The Co-Crystal Approach: An Avenue for Improving Drug Bioavailability

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ABSTRACT

The main concern of formulators while designing and developing a new pharmaceutical formulation is the poor water solubility and permeability in the present scenario. These problems are most common in group III and IV medications, and they affect the bioavailability of dose forms. There are many methods for dealing with these problems, but all of them have serious flaws, such as the fact that they all depend on the physical and chemical makeup of the medication. To deal with such issues, cocrystal is a simple and effective way to increase the solubility and permeability of a medicinal component without changing the pharmacological effects of the drug. The solubility, dissolution profile, pharmacokinetics, and stability of a drug can be improved by cocrystallization with a conformer. This review article provides an overview of cocrystals such as properties, preparation method, evaluation, advantages, and uses. This review will also surely give a brief introduction to cocrystals.

Key Words: *Pharmaceutical cocrystals, Coformers, Cocrystallization, Solubility*

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INTRODUCTION

Plenty of drug products have come to the consumer market in the past few years. Among them, poorly soluble drug substances have become more widespread in the pharmaceutical business [1]. It is seen that nearly 40% of immediate-release products are generally insoluble [2].

The therapeutic efficiency of pharmaceutical dosage forms is directly related to their physical properties, including their particle size, flowability, hygroscopicity, solubility, and compatibility, and impacts the manufacturing cost of the solid oral dosage form [3]. Researchers in the fields of pharmacy, chemistry, and drug regulatory agencies are interested in cocrystals, a concept derived from supermolecular chemistry because it can alter the physicochemical properties of active pharmaceutical ingredients without altering their pharmacological behavior. Supermolecular chemistry is the organization of things that comes from the association of two or more chemical species held together by non-covalent interactions, according to Lehn JM's definition of it as "chemistry beyond the molecule" [4]. With the aid of the Lock & Key theory, Emil Fischer explained selective binding via molecular interaction [5]. The chemical systems being studied fall into two categories: molecular recognition in solution, supramolecular chemistry, ordered self-assembly in the solid state, or crystal engineering [6]. Pepinsky R. introduced the term crystal engineering to the globe [7]. The physicochemical properties of the APIs, such as consistency, crystalline size, powder rheological properties, taste, hygroscopicity, solubility, and compatibility, determine the therapeutic effectiveness of any dosage form and affect the dosage form's manufacturing cost [3]. In dosage forms that are taken orally, gastrointestinal absorption is determined by the drug's solubility and rate of dissolution. Because it has been shown that nuclear wrapping in the unit cell and crystal lattice directly influences the properties of a specific crystallite, altering the patterns of crystal wrapping can be used to alter the physicochemical characteristics of solid medication forms. In the instance of oral formulation delivery, the drug's molecule's solubility and rate of

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dissolution influence gastrointestinal absorption. However, almost 90% of drug molecules today fall into the BCS classification of classes II and IV, which have issues with poor aqueous solubility and low bioavailability, restricting drug absorption in the gastrointestinal tract and, as a result, restricting the drug's clinical application. It is undeniable that the physicochemical characteristics of medicinal solids continue to affect how well a therapeutic product works. Crystalline materials' quality is influenced directly by atomic packing in their crystal lattice and unit cells. Therefore, altering the crystal packing structure can change the physical and chemical properties of solid dosage forms. Many solid-state methods have already been used in recent years to improve the properties of APIs like salts, polymorphs, hydrates, solvates, and cocrystals **(Figure 1)**. However, all of these approaches have some limitations as well. Salt production, for example, is limited to molecules with the correct ionizable groups, and hydrates/solvates are frequently unstable due to the loss of water/solvent molecules over time. As opposed to this, any API (acidic, basic, or nonionized) can form a cocrystal when it comes to the right conformer. Altering the crystal structure of APIs can help improve their physicochemical properties without affecting the API's pharmacological qualities, pharmaceutical cocrystal has attracted substantial attention from academics and several pharma companies over the last two decades. Pharmaceutical companies have endorsed several cocrystals due to the cocrystal's continuation, including Steglatro®, Entresto®, and numerous others that are currently undergoing clinical trials.

In pharmaceutical cocrystals, discrete neutral molecules are bonded by a noncovalent interaction between them (e.g., hydrogen bonding, van der Waals, and stacking interactions), one of which should be the active pharmaceutical and the other a pharmaceutically recognized compound [8]. In the early 2000s, the pharmaceutical cocrystal was discovered to be a promising approach for improving the pharmaceutical characteristics of active pharmaceutical molecules, leading to a flurry of cocrystal-related papers in 2003-04. These groundbreaking efforts laid the groundwork for cocrystal engineering and supermolecular synthons in pharma-based cocrystals, inspiring researchers to continue developing cocrystals and improving medication performance. The main driving force behind the creation of pharmaceutical cocrystals has been identified as a variety of potent supramolecular synthons that are crucial to the design of cocrystals [9]. Alcohol, amides, carboxylic acids, and other functional groups are particularly amenable to the creation of supermolecular cocrystal syntheses [10, 11]. Supermolecular homosynthons and supermolecular heterosynthons are the two categories of supermolecular synthons that are accessible. Self-reinforcing functional groups like carboxylic acid dimers or acid dimers make up supermolecular homosynthons. Additionally, supermolecular heterosynthons are made up of various functional units that work well together (e.g., the hydrogen bonding of carboxylic acid pyridine and alcohol-aromatic nitrogen). Pharmaceutical cocrystal has gained prominence among regulators as a result of its continuous development and increasing applicability. The US Food and Drug Administration (FDA) classified pharmaceutical cocrystals as drug product intermediaries in 2011 and defined them as "dissociable API excipient molecular complexes when both API and inactive ingredients are present in the same crystal lattice." However, this definition has been deemed the most simple by academic and industrial field researchers to distinguish the cocrystal. According to a new definition given by the FDA in 2016, "a cocrystal is a crystalline product manufactured of two or more distinct molecules inside the same lattice structure by non-ionic and non-covalent linkages" [12]. Pharmaceutical cocrystals are defined by "the FDA" as "a crystalline material composed of at least two separate molecules, one of which is the API, together in the same crystal lattice in a prescribed stoichiometric ratio." Coformers are defined as "a typically non-volatile component that interacts non-ionically with the API in the crystal lattice and is not a solvent (including water)" [13]. Cocrystals are described by the European Medical Agency as "homogenous (single-phase) crystalline formations constituted of two or more elements in a specified stoichiometric ratio where the architecture in the crystal lattice is not reliant on ionic bonding (as with salts)" [14]. The European Medicines Agency (EMA) defined cocrystals as an acceptable substitute for salts of the same API, which is in contrast to the FDA definition **(Table 1)** [14]. The cocrystal, in contrast, is considered identical to the API unless it demonstrates particular pharmacokinetic traits [15]. In this article, we will be dealing with a general review of cocrystals, including preparation, uses, and recent advancements in the pharmaceutical cocrystal.

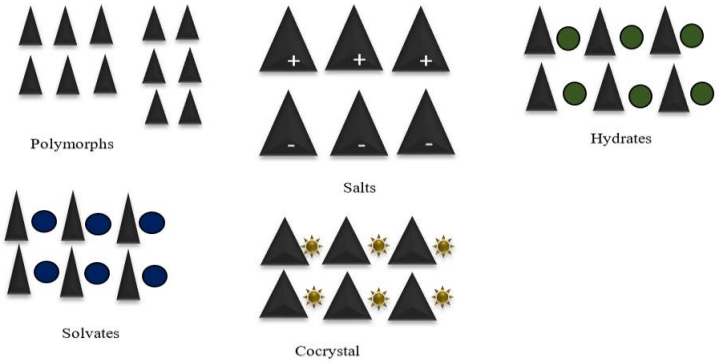

Figure 1. Polymorphs, salts, hydrates, solvates, cocrystal

Table 1. The regulatory status of pharmaceutical cocrystals in the US and Europe

Cocrystal Parameter	USFDA [16]	EMA [17]
Definition	Solids are crystalline materials composed of two or more molecules in the same crystal lattice.	Homogenous (single-phase) crystalline structures are made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts).
Regulatory status	Drug product intermediate (DPI), is not regarded as a new API	New active substance status is dependent upon the demonstration of safety and efficacy.
Coformers	Neutral guest compound (excipient)	Nonactive components or reagents (excipients)
Regulatory considerations	Similar to the polymorph of the same API.	Similar to the salt of the same API
Chemical Interactions	Nonionic	Nonionic
US-Drug master files (DMF)/EMA-Active substance master file (ASMF)	Nonfeasible being DPI.	Can be filed.
Applicable Good manufacturing practice (GMP) regulation/guide	cGMP for drug product	Part II of EU GMP Guide (active substances) and ICH Q7 and in rare cases Part I of EU GMP Guide (finished drug product)

RESULTS AND DISCUSSION

Preparation of cocrystals

Nowadays, a range of technologies can be used to create cocrystals. Solid-state grinding, solution reaction crystallization, liquid evaporation, slurry conversion, and hot melt extrusion are a few of the procedures used to create crystals, but both solution-based and solid-based techniques are frequently used **(Figure 2)**. The solvent used can affect the cocrystallization results by changing the intermolecular pull between the API and the coformer. In the solvent-based methods, a significant quantity of solvent is needed to dissolve the cocrystal's constituents. In addition, solid-state technologies can avoid using solvents in their applications.

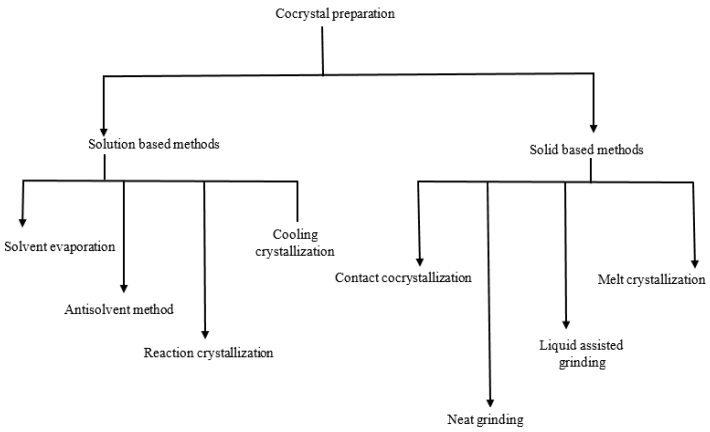

Figure 2. Different types of cocrystal preparation

Solution-based methods

The API, conformer, and solvent are the three components that make up this method's solution. The ideal phase occurs in laboratory settings when the crystal is supersaturated and the reactants are unsaturated or under-saturated. One can alter the degree of supersaturation required for co-crystallization by using API and conformers [18]. To direct cocrystal formation and depict the thermodynamically stable zone while preventing the crystallization of purified reactants, a phase diagram must be created. The location of a thermodynamically stable coformer is determined by the concentration of the reactants.

Solvent evaporation method

This is the most popular technique for creating cocrystals, and it is used to create crystals appropriate for X-ray diffraction-based structural analysis. The necessary chemicals for this technique should be dissolved in the right solvent. The less soluble compound precipitates when two improperly soluble compounds cocrystallize, giving rise to a solid combination of the cocrystal and its constituent parts. The choice of solvent is an important parameter in this technique, and it will affect the cocrystallization process and finally, it affects the bioavailability.

Antisolvent method

If we have to consider the quality, particle size, and properties of the cocrystal then the Antisolvent technique **(Figure 3)** is considered to be the best, where the crystallization is performed either by semi-batch or continuous production process [19-23]. As an example, the indomethacin-saccharin cocrystal was prepared by Chun *et al*. [23] by using the antisolvent technique. This entire process is shown schematically below.

A solution of 0.034 mol/L indomethacin and 0.05 mol/L saccharin was mixed in 150 ml of methanol.

↓

75 ml of water (antisolvent) was also then added to the solution vessel, using a peristaltic pump with 300 rpm speed for one hour at 25 °C.

↓

Rod-like or columnar cocrystals with better dissolution rates were produced.

The antisolvent was included in this ongoing procedure to lessen the solubilization of the cocrystal and obtain supersaturation. The precipitation of cocrystals happens as a consequence. Therefore, selecting the ideal miscible solvent mixture is difficult because the cocrystal will be poorly soluble in an inadequate solvent. While the solvent composition may affect the solubility of the cocrystal and individual components, the ratio of the cosolvent in the cocrystal formulation can significantly affect the product yield of the cocrystal.

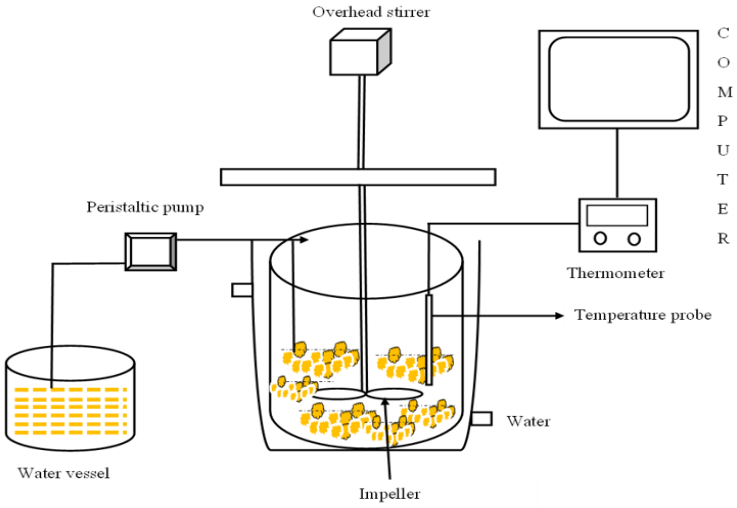

Figure 3. Apparatus for the anti-solvent cocrystallization process

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Cooling crystallization

When a large, pure crystal is required, cooling crystallization is used. These characteristics are determined by the distribution size, purity, shape, and crystal polymorphism, along with other process variables like heat and mass transformation [24]. Due to the numerous solid-liquid equilibria, these variables must be precisely controlled during the cocrystal preparation procedure. The operating region and the stable portion at the starting and finishing temperatures are determined by the cocrystal's stoichiometry in this procedure [25]. Much research has been conducted, and the result is that this is the most successful technique for preparing cocrystals [25-28].

The oscillatory crystallizer was used to create a 99% pure Lipoic acid-nicotinamide cocrystal with reliable particle size. The baffled crystallizer will operate at 330 g/h, and to encourage the nucleation of the cocrystal, a 10% w/w seeding suspension solution was introduced into the crystallizer for 10 seconds at 10 °C [29].

Reaction cocrystallization

When the cocrystal's constituent parts have different solubilities, reaction cocrystallization is a procedure that is carried out. To create a concentrated solution of cocrystal, the reactants having non-stoichiometric conditions are combined in this technique. The formation and growth of the crystal are controlled by the ability of reactants to reduce the solubility of cocrystals [30]. Meloxicam-salicylic acid crystals [31], carbamazepine-saccharin crystals [32], and indomethacin-saccharin crystals [33] have all been produced with the aid of the reaction crystallization method.

Slurry conversion

The slurry conversion technique is a solution-based procedure that calls for the solvent to also contain additional cocrystal components. During the slurry preparation, each element progressively dissipates to produce a mixture that promotes the growth and development of cocrystals. Cocrystals are formed when the concentrations of the reactants gradually decrease and make under-saturation formation, which continues the removal of components after the cocrystals are formed. The ternary phase diagram helps to regulate the actual operating range of component concentration and temperature, which gives the cocrystal the navigation for the generation of supersaturation. Scientists Huang and coworkers found that the rate of theophylline-benzoic acid cocrystal formation was strongly influenced by the starting component concentration and operating temperature [34]. Because a better preliminary awareness should cause a stronger collision possibility of the components, the beginning awareness of the reactants and temperature confirmed an excellent affiliation with the cocrystal formation rate. A higher temperature, on the other hand, allows the reactants to reach the active site more quickly.

Solid-based methods

Nowadays if the motto is to prepare a formulation then the researchers must have to consider the environmental factor. The 'solid-based' technologies for cocrystal preparation are the most environmentally sustainable because there is little or no demand for the solvent. The cocrystals are voluntarily formed by direct contact or grinding with higher energy inputs. They could be an appropriate alternative to the solution-based approaches that might cause environmental risk during their formulation process due to the requirement of a large amount of solvent. Solid-based approaches have been used to construct a diverse range of cocrystals [35-38].

Contact cocrystallization

It is found that after ‘soft mixing’ of the materials interactions are found between the API and the conformer [39-41]. The creation of the eutectic phase, moisture sorption, amorphization, and long-range anisotropic molecular migration are some of the potential mechanisms that could account for spontaneous crystallization [42]. Higher humidity, higher temperature, and smaller raw material particle size are the other factors that can affect cocrystal formation [43]. It has been observed that by mixing the pre-milled raw materials while maintaining room temperature and 30% relative humidity, the caffeine-urea cocrystals were formed in three days. This process is described by scientist Macfhionnghaile and co-workers [44]. The authors disclosed that the contact between the inter-particle surfaces of the solids is the x-factor for forming the caffeine-urea cocrystal.

According to a theory put forth by Ervasti and colleagues, there was no mechanical grinding involved in the phase transition of theophylline-nicotinamide from its physical form to its crystal form. The cocrystallization of isoniazid and benzoic acid is another instance of spontaneous crystallization, and this process demonstrates the reorganization of cocrystals on the surface of the isoniazid. Moisture accelerated this process because it encouraged the contact of isoniazid with benzoic acid and vapor. Additionally, the cocrystal physical mixture's pre-milling shortens the time it takes for cocrystals to develop, increasing the rate at which they do so.

The kinetics of spontaneous cocrystal formation were disclosed by Nartwoski, who proposed that this process could be managed by adjusting the amount of moisture added [45]. The transformation rate of the caffeine-malonic acid cocrystals was sped up by the malonic acid surface's deliquescence [45]. The solvent vapors can serve as catalysts to quicken the creation of the caffeine-malonic

acid cocrystal, according to Ji *et al*. [46]. Recent studies claim that cocrystal formation can be aided by subjecting cocrystal components to the proper vapors [47, 48]. The deliquescence of the compounds was found to be the controlling factor in the optical microscopic investigation of moisture-loaded carbamazepine-nicotinamide cocrystal formation.

Solid-state grinding

Additionally, there are two subtypes of solid-state grinding: liquid-assisted grinding and plain grinding. The process of "neat grinding," requires the energy necessary for mechanical milling or manual grinding (using a mortar and pestle) to produce cocrystals (by using a ball mill and a vibrating mill). This approach does not necessitate the use of a solvent. However, in liquid-aided grinding, just a minimal quantity of solvent is required for cocrystal formation.

Neat grinding

According to earlier research, neat grinding causes molecular diffusion and results in the creation of a eutectic or momentary amorphous intermediate, which leads to the formation of cocrystals [49, 50]. The grinding used in this process produces a movable solid surface, which leads to further vaporization or energy transfer. Higher solid-state component vapor pressure (10^{-1} to 10^{-4} mmHg) is needed during the neat grinding process for the cocrystal to develop on the crystal's surface as a result of gas phase diffusion. Additionally, the migration occurs to remove the cocrystals from the reactant surface to form a new surface for additional crystallization, and the grinding can provide the energy for surface diffusion [51].

Picric acid and aromatic hydrocarbon crystallization occurred using the molecular diffusion technique with the aid of grinding. Rastogi and colleagues created this [51]. Several items are seen during the eutectic-induced cocrystallization process. Those are:

- On a new solid surface, an uncontrolled and metastable eutectic phase will inevitably form; this is done by agitation.
- Grinding has an impact on the cocrystal's nucleation event [49]. When diphenylamine and benzophenone cocrystals were created, a liquid eutectic phase was spotted in the contact of the solids under a microscope.

Chadwick and coworkers discovered this. As a result, the nucleation of a cocrystal can cause the liquid phase to solidify and form a cocrystal. The strong intermolecular contact between the API and coformers is key for cocrystal formation in amorphous-mediated cocrystallization [51].

A stepwise procedure has been described for the situation of neat grinding, using which a kinetic and thermodynamic cocrystal was created [51]. This characteristic is typically present if the reactant compounds contain halogen or hydrogen bonding sites. This process is most likely caused by the hierarchy of powerful acid and weak hydrogen bonding forces that exist during cocrystal formation.

Liquid-assisted grinding

If our target is to get products having high yield value and high crystallinity then we should go for liquid assisted grinding method. In comparison to neat grinding, this methodology produces a better yield and crystallinity, and it is excellent for quick cocrystal screening. The solubility of the essential ingredients cannot be able to hamper this process. Molecular transport is accelerated by the addition of a small quantity of liquid, which catalyzes accelerating cocrystal formation. The amount and type of liquid used during the formation of the cocrystal are crucial because they affect the creation of various solid goods and the quality of the cocrystal.

Melting crystallization

An alternative method for creating pharmaceutical cocrystals is melting crystallization [19]. Despite the absence of liquids, the thermal solubility needs to be carefully considered beforehand. Melatonin-pimelic acid cocrystals were created by scientists Yan *et al*. [52] using a melting crystallization method. The cocrystals crystallized when the temperature was between 50 and 70 °C. The carbamazepine-nicotinamide cocrystal was produced through the melting crystallization process. In this procedure, the drug and coformer combination was heated to 160 °C, and the melt was then cooled to an ambient temperature to promote crystal growth [53]. There are separate heating rates involved for two different heating paths, which are as follows:

- The carbamazepine-nicotinamide cocrystal nucleates at a gradual heating rate of 3 °C/min, and it then changes into a stable form.
- Individual components crystallized at a rapid rate of 10 °C/min, were then melted, and the stable shape of the cocrystal emerged from the melt [53].

Advantages of cocrystals

Amorphous drugs, solid dispersion, salt formation, micronization, and encapsulation are some of the methods currently available to alter the physicochemical properties of the drug. All of the cocrystals among them have benefits due to their stable crystalline shape and lack of other excipients. The characteristics of APIs and coformers, the type of molecular interaction between them, and the synthetic processes employed are the main factors that decide the physicochemical properties of the medication. Because cocrystals can alter APIs' physicochemical characteristics without altering their pharmacological action, coformers are advantageous for APIs. The ability to

make cocrystals from non-ionizable APIs and for medications with sensitive functional groups that cannot endure harsh acidic or basic conditions is another benefit of cocrystals over the most common salts. In addition to these, cocrystals have several other benefits, such as the ability to speed up the production of an API, leading to a more economical composition. Pharmaceutical cocrystals may enhance several physicochemical characteristics, including melting point, tabletability, solubility, stability, bioavailability, and permeability. These characteristics are listed below with some examples.

Melting point

The physical properties like the melting point are used to study the purity of the products. The high melting point of the compound symbolizes the API is thermodynamically stable. Cocrystals with lower melting points can also be beneficial when considering thermolabile drugs.

Manufacturers always prefer solid dosage forms because they are easier to filter, identify, transport, and store than liquid dosage forms. Solid medication forms are always preferable to liquid dosage forms for patients since they are easier to transport and give than liquid forms. However, there are significant limits, such as the fact that some medications are only available in liquid form due to their low melting points. In this situation, cocrystals may be able to solve the problem by introducing a suitable conformer into the crystal lattice. For example, a general anesthetic is created and maintained using medications like propofol. Because of its lower freezing point of 18 °C, which causes instability, uncomfortable injections, and hyperlipidemia, it is made as an oil-in-water emulsion. To address this issue, McKellar *et al*. [54] presented a cocrystal method using isonicotinamide as the coformer to produce a distinct solid form of propofol. The cocrystal of propofol and isonicotinamide has a 50 °C greater melting point than the original substance, making it a stable solid at room temperature. Propofol-bipyridine and propofol-phenazine cocrystals can transform liquid propofol into a crystalline phase, according to different research published by Bacchi *et al*. [55].

Tabletibility

Cocrystallization of the API is usually beneficial because it has a considerable impact on crystal packing, tablet ability, and compaction, all of which are crucial criteria to consider during the preformulation study. It has been demonstrated that the compaction behavior of paracetamol cocrystals with trimethylglycine and oxalic acid is better than that of the drug in its pure form. Resveratrol's tabletability was enhanced by the creation of cocrystals using 4-aminobenzamide and isoniazid during crystallization. Cocrystals had greater tablet ability than either pure drugs or coformers. Without affecting the API's pharmacological action, cocrystallization could be used to alter the mechanical properties of the API.

Solubility

Any dosage shape can be designed and formulated using the concept of solubility. It is a crucial variable for formulating weakly soluble drug estimates. To increase the bioavailability of weakly soluble drugs, a variety of techniques are available, including salt formation, solid dispersion, particle size reduction, and many others [56]. Cocrystal is the one of them that has the greatest advantages over the others. By synthesizing salts and cocrystals, respectively, it was found that the antifungal medication ketoconazole is about 53 and 100 times more soluble than regular ketoconazole. Therefore, it is evident that the cocrystal's solubility is always superior to that of the salt version [57]. Another illustration is the cancer drug 6-mercaptopurine cocrystals with nicotinamide, which have been found to have two times greater solubility than the pure drug [58]. A theoretical method based on Keu (the ratio of solution concentrations of cocrystal components at the eutectic point) was used to determine the solubility of the cocrystals in a pure solvent. This method is useful for cocrystal selection and formulation without the material and time requirements of conventional methods [59]. Using a collection of more than 40 cocrystal and solvent combinations, K_{eu} can be used to characterize the solubility ratio of cocrystals and solution chemistry [60]. According to different research, for cocrystals with acidic, basic, amphoteric, and zwitterionic components, the solubility concerning product solubility, cocrystal component ionization constant, and solution pH were determined [61, 62].

Stability

It is critical to conduct a stability study when developing a new dosage form. Several tests are carried out during the development cycle of pharmaceutical cocrystals to ensure the formulation's durability. Investigations are conducted into relative humidity stress, chemical stability, temperature stability, solution stability, and photostability. To ascertain the impact of water on the formulation, automated water sorption/desorption tests are run under relative humidity stress. The cocrystal under relative humidity stress has been the subject of extensive study by numerous scientists. In contrast to the normal form, cocrystals of glutaric acid and 2-[4-(4-chloro-2-fluorophoxy)phenyl]pyrimidine-4-carboxamide exhibited 0.08% moisture at a high 95% RH [63]. In the instance of the Indomethacin-saccharin cocrystals, relative humidity studies revealed low water sorption, and there is no dissociation or transformation under experimental circumstances [64]. Theophylline cocrystals with various conformers, such as oxalic acid, malonic acid, maleic acid,

and glutaric acid, showed relative humidity stability behavior at various RH values of 0, 43, 75, and 98% for various periods of 1 d, 3 d, 1 w, and 7 w. The outcome shows that, when compared to hydrates, cocrystals' durability and physical properties have improved [65]. In the case of chemical stability, any chemical changes or degradation must be analyzed for the formulation, especially for the accelerated stability condition. In the literature, just a few papers describe the chemical stability of cocrystals. Glutaric cocrystal with an API showed no signs of degradation and was chemically stable for two months at varied temperatures (40 °C/75% RH and 60 °C) [65]. It is based on accelerated stability circumstances that high-temperature stress is utilized to predict physical and chemical stability. Thermal stability was mentioned by a few researchers [66, 67]. When heated with 4,4-bipyridine, paracetamol cocrystals demonstrated superior stability on DSC than other coformers [66]. In stoichiometries varying from 0.3:1 to 0.9:1, the thermal stability of cocrystals containing tartaric acid, such as L-883555, a phosphodiesterase IV inhibitor, was examined. Cocrystals with stoichiometries of 0.5:1.0 are the most stable because acid content can block crystal channels and create different binding states [67]. Solution stability is an essential factor to take into account when considering the formation of cocrystals to ascertain solution stability. Studies on solution stability aid in the comprehension of cocrystal behavior in release media [9]. For instance, it was found after studying the behavior of carbamazepine cocrystals in water for 20–48 hours that the cocrystals with high water solubility changed into dihydrates, whereas the cocrystals with low water solubility remained unchanged in the solution [68]. When the materials were slurried in water at room temperature for two days, there was no discernible change in the physical shape of the caffeine/oxalic acid cocrystals, making them more stable than others at all RH values up to 98% for seven weeks [69]. To evaluate for stability, equal amounts of carbamazepine and saccharine cocrystals were dissolved in water for 24 hours. Only cocrystals were found in the solution, according to a powder X-ray diffraction (PXRD) analysis, with no other form discernible [26]. The photostability study can investigate the impact of light on photosensitive drugs. Many different medications are light-sensitive, and photostability studies are necessary for this kind of prescription. There were not many accounts of the cocrystals' chemical stability in the literature. In comparison to the pure drug and physical combinations, the photostability of nitrofurantoin cocrystals with various conformers was higher. The tests revealed that none of the cocrystals significantly degraded in the presence of light, but cocrystal is also a suitable method for preventing the degradation of pharmaceuticals that are photosensitive.

Bioavailability

The percentage of a drug that reaches systemic circulation in an unchanged state is known as bioavailability. Making a mixture is difficult for formulators because of low bioavailability. Pharmaceutical cocrystals with enhanced water solubility and oral bioavailability are mainly created and produced using crystal engineering. The pharmacokinetic study has shown that beagle dogs' pharmacokinetic studies of apixaban-oxalic acid cocrystals were improved by 2.7 times [70]. By creating a cocrystal formulation with nicotinamide, the oral bioavailability of baicalein was increased in rats. The cocrystals had 2.49 times higher maximal plasma concentration (Cmax) and 2.80 times greater area under the curve (AUC) than the pure drug [71].

Permeability

Permeability, like bioavailability, is an important characteristic. Because of their limited permeability, the formulation of BCS class III and class IV medicines is complicated. The permeability of the drug ingredients plays a significant role in drug absorption and distribution. For the unaltered form of a medication, the n-octanol/water partition coefficient is primarily determined using log P and C log P [72]. A pure drug's permeability is improved via cocrystallization. For example, 5-fluorouracil, a BCS class III medication, has a low permeability problem. The drug's difficulty is solved by employing a cocrystallization process with various conformers [73]. The permeability of hydrochlorothiazide and cocrystals with various coformers was studied using Franz diffusion cells.

Characterization studies of cocrystal

Several methods are available for the characterization of the cocrystal. In recent times, scientist Pindelska and coworkers have introduced a detailed review of the current advancement in the field of characterization and identification of cocrystals, salts, and polymorphs. The various characterization and identification tests are described below **(Figure 4)**.

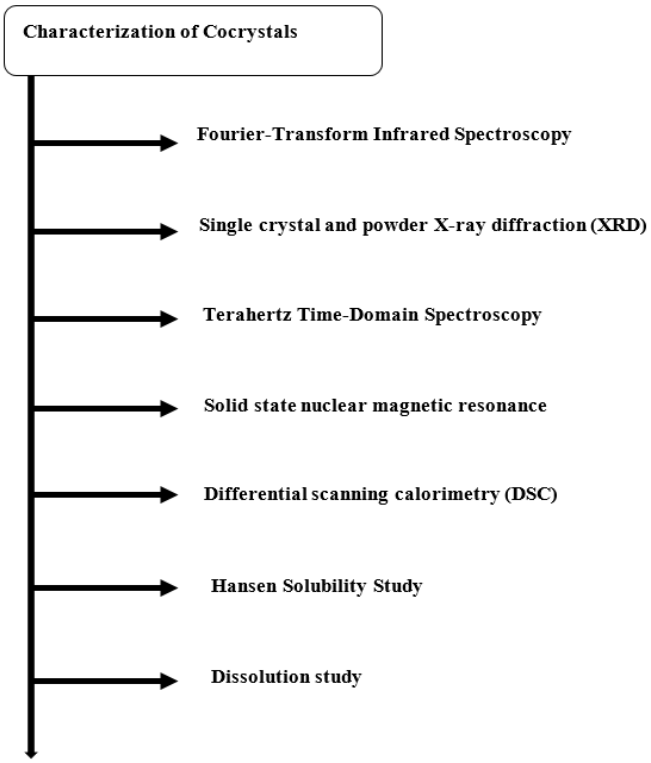

Figure 4. Characterization techniques of cocrystals

Spectroscopic analysis

Fourier-transform infrared spectroscopy

This method has several uses in the characterization of cocrystals, such as forecasting chemical conformation, figuring out intermolecular interactions, and figuring out how API and coformers interact with one another. This method uses a wavelength of 400–4000 cm^{-1}. This method uses a wavelength of 400–4000 cm^{-1}. This technique can identify a functional group and is fast, non-destructive, and sensitive to changes in molecular structure.

Single crystal and powder X-ray diffraction (XRD)

The XRD technique is a crucial instrument for characterizing cocrystals. The cocrystal's structural solution is determined using single-crystal XRD, while identification is accomplished using powder XRD. Sharp points produced by crystals are distinct from the crystal's constituent parts. Presently various software programs are available like DIFFRAC.TOPAS (Bruker AXS Karlsruhe, Germany). By using this, structural analysis can be performed. They are also used to determine the yield of cocrystallization.

Terahertz time-domain spectroscopy

This method is comparable to powder X-ray diffraction (PXRD) for the characterization and determination of cocrystals. This technique allows for the distinction of chirality, racemicity, and molecular structures. For instance, theophylline cocrystals with various conformers.

Solid-state nuclear magnetic resonance

Solid-state cocrystals are one of the many types of solid pharmaceutical products that are identified and characterized using NMR. The structure of salts and cocrystals can be identified by a local conformational shift and hydrogen bonding. This quantitative and qualitative method establishes the reaction mixture's molar ratio and the sort of hydrogen atom that exists in a specific molecule.

Thermal gravimetric method

This technique is useful for estimating sample weight when temperature is a factor for a specific period.

Differential scanning calorimetry (DSC)

The presence of an exothermic crest followed by an endothermic crest in the DSC bands is useful for identifying cocrystal formation. The compound's crests (peaks) serve as evidence that the cocrystal formed there. Additionally, it is used to establish a compound's or molecule's melting point, polymorphism, glass temperature, heat of fusion, and exothermic or endothermic behavior. The thermogravimetric analysis provides the precise drying temperature and a breakdown of the component's different reaction steps. This technique is additionally used to identify the hydrated or solvated types of crystals, identify the volatile component, and examine cocrystal decomposition or sublimation. With the help of this technique, we can forecast the cocrystal purity, temperature stability, and compatibility.

Hansen solubility study

To characterize the cocrystal Hansen solubility study is an important tool. A parameter called the Hansen solubility parameter can be used to predict whether a drug and coformer are miscible during crystallization or with excipients/carriers. This study has an impact on the pre-formulation and formulation of a tablet, as well as predicting the compatibility of pharmaceutical materials. By calculating a compound's cohesion energy, one can predict physicochemical properties, such as melting point and solubility. Molecularly, crystals are miscible because of weak hydrogen bonds that hold them together.

The research on solubility makes use of water, buffer solutions with various pH levels, stimulated intestinal fluid, and gastric fluid. It is a crucial element of drug research when developing new medications.

Dissolution study

To determine the API's dissolving efficacy in a specific formulation, *in vitro* dissolution research is conducted. Dissolution study is the process where the rate and extent of solution formation from a dosage form are measured. It is important to perform the dissolution study to check the bioavailability and effectiveness. This research is carried out using a USP dissolution apparatus and the appropriate dissolution medium for the dosage form. Samples are collected and examined using an HPLC or a UV spectrophotometer at preset intervals. The Higuchi and Connors technique is used to calculate the solubility of cocrystals. The approved compendium is used to assess the solubility of cocrystals, pure API, and physically mixed API and coformers in water and other media.

Applications of cocrystal

Cocrystal has the greatest advantage in the field of formulating class III and class IV drugs because these groups of drugs have low solubility and permeability. In these cases, the cocrystals come into the picture. It can increase the physicochemical qualities of a medicine without changing its chemical structure or pharmacological effect. Salts sometimes have greater physicochemical qualities than cocrystals, such as increased inherent solubility in water. When the drug's dissolving rate is the most significant factor, the cocrystal would be preferable to the salts and other forms in this instance. Increasing the solubility and bioavailability of poorly soluble, neutral, or weakly ionized compounds through cocrystallization is a helpful technique. Aside from these advantages, cocrystallization raises the melting point, tabletability, solubility, stability, bioavailability, and permeability of a dose form.

Future scope and challenges of cocrystal

Cocrystal is a useful and promising method for improving the physicochemical properties of medicinal ingredients without affecting the API's therapeutic qualities. The selection of the conformer for the specific pharmacological compounds, however, is the fundamental issue of this strategy. A variety of procedures are available for selecting and screening suitable conformers for APIs. Despite the large number of options available, each one has its own set of constraints. However, GRAS classification does not ensure their use as cocrystal-forming agents. Chemicals listed as GRAS by the USFDA in the EAFUS database should mainly be used as co-formers. For the production of cocrystals, stability in the presence of excipients is a crucial issue that has yet to be researched. Another issue that prevents the industry from using cocrystals economically is scaling up the production of high-purity cocrystals. In 2011, the US Food and Drug Administration (FDA) recommended against cocrystal patenting for the pharmaceutical industry. The FDA states that cocrystals are "API excipients," a molecular complex, an intermediate in a medicine product, and not a novel API. Furthermore, the EMA mandates that cocrystals be recorded in the same manner as salt. Despite the divergent regulatory philosophies of the USFDA and the EMA, this illustrates the increasing interest in pharmaceutical crystals as potentially marketable pharmaceuticals.

CONCLUSION

One of the best ways to enhance the stability, solubility, micrometric properties, dissolution bioavailability, and pharmacokinetic characteristics of active pharmaceutical ingredients is through the cocrystallization procedure. In addition to the advantages, there are some disadvantages, such as the fact that it cannot be applied to all drugs and that there is no established procedure for choosing conformers. It is undeniable, though, that this method has a lot of promise for producing dosage forms. This review ends with a thorough explanation and illustrations of cocrystal preparation techniques, their physicochemical characteristics, and a variety of benefits and uses. With the advancement of various strategies and proper regulatory guidance, the application of cocrystals in the pharmacy sector will undoubtedly be improved. Though cocrystal has plenty of limitations in the future with the development of strategies, it will acquire a significant place in drug delivery.

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