensive equipment with less thermal efficiency. [52, 53]

Freeze Drying

The freeze drying method works by freezing and lowering the surrounding pressure, which allows the material to undergo sublimation and hence leads to a phase change . Freeze drying is a distinctive process that has several advantages over other methods, as it is used in large scale production, eliminating the issue of differences in solubility of the conformer. Oxalic acid and theophylline cocrystal preparation concluded that the freeze drying method allows the formation of additional solid forms which cannot be achieved by other standard methods. [24, 54]

Electrochemically Induced Cocrystallization

Electrochemically induced cocrystallization can create a potential cocrystallization of ionizable compounds. While preparing a cocrystal of cinnamic acid and 3-nitrobenzamide, the electrochemical application can shift the pH to get neutral carboxylic acids and thus act as a driving tool for the cocrystallization.[55]

Resonant Acoustic Mixing

Resonant acoustic mixing includes the mixing of constituents without grinding in the presence of any suitable liquid to get the desired cocrystal. Several cocrystals of carbamazepine have been formed using this method, with the addition of different solvents. Indeed the benefit of this process is that it can easily produce cocrystals on a large scale since it preblends and then cocrystallizes. Furthermore, it could re-slurry in the same equipment, which is a boon for the pharma industries. With the ever-growing demand for cocrystals in the market, the demand for the proper equipment and the knowledge of the desired method, both are required. The above study aimed at highlighting the different methods of getting a

suitable cocrystal, which could further be characterized using various techniques. [56]

APPLICATION OF COCRYSTAL [58, 59]

Crystal formation results in a new crystal structure, which is entirely independent from any of the starting materials. This new crystal structure imparts a new set of physical properties, also independent of and indifferent to the physical properties of any of the starting materials. Currently, the crystal structure and resulting physical properties of a cocrystal cannot be predicted from any property of the starting materials. As a result of potential physical property improvements, cocrystal applications are many and continue to grow.

Solubility

By far the most prolific utility of cocrystals to date has been to improve the solubility of the starting material, particularly when that starting material is an active pharmaceutical ingredient. Low aqueous solubility is a barrier to satisfactory drug delivery and, as such, often prevents a medicine from being fit for its purpose. Inherently, a cocrystal will have a different solubility than that of either of the starting materials due to the altered underlying crystal structure. The solubility alteration can be in either direction. Enhanced solubility is desirable, as it will improve the bioavailability of the drug, but excessive enhancement can be problematic as it can lead to undesirable precipitation of the starting material due to the generation of a supersaturated solution.

There are many other accounts of improved solubility upon cocrystal formation available in the literature, but it is worth recalling the true nature of solubility as we consider the cocrystal solubility impact. Solubility is a thermodynamic measure of the amount of a solute that can be contained in a given volume of solvent at fixed conditions (temperature and pressure). The presence of impurities in the solvent or solute will affect solubility measurements. In the case of cocrystals, the coformer can be considered as an impurity and therefore be expected to alter the solubility of the starting material. This is often not accounted for in reported solubility measurements where cocrystal solubility is compared to the starting material solubility in the pure solvent. To compare like with like, it is more accurate to compare the solubility of the cocrystal with the solubility recorded for the equivalent physical mixture, or
at least in the presence of some known concentration of the coformer.

Bioavailability

Crystal's bear the potential to enhance the delivery and clinical performance of drug products by modulating drug solubility, pharmacokinetics, and bioavailability. Particularly, using crystals to improve oral drug absorption of BCS class II and IV drugs has been a strongfocus of several case studies published in the literature. Interestingly, polymers and other excipients can provide a huge contribution to improving

the bioavailability of cocrystals by acting as crystallization inhibitors and prolonging the supersaturating concentration of cocrystals during dissolution. This approach is particularly important in situations where the cocrystal transforms rapidly to a low-solubility form of the drug and is unable to maintain desired solubility levels necessary to ensure optimal absorption.

Controlled Release

Cocrystallization provides an opportunistic approach to modulate the physicochemical properties of pharmaceutical drugs, which include solubility and dissolution rate. Particularly, depending on the conformer that cocrystallizes with the API, the dissolution rate of the API in water or a buffer solution can be increased or decreased over time. Cocrystals also bear the potential to reduce the dissolution rate of the original APIs.

Multidrug Cocrystals

Combining multiple active pharmaceutical ingredients (APIs) into one unit dose has become a popular trend in the drug formulation industry. The need to target multiple receptors for effective treatment of complex disorders such as HIV/AIDS, cancer, and diabetes in addition to the increasing demand for facilitating the reduction of drug manufacturing costs are the two main reasons for this growing trend. Salts, mesoporous complexes, coamorphous systems, and cocrystals are systems which have been used for combining multiple APIs in a single delivery system. Multidrug cocrystals (MDCs) are advantageous compared to coamorphous systems in terms of their enhanced stability and in terms of their reduced payload compared to the mesoporous and cyclodextrin complexes.

Chemical stability

Chemical degradation of drug substances tends to occur during the manufacturing and storage stages, which challenges the development of a stable pharmaceutical formulation. It is critical to develop an effective strategy to eliminate or minimize drug degradants. Recently, pharmaceutical cocrystals have emerged as a prospective approach to overcome the chemical instability of APIs in the solid state shows the list of cocrystals with enhanced photostability. Hence, this section is focused on discussing the mechanisms by which cocrystallization solves the problem of chemical degradation through changing the crystal packing of APIs. The factors giving rise to the enhancement of solid-state chemical stability by pharmaceutical cocrystals were summarized . In particular, structureeproperty relationships were established to further provide theoretical guidance for addressing the chemical stability issues of drug candidates.

Sustained release

The sustained release dosage form exhibits considerable advantages in reduced dosing frequency, improved patient compliance, and mitigated side effects due to the steady-state blood level with less plasma fluctuations. Various formulation strategies have been used to achieve sustained release profiles, such as polymeric matrices, membrane-controlled and osmotic pump drug delivery systems. In the recent years, cocrystallization has been

demonstrated as an alternative approach to sustain the drug release.

Therapeutic effect

The therapeutic effect of a drug substance is often influenced by its physicochemical properties. The limitation of low solubility or permeability of BSC II and BCS IV class drugs would immensely restrict the therapeutic effect of the medicines. The cocrystal strategy has been considered an effective technique to improve bioavailability and thus enhance the therapeutic effect .

Multidrug Cocrystals.

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Concluding remarks and future perspectives

In the past decade, cocrystal engineering has become a promising approach to improve the performance of drug substances by modifying their undesired physicochemical properties. Large numbers of pharmaceutical cocrystals have been reported, and some of them have been approved by the FDA or in the clinical trials . Nevertheless there are still some considerable challenges for developing cocrystals into commercial drug products. In designing a pharmaceutical cocrystal, it is critical to select a suitable coformer. However, the selection of coforms has still largely relied on trial and error, which is time consuming and labor-intensive. Recently, a variety of computer-assisted approaches have emerging as attractive tools to accelerate the screening process of cocrystals214e218. For example, the artificial neural network models are developed to predict cocrystal formation by analyzing a network of coformers

extracted from the Cambridge Structural Database (CSD)218. An enhanced understanding of the structure-basis physicochemical properties is critical for the rational design of cocrystals with desired functions and performances. In addition, the compatibility between cocrystals and other excipients, pharmacokinetic profiles, therapeutic efficacy and toxicity issues should be carefully taken into consideration in developing the formulation of cocrystal.

CONCLUSIONS

Cocrystallization offers one of the most promising approaches to improve physicochemical properties of APIs. A wide range of options exist to prepare cocrystals ranging from routine lab scale synthesis methods to potentially large scale continuous production methods. This review offers standard descriptions and examples of established and emerging cocrystal preparation routes. Moreover, detailed insight is given on the proposed mechanisms of cocrystallization in different techniques. As cocrystals continue to gain interest and prove their value, the range of demonstrated cocrystal application areas continues to expand. All demonstrated application areas for pharmaceutical cocrystals are included in this review with the aim of highlighting the wide ranging potential of these materials. It is anticipated that cocrystals will become more and more routine in pharmaceutical development as their benefits continue to be demonstrated and routine routes of manufacturing are proven.

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