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Cocrystals: An Overview on methods of synthesis, characterization and applications in Pharmacy

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Abstract:
The limited bioavailability observed in many contemporary pharmaceuticals can often be attributed to their poor oral solubility. A significant proportion of new chemical entities (NCEs) and recently approved active pharmaceutical ingredients (APIs) fall into Biopharmaceutics Classification System (BCS) Class II and Class IV, characterized by low solubility in aqueous environments. This challenge has led to an increased demand for effective strategies to enhance solubility and, consequently, bioavailability. Since its serendipitous discovery in 1783, the use of cocrystals has been explored to address various physicochemical issues associated with suboptimal performance in both oral and other delivery routes. Cocrystals offer benefits beyond mere dissolution enhancement; they also improve tabletability, flow properties, and physicochemical stability against environmental factors such as light. The versatility of cocrystals extends to the formulation of fixed-dose combinations, enabling the concurrent delivery of multiple drugs. This review aims to elucidate the critical factors in selecting appropriate coformers, suitable preparation methods, and the analysis of cocrystals formed from APIs and coformers. Additionally, the review discusses the advantages that cocrystal technology offers within the pharmaceutical industry.
Keywords: Cocrystals, dissolution enhancement, improved physicochemical properties, methods of synthesis, Applications of cocrystals.

1. INTRODUCTION:

Despite the wide variety of dosage forms available on the market, (oral) solid dosage forms constitute more than 80% of the total [1]. This predominance is due to several factors, including ease of administration, enhanced patient compliance, and the availability of different formulation options, such as immediate onset (buccal, sublingual), conventional immediate release, and delayed or controlled release forms. Furthermore, these forms are non-invasive. The dissolution, solubility, and permeability of drugs are critical determinants of their absorption into systemic circulation and their therapeutic effectiveness [2]. Nonetheless, over 90% of new chemical entities and 40% of marketed products are classified as Biopharmaceutics Classification System (BCS) Class II, characterized by poor solubility, or Class IV, characterized by both poor solubility and permeability [2]. The solubility of an Active Pharmaceutical Ingredient (API) in an appropriate aqueous medium is a key factor influencing its dissolution, permeability, and bioavailability during the early stages of drug development. This step is essential for formulating a suitable drug product for preclinical and clinical trials.

Given the decline in the discovery of new chemical entities, pharmaceutical companies and formulators are focusing on creating modified versions of existing drugs. The most common strategies to improve solubility include salt formation, polymorphism, the pro-drug approach, and the increasingly popular cocrystal or crystal engineering approach [3]. The cocrystal method is favored for its ability to produce combinations with enhanced solubility and stability, which can, in some cases, prolong the product's market life indefinitely [3]. However, the challenge remains in identifying the optimal combination of API and coformer to economically produce a novel and enhanced formulation.

Cocrystal formation involves modifying the crystal lattice of a solid API using non-ionic interactions. These interactions can be non-covalent, such as π-π interactions, hydrogen bonding, or Van der Waals forces. Cocrystals can be defined as crystalline structures comprising two or more components in a specific stoichiometric ratio. Typically, a cocrystal contains one or more APIs and a coformer selected from the non-toxic substances listed in the Generally Recognized as Safe (GRAS) list by the USFDA. The primary advantages of the cocrystal approach are the broad selection of coformers available and the ability to modify the physicochemical properties of the API without compromising its therapeutic or pharmacological effects [1].

The earliest known cocrystal was accidentally discovered in 1783, comprising urea and NaCl [5]. Since then, progress in the field, particularly in pharmaceuticals, has gained the attention of regulatory bodies such as the USFDA. The FDA released its first draft guidance in 2011, defining pharmaceutical cocrystals as drug product intermediates [4]. This development eventually led to the approval of cocrystal-based drugs such as Odomzo®, Steglatro®, Suglat®, Entresto®, Beta-Chlor®, and Seglentis®, the latter of which was approved on February 14, 2022 [6].

Significant research in the field of cocrystals has led to groundbreaking innovations like Drug-Drug Cocrystals (DDC), an application of multicomponent systems in which both components of a cocrystal are different APIs. This innovation facilitates the development of Fixed Dose

Combination drugs (FDCs), which have the potential to target multiple pathways simultaneously.

1.1. Coformer selection:

A cocrystal consists of one or more active pharmaceutical ingredients (APIs), which may or may not be chemically inert, combined with a suitable coformer. A coformer is defined as "a component that interacts non-ionically with the API, is not a solvent (such as water), and is typically inert" [4]. The selection of an appropriate coformer is crucial as it directly influences the stability and functionality of the cocrystal being developed or studied. Traditional methods for selecting coformers primarily relied on trial-and-error or knowledge-based approaches [7]. Another older method, known as the "tactless" approach, involved examining a list of previously approved or accepted pharmaceutical cocrystals to gain insights or clues for formulating new API and coformer combinations [8].

In contrast, contemporary methods for coformer screening incorporate more sophisticated techniques such as assessing hydrogen-bonding propensities, utilizing pKa-based models, calculating the crystal lattice energy of the potential cocrystal, and applying quantum chemistry-based thermodynamic approaches like COSMO-RS (COnductor-like Screening MOdel for Real Solvents). These methods also involve measuring saturation temperature, employing the Hansen solubility parameter, synthonic engineering, and the Kofler contact method, which is used to observe phase transitions and conduct other advanced thermal analyses. Another innovative and increasingly popular approach involves using the Cambridge Structural Database. This database evaluates intermolecular interactions, packing-related factors, and other critical parameters to suggest coformers that are likely to form cocrystals with the desired stability and physicochemical or pharmaceutical properties [9].

2. Methods of Cocrystal Synthesis:

The preparation methods for cocrystals are generally categorized into solid-state methods and solution-based methods. Solid-state methods utilize minimal to negligible amounts of solvent, whereas solution-based methods involve the use of a significant excess of solvent, necessitating an additional step to isolate or extract the cocrystals from the solvent medium [10]. Apart from these, there are various other miscellaneous methods and emerging technologies available for cocrystal preparation, some of which are briefly outlined below

2.1. Solid State:

Solid-phase techniques refer to methods that use little to no solvents in the synthesis of cocrystals. The minimal solvent usage in these techniques reduces the time needed for drying the product and decreases the risk of potential solvent contamination. Solid-state methods are increasingly favored in the pharmaceutical industry due to their lower production and drying costs associated with cocrystal formation compared to solvent-based methods. Table 1 provides an overview of various solid-state techniques along with recent examples of their applications in producing novel cocrystals. Figure 1 presents a general flow diagram outlining the steps and considerations involved in solid-phase synthesis techniques.

Table 1: Solid state methods for cocrystal formation

Sl. No	Name of the Technique	Description	Example
1.	Grinding or co-grinding method	Due to the absence of an excess of solvent, solid-state grinding has been used extensively for the preparation of cocrystals in the past.	
	Neat grinding	The API and coformer are ground together. The temperature of the mixture during the grinding process is monitored to ensure that the API or coformer do not melt due to the pressure induced by the process.	Hossain and team reported cocrystals of ketoconazole using succinic acid and fumaric acid as coformers in an oscillating ball mill (Retsch MM 400) at 19Hz frequency for 60 min. During this time, there was a periodic break for 2 minutes between every 15 minutes of grinding to ensure the temperature is maintained during the process [11].
	Wet grinding	In the wet grinding or solvent drop grinding method, a small amount of solvent is added dropwise to the constituents before grinding. The solvent serves the purpose of a catalyst to ensure the formation of cocrystals.	Jafari and team reported a cocrystal of Nevirapine using two coformers, salicylamide and 3-HBA. These cocrystals were prepared by wet grinding using the dropwise addition of acetone for 30-45 minutes [12].
2.	Hot melt extrusion	In the HME process, the API and coformer together are melted and extruded through a heated screw extruder. Prior to extrusion, the constituents are thoroughly melted and mixed to obtain a uniform blend which crystallizes upon cooling	Butreddy et.al reported a cocrystal of Arpiprazole and adipic acid using a Process 11, Thermo Fisher Scientific co-rotating twin screw extruder (11mm) with a length-to-diameter ratio of 40:1 [13].
3.	Contact crystallization	Contact co-crystallization refers to the spontaneous crystallization of API and coformer after they undergo soft mixing. This reaction is facilitated by higher humidity, higher temperature and smaller particle size which require a prolonged duration for co-crystallization	MacFinnoghaile et.al reported a cocrystal of caffeine and urea after pre-milling and soft mixing at 30% relative humidity and room temperature. This cocrystal formation was reported after 3 days and was largely attributed to the interparticle surface contact [14].

Table 2: Solvent based techniques for cocrystal synthesis

Sl. No	Name of the technique	Description	Example
1.	Evaporation crystallization	In Solvent evaporation or evaporation crystallization, a known excess of solvent is used in the crystallization process to ensure that a single cocrystal which is suitable for structural analysis is produced.	Çözünürlük and team reported a cocrystal of rosuvastatin and L-asparganine using solvent evaporation in which methanol and water were used as solvents respectively. The separate mixtures were stirred magnetically at 900 RPM under heat until the solvent was completely evaporated. The produced cocrystal was washed with methanol: water to remove impurities and subjected to analysis [15].
2.	Reaction crystallization	Reaction Crystallization is a process in which the solubility of molecular complexes which help form cocrystals is hindered resulting in conditions required for the nucleation of cocrystals and their formation	Cavanagh and team reported a cocrystal of lamotrigine and nicotinamide produced by reaction crystallization using supersaturation [16].
3.	Isothermal slurry conversion	In isothermal slurry conversion, a known excess of API and coformer is suspended in a solvent. The kinetics of cocrystal formation from a slurry can vary to a considerable extent as it depends on the relative concentrations of API and coformer and solubility driving force.	Jia and team reported cocrystals of hexanitrohexaazaisowurtzitane and HMX using isothermal slurry conversion. Based on information from the tertiary phase diagrams, two thermodynamic stability regions were selected and the physical mixture was agitated for 72 hours. After the establishment of solid solution equilibrium, the cocrystals were separated and analyzed [17].
4.	Anti-solvent crystallization	Anti-solvent approach is a technique to produce cocrystals using precipitation in an insoluble solvent.	Wang and team produced cocrystals of carbamazepine and saccharine was dissolved in methanol and the solution was aged at 25°C and the resulting solution was concentrated over 10hrs to produce a slurry. This slurry was dried further by vacuum drying to produce cocrystals [18].
5.	Spray drying	Spray drying is a process which allows for the production of cocrystals in a single-step process and can be used in continuous process.	Alhawaleh and team produced cocrystals of theophylline and urea by spray drying method using methanol as the solvent and nitrogen as the drying gas. The inlet temperature was maintained at 70°C and the outlet temp was 55°C. The aspiration rate was 100% and the solution feed rate was 5mLmin-1[19].
6.	Freeze drying	Freeze drying or lyophilization is a widely used process for the thorough and complete drying of pharmaceuticals and foodstuff. Recently it has shown promise as a feasible method to produce cocrystals	Tanaka and team produced cocrystals of theophylline and oxalic acid by mixing the two into the water and spraying them into liquid nitrogen to produce ice droplets which were dried using a lyophilizer (DC800, Yamato Scientific) [20].

2.2. Solution state

Solution-oriented techniques involve the use of a known excess of solvents to facilitate the crystallization of cocrystals from their respective APIs and coformers. While these techniques require a solvent medium, they have been widely employed in the synthesis of novel cocrystals in the literature due to the potential beneficial effects that solvents can have on the crystallization process. These effects may include the stabilization of cocrystals or the creation of a specific chemical environment necessary for cocrystal formation and growth. Certain cocrystals necessitate particular quantities of solvents or specific media for their formation. Figure 2 and Table 2 provide an overview of various solvent-oriented techniques used in cocrystal synthesis, along with recent examples of their application.

3. METHODS OF COCRYSTAL ANALYSIS:

Physicochemical analysis of cocrystals is essential to verify their authenticity and to ensure that the resulting cocrystals exhibit distinct physicochemical or pharmaceutical properties compared to a simple mixture of the API and coformer. These analytical techniques are also employed to confirm the successful crystallization and to monitor the kinetics during the cocrystal synthesis process [3]. Below, various methods used for the analysis of cocrystals are outlined, along with some relevant examples

3.1. FTIR

Fourier Transform Infrared Spectroscopy (FTIR) is one of the primary analytical tools routinely used to analyze cocrystals. FTIR is valuable for determining the characteristics of cocrystals and predicting their chemical composition. It allows for differentiation between a cocrystal, a salt, or a simple mixture of constituents by analyzing and characterizing the presence and extent of hydrogen bond formation between the API and the coformer [21].

3.2. DSC

Differential Scanning Calorimetry (DSC) is another commonly employed method for analyzing cocrystals. In this technique, a measured amount of cocrystals and a separate physical mixture are placed on an aluminum pan and heated over a specific temperature range. The resulting exothermic peaks of the cocrystals and the physical mixtures are then examined. The presence of a single, distinct exothermic peak, as opposed to two separate peaks,

can be indicative of successful cocrystal formation. Additionally, DSC can provide valuable information about other characteristics, such as glass transition temperature, melting point, heat of fusion, and polymorphic forms [22].

3.3. PXRD

Powder X-Ray Diffraction (PXRD) is a widely used analytical technique for examining powder samples of cocrystals or other physical mixtures. PXRD is employed to determine the structure and crystal lattice arrangements of powdered compounds. Cocrystals can be distinguished from their individual constituents by observing a distinct diffraction pattern on the diffractometer that differs from those of the API and coformer. The most commonly utilized form of PXRD for this purpose is the Single X-Ray Diffractometer [23]

3.4. THZTDS

An alternative to Powder X-ray Diffraction (PXRD) is Terahertz Time-Domain Spectroscopy (THz-TDS). THz-TDS is a spectroscopic analytical method in which the target molecules are investigated using radiation in the terahertz frequency range. This technique is particularly effective for identifying and differentiating specific chiral configurations of a drug or molecule within a racemic mixture [24].

4. Applications of cocrystals:

In pharmaceutical applications, cocrystals hold significant potential for modifying the physicochemical properties of the active pharmaceutical ingredient (API) without substantially affecting its therapeutic efficacy or potency. Advances in research have facilitated a comprehensive understanding of the cocrystallization process, enabling the optimization of specific physicochemical properties of a cocrystal, and in some cases, the simultaneous enhancement of multiple properties [25,26]

5. Conclusion:

Cocrystals represent a highly adaptable strategy for modifying the physicochemical and pharmaceutical properties of active pharmaceutical ingredients (APIs), as well as enhancing their stability and shelf life. like Steglatro®, Setlujan®, Entresto®, and the recent Seglentis® [27-34].

One of the primary challenges in cocrystal production remains the selection of appropriate coformers and the influence of various manufacturing techniques on the physicochemical characteristics of the cocrystals. Extensive research has been conducted to evaluate the impact of manufacturing processes on the final product, with particular focus on the effects of scale-up techniques on established manufacturing processes. While methods such as spray drying are convenient for scaling up, the choice of method ultimately depends on the properties of the API, coformer, and solvent system employed.

The field of cocrystals continues to advance, with formulators using this approach to develop and market innovative, targeted, and stabilized therapies for various disorders. Ongoing advancements, including the application of mechanochemistry for environmentally friendly cocrystal production and the exploration of novel anti-solvent techniques, hold promise for the development and release of advanced, cost-effective, and safe therapies for conditions such as cancer, retroviral diseases, and lifestyle disorders like hypertension and diabetes.

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