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REVIEW ARTICLE

Selection of Cocrystal and Coformer in Cocrystal Formulation: A Comprehensive Review

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ABSTRACT

Cocrystals: A Promising Class of Crystal Forms for Pharmaceutical Applications "Cocrystals, as defined by the FDA, are crystalline substances that have more than one molecule contained in a single crystal lattice.". Pharmaceutical cocrystals, a subset of cocrystals, have rapidly gained prominence in pharmaceutical science and engineering due to their capacity to alter important physicochemical characteristics including equilibrium, lubricity, and accessibility to patients. Consequently, they hold promise for use as active pharmaceutical ingredients in both immediate and extended-release formulations Because there is a wide variety of API crystal shapes., classifying solid forms into exclusive categories (polymorphs, salts, cocrystals) proves challenging. Nevertheless, this review attempts to categorize cocrystals. While extensive literature on cocrystals exists, a comprehensive review of cocrystal preparation methods remains lacking. This review aims to address this gap by covering various methods described in the literature, including: Grinding methods (neat and solvent drop), Co-crystallization from solution, Sonocrystallization, Hot melt extrusion Additionally, this review briefly discusses characterization techniques commonly employed for cocrystals and highlights the advantages of employing the cocrystal approach. A summary of reported work on cocrystals is also provided.

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INTRODUCTION

Innovative approaches in medicine have been made possible by pharmaceutical cocrystal technology, which has made it possible to create new entities with improved pharmacokinetic and pharmacodynamic properties, as well as improved dissolution, soluble content, and micrometric properties. A cocrystal is defined as two or more molecules that are harmoniously integrated inside the same crystal lattice. A cocrystal is a crystalline, stable solid mass. The field of pharmacology defines pharmaceutical cocrystals as solid crystals made up of two or more different molecules that are joined together in a fixed stoichiometric ratio. They are not simple salts or solvates; rather, cocrystals are single-phase crystalline solids composed of two or more different molecular and/or ionic compounds, typically combined in a stoichiometric ratio. In other words, cocrystals are crystalline solids made from a specific stoichiometric mixture of two or more compounds. This is the accepted definition for pharmaceutical cocrystals in pharmacology"[1]. Cocrystallization refers to modification of drug's physical characteristics at the molecular level, allowing for the customization of its physiocochemical properties. This eliminates the need for additional additives to enhance the desired properties of the substance. By employing various methods, cocrystallization offers a means to improve the physiocochemical properties of drug, such as soluble content, bioavailability, and stability [2]. Since most medications are administered as solids, it is imperative that drugs' physical qualities be improved. The digestion, administration, and efficacy of the medication are all directly impacted by the physical characteristics of these solids. For example, a solid's solubility in a solution is influenced by its crystal structure. For medication goods to be bioavailable in the body, they must have a certain solubility. Up to 90% of newly developed chemical entities and 40% of currently available pharmaceutical drugs are thought to have low solubility in water, making it difficult to deliver them to the body using conventional methods [3]. Co-crystallization can improve solubility by

changing the basic crystal structure. This can potentially make the compound more bioavailable. Research on cocrystallization has revealed a range of application areas for adjusting physical properties. Cocrystallization has been shown to improve resolvable, secureness, context sensitive half-time, and mechanical properties. Taste masking and the extension of intellectual property are being researched for newer applications [4,5]. A variety of successful cocrystal preparation techniques exist today. Unfortunately, researchers often lack consistency in their terminology and documentation of such methods. Crucial information is frequently left out, including the recovery procedure, target molecule concentration, equilibration period, and solvent selection. Because of this mistake, it is challenging to duplicate cocrystal preparation techniques, which may cause confusion for investigators who are not familiar with the field [6].

Comparison of cocrystal with salts

The pharmaceutical business can benefit from cocrystallization in two unique ways when compared to salt formation. 1. Unlike with salt formation, cocrystallization enables the synthesis of crystals with weakly ionisable or non-ionizable APIs. As a result, cocrystallization becomes a more flexible method for enhancing physical attributes. 2. For toxicological reasons, When making salt, only basic or acidic counter-ions are studied. Nevertheless, a large variety of viable cocrystal donors are accessible in cocrystal screening, unrestricted by toxicological concerns. Numerous compounds that are "genetically recognized as safe" (GRAS) are listed by the US Food and Drug Administration and represent hundreds of possible co-formers for pharmaceutical cocrystals. In the crystal lattice, cocrysals are made up of an API and a neutral molecule (conformer chemical), in contrast to polymorphs, which have only one API. [7].

Definition of Cocrystal

“Cocrystals have a set stoichiometric ratio and exist in the same crystal lattice. It is important to note that cocrystals differ from salts, polymorphs, solvates, and hydrates” [8].

Coformer selection

For cocrystals to form, coformers are essential, as was previously mentioned. The molecule size, pKa, physical form, and kind of functional group in a cocrystal must all be considered when developing a conformer [9]. The two main techniques utilised in the coformer selection process are the experimental technique and the knowledge-based approach. The experimental technique is built on trial and error. By mixing an API with conformers that have been selected empirically, cocrystal formation can be confirmed analytically using techniques like powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC). Both time and resources are greatly expended in this type of cocrystal screening. As an alternative, several knowledge-based strategies might be employed [10,11]. Aligning the aqueous solubility of coformer and active pharmaceutical ingredient (API) increases the possibility of cocrystal formation, as predicted by Hansen solubility parameters (HSPs) [12]. Knowledge-based approaches can anticipate cocrystal development based on the structural composition of the API and coformer, even before going into the lab. Another approach to choosing coformers is through supramolecular synthons. Within the supermolecule, they are basic building units resulting from intermolecular interactions. Supramolecular synthons come in two types: self-complementary supramolecular homosynthons and complementary supramolecular heterosynthons. The latter is usually more durable. In general, preference is given to heterosynthons like amide and carboxylic acid homodimers. Some common supramolecular synthons as follow figure 1 [13,14].

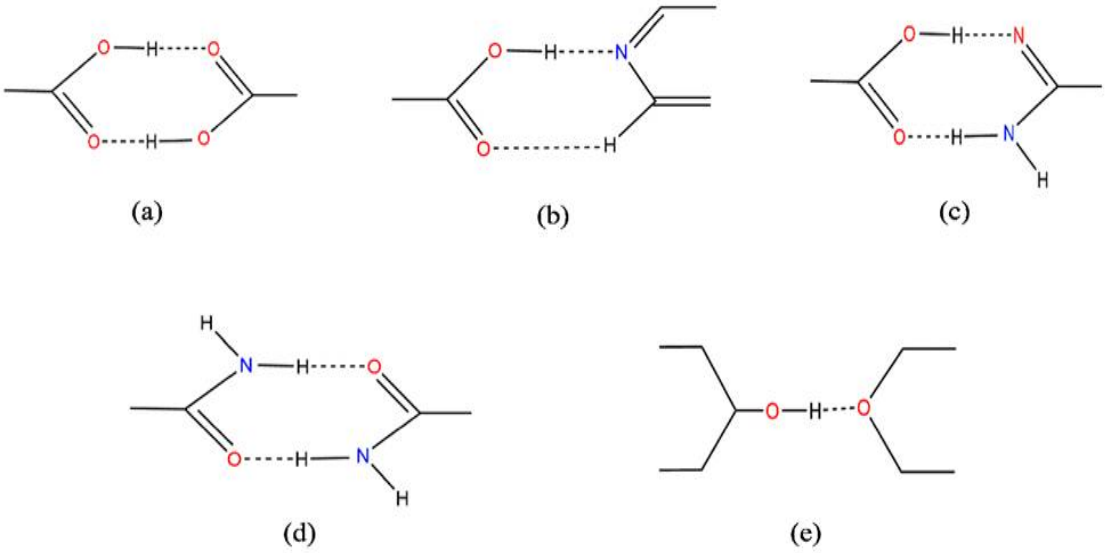

Fig 1: The most common supramolecular synthons utilised in crystal engineering .

A few of these are (a) homosynthons involving carboxylic acid dimer, (b) heterosynthons involving carboxylic acid and pyridine group, (c) heterosynthons involving amide dimer, (d) heterosynthons involving amide group, and (e) heterosynthons involving alcohol and ether group.

The usual methods for selecting a coformer and making cocrystals include explaining detail as follows-

1.The Cambridge Structural Database [CSD]

CSD contains information about molecules and their structures. The data in the CSD can be used to carry out supramolecularbased on chemical reaction. This involves finding patterns of molecules that can be used to create a desired crystal structure [15]. CSD is a repository of crystallographic information. CSD contains data on the hydrogen bonds that form between drugs and coformers. As of now, CSD contains crystal structures that are more than 1.2 million in number [16,17]. CSD contains information on chemical structures and geochemical information, including the orbiting groups, web, alignment, crystal structure, transform packing, the molecules aspects, the geometry of moles, stereochemistry, structure accountability, and conformational analysis.. This data can be used to design and create cocrystals, which are solid-state combinations of two or more molecules [18]. By understanding the geometry and the existing intermolecular interactions' optimum perspectives, researchers can select coformers that will co-crystallize with the APIs [19].

2. Hydrogen-Bond Rules

A different method for choosing coformers is the hydrogen-bond rule. Between an electronegative atom (X) and a hydrogen atom, hydrogen bonding (X-H) is an attractive contact. Both inside a molecule and between two distinct molecules can form this link. [20]. It's important to understand how molecules establish hydrogen bonds. There are three guidelines that govern the formation of hydrogen bonds. In a molecular crystal structure, Donohue's law states that every acidic hydrogen atom will participate in hydrogen bonding [21].

3.Pka Rules

The difference in acidity (pKa) of two compounds can help determine whether they will form a salt or a cocrystal [22]. Certain medications' acid ionization constant (pKa) affects how well they are absorbed by the mouth. Depending on their pH-dependent solubility, Medication under BCS Class II is further divided into three categories: Iic (neutral drugs), Iib (basic drugs), and Iia (acidic drugs). Class Iia drugs, which include Froben and ketoprofen, dissolve better in the colon's alkaline environment and have a pKa of less than 5. But drugs that are weakly basic (pKa ≥6), including carbamazepine and rifampicin, dissolve more easily in the stomach's acidic environment and are categorised as class Iib drugs. Drugs with no pH-dependent solubility fall under the class Iic category, which includes neutral drugs like danazol and fenofibrate [23,24,25]. You can determine whether a crystal or salt will form by looking at the transfer of protons. This is determined by the differential, or ΔpKa, between the acid and base pKa values. The oral absorption of several drugs is influenced by their acid dissociation constant (pKa). BCS Class II pharmaceuticals are subdivided into three categories based on their pH-dependent soluble: Iia (acidic drugs), Iib (basic drugs), and Iic (neutral drugs). Ketoprofen and flurbiprofen are examples of class Iia medicines that dissolve easier in the alkaline colonic environment (pKa ≤ 5). However, medications that

are weakly basic (pKa ≥6), including rifampicin and carbamazepine, dissolve more readily in the acidic environment of the stomach and are classified as class Iib medicines [26].

4.Hansen Solubility Parameters

The propensity of a coformer and medication to create a cocrystal can be inferred by leveraging Hansen Solubility Parameters (HSPs). This can assist in preselecting prospective coformers before undergoing thorough cocrystal screening processes. The HSPs can anticipate the impulsiveness of cocrystal components, thereby directing the selection of appropriate coformers [27].

5.Supramolecular synthone approach

It is possible to construct a medicinal cocrystal by crystal engineering. This is carried out in an effort to enhance an API's characteristics (active pharmaceutical ingredient) in solid form without impacting its innate structure [27].

Corey proposed the term synthon to describe the structural units within supermolecules that could be built by known or theoretical intermolecular interactions. In a crystal lattice, these interactions form a repeatable pattern known as a supramolecular synthon.

Two further types of supramolecular synthons can be distinguished:

1.Supramolecular homosynthons: These consist of the interchangeable, self-complementary functionalities.

2. Supramolecular heterosynthons: They consist of many capabilities that work well together, which can be used to bind molecules with different structures.

Preparation of co-crystals

Different types of method are used for cocrystal preparation as follows

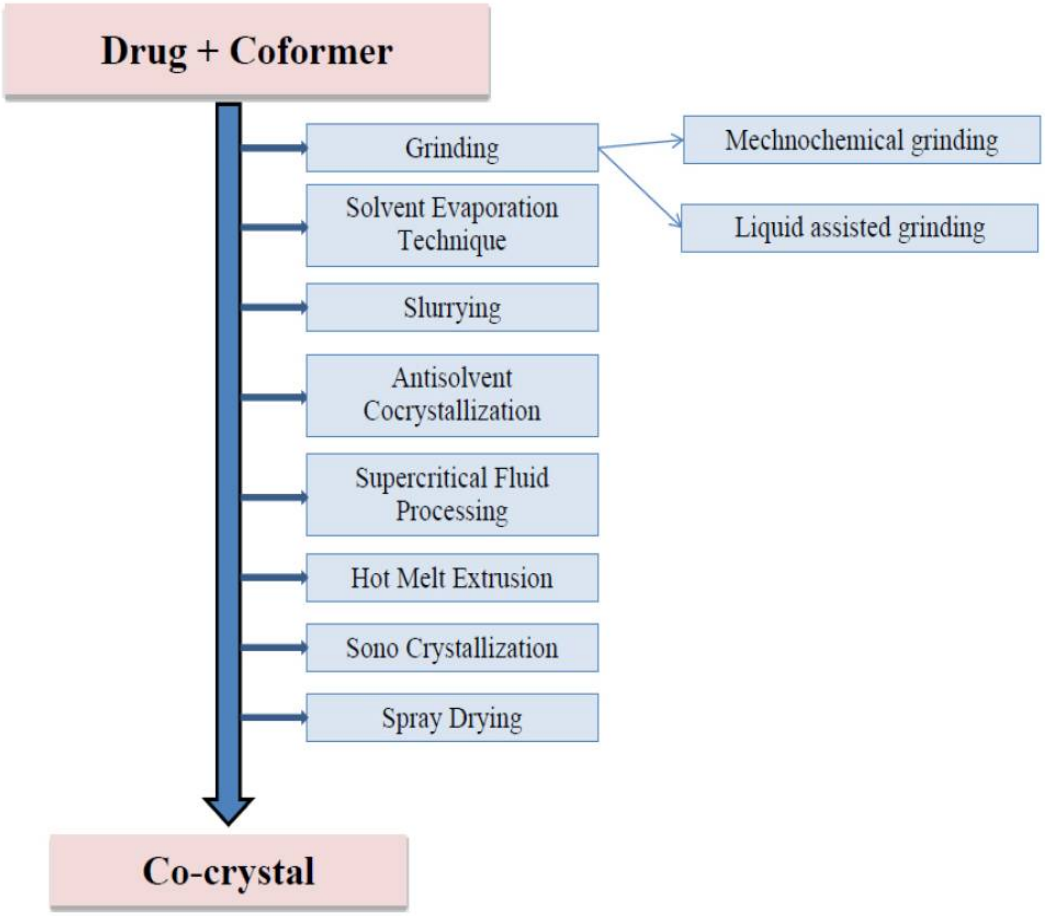

Figure 2. Various Methods of Preparation of cocrystal

Grinding Method

a. Mechanochemical grinding

also known as solid-state grinding or dry grinding [28], is a method of grinding materials together in the absence of a solvent. This can be done using a variety of techniques, including ball milling, attritor grinding, and vibratory grinding [29]. The absence of crystal arrangement caused by inadequate grinding may hinder the possibility of synthesizing cocrystals by this technique [30]. Using 8-hydroxy-

7-iodoquinoline-5-sulfonic acid as a coformer, researchers under the direction of Quashie devised a novel mechanochemical technique to produce co-crystals of sulfamethoxazole. This method involves grinding together solid ingredients using a ball mill to induce chemical reactions and form new crystalline materials [31].

b. Liquid-assisted grinding

Grinding solids together to create new, co-crystal compounds can be aided by adding a few amount of water. This liquid acts as a stimulant for the formation of co-crystals [32]. With less time and solvent needed, this approach is superior to the solvent evaporation process. Utilizing LAG, Thenge et al. synthesized diacerein co-crystals from tartaric acid and urea. For ninety minutes, the co-former and drug were mashed in a mortar and pestle at a ratio of one to one, adding small amount of ethanol (about 10% of the total weight) [33].

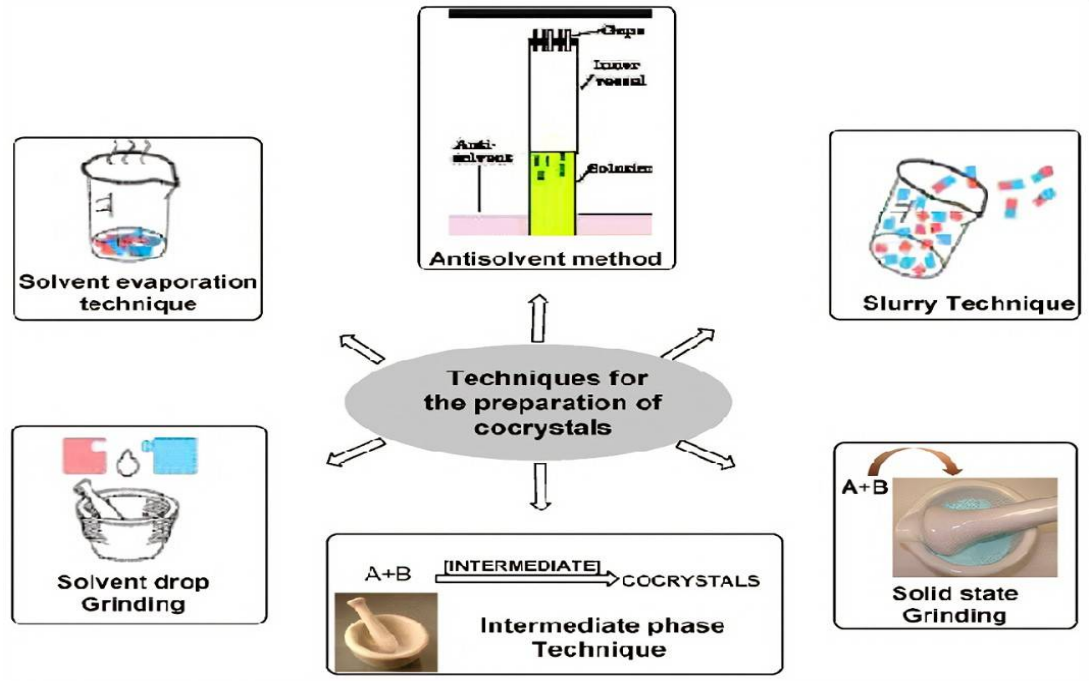

Figure no- 3 Techniques for preparation of Cocrystal

1.Solvent Evaporation Method

The process of solvent evaporation is a popular and efficient way to make co-crystals. It entails achieving the proper ratio by releasing the medication and coformer in the right solvent. When selecting a common solvent, the solubility of the medical products and coformers is an important consideration. The functional groups of drugs and coformers interact intermolecularly, such as through H-bonding, to form cocrystals. However, this method requires more solvent than LAG, which is a major disadvantage [34]. Researchers compared different methods for preparing a drug called fexofenadine-tartaric acid as co-crystals. They discovered that the solvent evaporation procedure was the simplest and most successful approach, increasing the medicine's eqillibrium and soluble capacity [35].

2.Slurrying

Slurry co-crystallization involves adding a solvent and a coformer to an active pharmaceutical ingredient (API). The choice of solvent is based on how well the API and coformer dissolve in it. The mixture is stirred to facilitate the formation of co-crystals [34].

3.Antisolvent crystallization

Antisolvent crystallization is a further way to obtain co-crystals of high quality [36]. During this process, an additional solution like natural cleaner or buffer is introduced to the drug mixture to make it entirely dissolved [37]. A large quantity of solvent is needed to conduct this preparation, which is a limitation of this method [38].

4.Supercritical fluid processing

Since carbon dioxide (CO_2) can permeate solids, it is often used as a supercritical fluid for the creation of co-crystals. The medication and coformer are mixed together in a stainless-steel container by dissolving them in CO_2. Co-crystals are then formed as a result of the solution's rapid expansion caused by a steady

decrease in pressure. The principal disadvantages of this technique are the lower quality of the co-crystals and the drug's and coformer's limited solubility in the supercritical fluid [39].

5.Hot Melt Extrusion

Co-crystals can be continuously prepared in a single step using hot melt extrusion. In this method, high-intensity mixing provides heat energy and makes the medication and coformer miscible when melted [40].

6.Sonocrystallization

In sonoreactors, co-crystallization is achieved. An overview of clinical co-crystals Advancement Pharmaceutical Bulletin, 10(2020), 277–288. Medications and coformer are combined and released into a common solvent in this approach and then they are vibrated at a constant temperature. [41] To keep the sonicator at a consistent temperature, cold water is supplied42. The immense energy also generates tiny air bubbles or slits, which leads to crystallisation, size reduction, and supersaturation [43].

7.Spray Dryers

Spray drying methods are a viable way to create co-crystals. A rigorous examination of the cocrystals was carried out in order to confirm and determine their purity. The co-crystals section that follows discusses a few characterization methods that are relevant to the assessment [41,42].

APPLICATIONS OF COCRYSTALS

1.Bioavailability

How much of a medication enters the bloodstream depends in large part on its bioavailability. The bioavailability of cocrystals has not been extensively studied in animals. Through the addition of coformers, cocrystals are designed to enhance the physiochemical oddities of APIs such as permeability, resolvable, and context sensitive half-time. It has been demonstrated that the oral bioavailability of -pyrimidine-4-carboxamide is improved by cocrystals of glutaric acid and 2-[4-(4-chloro-2-fluorphenoxy) phenyl] over pure indomethacin.43.

2.Solubility

In the quest to elevated the dissolution of low solubility drugs, cocrystal formation has emerged as a prospective approach. This technique involves combining the drug with a highly soluble substance known as a conformer. The resulting cocrystal exhibits improved solubility, leading to enhanced bioavailability and faster onset of action. A notable example is the combination of meloxicam and aspirin in a cocrystal formulation. Mobicox is a nonsteroidal anti-inflammatory medication (NSAID) that has elevated permeability and limited dissolution in water, initially faced challenges in achieving a rapid onset of action due to its slow dissolution rate. In this formulation, aspirin acted as the conformer, aiding in the enhanced solubility and bioavailability of meloxicam44. To address the solubility problem with ibuprofen and flurbiprofen, a cocrystal was created with each medication using nicotinamide coformer. The tableting behaviour and sorption of water increased the dissolving rate by 8 and 5 times, respectively. Similarly, AMG 517 cocrystal reduces the dosage by elevated the pace at which the active moiety disintegrates. Itraconazole's solubility problem was solved by a cocrystal with malic acid, which significantly increased the rate of dissolution [45].

3.Stability

Cocrystals of the anticancer medications temodal-succinic acid, TMZ-malic acid, and TMZ-tartaric acid are more stable than the pure drug between pH 2 and 6. Within a week, all TMZ except TMZ-succinic acid and TMZ-oxalic acid began to degrade at a temperature of 40°C and a relative humidity of 75%. This stabilization pattern was discovered via powder X-ray diffraction (PXRD) [46].

4.Melting point

Temperature indicating the balance between solid material and liquid phase [47]. The co-precious stone type of medication for the most part diminishes the liquefying point than its unadulterated medication and co-former. The liquefying point of hexamethylenebisacetamide (disease fighting agent)-dicarboxylic corrosive co-precious stones had diminished dissolving point than its unadulterated medication alongside the enhancement of the pharmacological characteristics of a drug [48].

5.Tablet Stability

In the development of cocrystals, attaining the desired tablet stability is crucial. Several studies have demonstrated remarkable improvements in tablet properties, including enhanced plasticity and flowability, upon the formation of cocrystals. For instance, efavirenz adipinic acid and efavirenz-acid milk acid cocrystals exhibited a 3-3.5-fold increase in solubility, accompanied by improved tablet characteristics49. Furthermore, Cocrystals of fenofibrate and nicotinamide made via solution method using ethanol exhibited enhanced tableting properties, making them suitable for further pharmaceutical development [50].

6.Coformers

Coformers are inactive ingredients used to create cocrystals, which improve the properties of drugs. Selecting the right coformer is crucial in cocrystal development. Coformers can enhance drug micromeritics, stability, and dissolution, depending on the drug's characteristics. They can be drugs or excipients and must be safe, inert, affordable, and readily available [50].

COCRYSTAL TYPES

1.Cocrystals of molecules

Molecular cocrystals consist entirely of neutral components known as coformers.

2. Crystals of Ions

In ionic cocrystals, the predominant interaction involves electrostatic forces. Additionally, hydrogen bonds may form between common donors and acceptors (such as OH, NH, O, and N). A notable example of this phenomenon can be observed in ionic cocrystals of sodium chloride and carbohydrates [51]. There are several types of ICCs available, containing more stable onglyza, improved Achromycin hydrochloride ICCs, and streptomycin acid salts, which include alkaline earth metals [52].

3. Multidrug cocrystals

Multidrug cocrystals consist of two or more medicinal compounds in an exact ratio as crystalline solids. Known by another name, drug-drug cocrystals, they are a novel method in the creation of medicines53. Many crystal structure prediction programs have been created, and an organic molecule's crystal structure can be solved using the chemical diagram. Nevertheless, polymorphism—the creation of many crystal forms from a single molecule—quickly proves that certain crystal forms are not the most thermodynamically stable. Initially crystallising in a metastable polymorph, molecules can subsequently transform into a stable state [54].

ASSESSMENT AND RECOGNITION OF CO-CRYSTALS

Fourier-transform infrared spectroscopy

FTIR is a commonly utilized technique for foreseeing and establishing chemical structure, interactions between molecules, and analysis of communication between Active Pharmaceutical Ingredients (API) and coformers. This approach is rapid, non-invasive, sensitive to alterations in molecular configuration, and capable of identifying functional groups.

Differential scanning calorimetry (DSC)

The DSC technique is employed to ascertain the formation status of a certain cocrystal. The DSC spectra's presence of an endothermic peak and an exothermic peak instead of a peak confirms this 55. The compound's peak presence is a key factor in deciding whether or not cocrystals will form. Finding the compound's melting point, polymorphic features, window transition temperature, heat of fusion, and whether the molecule or compound has exothermic or endothermic properties can also be helpful56.

Thermal gravimetric method

The thermal gravimetric method is valuable in identifying the weight of a sample as it reacts to changes in temperature over a defined duration. It provides precise drying temperatures during different stages of the component's reactions. This technique is employed to forecast the stability, purity, compatibility, as well as the forms of solvates/hydrates in cocrystals57.

Terahertz time-domain spectroscopy

THz-TDS, akin to PXRD is employed to analyze and distinguish cocrystals58. Additionally, cocrystals of theophylline with various conformers are included in the examples59.

Solid-state nuclear magnetic resonance (SSNMR)

SSNMR is commonly employed to analyze and distinguish different solid states of pharmaceutical substances, such as cocrystals. The fundamental concept behind SSNMR involves the irradiation-induced nuclei shift, which allows for differentiation from excipients. Some typical nuclei examples used in SSNMR include 13C, 31P, 1H, and 19F60. It is feasible to identify the type of hydrogen atom included in a particular molecule as well as the effect of the mixture's ratio of moles as determined by by combining quantitative and qualitative approaches61,62.

PXRD

PXRD is a technique that researchers use to investigate the crystalline behavior of powdered materials, including drugs. In a study by Bolla et al., PXRD was applied to acemetacin cocrystals to characterize the sample's crystalline cell dimensions, structural purity, and textural properties63.

Dissolution studies

Dissolution refers to the rate that a given amount of a drug changes into a liquid solution under specified circumstances, including liquid to solid ratio, solvent composition, and temperature. Dissolution studies are performed in-vitro on solid drugs to assess how well the drug dissolves under specific conditions [64].

CONCLUSION

Co-crystallization offers a possible way to enhance the characteristics of non-steroidal anti-inflammatory drugs (NSAIDs) by forming crystalline solids. This process can enhance their mechanical and physicochemical qualities, potentially leading to safer and more effective active pharmaceutical ingredients (APIs). By creating co-crystals with Generally Recognized As Safe (GRAS) co-formers and specific hydrogen molecules, NSAID medications can be modernized and patents made greener. Solid-state techniques have proven most efficient for producing NSAID co-crystals. Renewing NSAID co-crystallization involves selecting co-formers from databases, optimizing scale-up processes, and modifying drug delivery for improved physicochemical properties. Moreover, NSAID co-crystals have shown to decrease tolerance doses, prolong the time that the medication works, and accelerate its onset of action.

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