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Exploring Cocrystal Strategies for Improved Drug Delivery Unlocking the Potential of Cocrystallization in Pharmaceutical Innovation

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Abstract

Enhancing the solubility of poorly aqueous soluble drugs and improving their oral bioavailability pose significant challenges in new product development within the pharmaceutical industry. Several methods have been explored to tackle these issues, with their effectiveness depending on the specific physical and chemical properties of the molecules being developed. One promising approach is the cocrystallization of drug substances, which offers the potential to create new drug products with enhanced physicochemical characteristics such as melting point, tabletability, solubility, stability, bioavailability, and permeability, while maintaining the pharmacological properties of the active pharmaceutical ingredient. Cocrystals are composed of multiple components, with an active pharmaceutical ingredient and a coformer present in a specific ratio and bonded together through non-covalent interactions within the crystal lattice. This review article systematically outlines pharmaceutical cocrystals, detailing various methods of formation and evaluation, and highlighting their applications and benefits.

Key word: - Cocrystal, Coformers, crystallization, Hydrate, Solubility

1. INTRODUCTION

In recent years, there has been a surge in the development of drugs with low aqueous solubility. A significant portion of these discoveries, around 60-70%, falls within BCS Class II (low solubility/high permeability) and IV (low solubility/low permeability).[1] Many active pharmaceutical ingredients (APIs) remain unformulated due to their low aqueous solubility, resulting in reduced drug bioavailability.[2] The gastrointestinal tract exhibits varying pH levels across its different segments, leading to different solubility profiles of orally administered drugs in gastrointestinal fluids at different pH levels.[3] This often leads to unpredictable and nonlinear drug absorption, making it challenging to evaluate drug efficacy and safety. Consequently, the limited solubility of drugs poses a significant challenge in the development of oral dosage forms. The physicochemical characteristics of APIs, including stability, particle size, powder flowability, taste, hygroscopicity, solubility, and compatibility, play a crucial role in both the therapeutic efficacy and manufacturing costs of solid dosage forms.[4] In oral drug delivery systems, gastrointestinal absorption heavily depends on the solubility and dissolution rate of drug molecules. However, a large proportion of new chemical entities (around 90%) and currently marketed drugs (about 40%) fall into the Biopharmaceutical Classification System (BCS) II and IV classes, facing challenges related to poor water solubility and reduced bioavailability.[5] As a result, drug absorption within the gastrointestinal tract is limited, impacting the clinical usefulness of these drugs. Clearly, the physicochemical properties of pharmaceutical solids significantly affect the performance of drug products.[6] It is widely recognized that the atomic arrangement within the unit cell and crystal lattice profoundly influences the properties of a given crystalline material.[7]Thus, modifying the physicochemical properties of solid drug formulations can be accomplished by making tailored adjustments in crystal packing arrangements. Researchers have developed numerous strategies to increase drug solubility, thereby improving bioavailability.[8] Methods such as size reduction, solid dispersion, complexation, salt formation, nanoparticles, self-emulsifying drug delivery systems (SEDDS), co-solvent addition, nano-suspension, emulsion, and cocrystal formation are employed to enhance the solubility of poorly water-soluble drugs. Each technique has its own advantages and drawbacks, and various factors (including API properties, excipient selection, development methodology, and dosage form nature) must be considered when choosing a technique.[9,10,11]Among these methods, cocrystal formation stands out as unique because it maintains the pharmacological properties of the drug while potentially enhancing its bioavailability and improving several physicochemical attributes such as melting point, tabletability, solubility, stability, bioavailability, and permeability. [12,13]Cocrystals involve multiple components that form a crystal lattice through non-covalent interactions. Recent intensive research efforts into their development and application in pharmaceutical formulations have focused on improving material handling during processing, ensuring storage stability, and enhancing the dissolution of active pharmaceutical ingredients (APIs).[14,15] Moreover, regulatory guidance provided by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) regarding the requirements and approval processes for pharmaceutical cocrystals should facilitate product development.[16,17]

2. COCRYSTALS

Etter was the first to introduce the term "cocrystal" and outline the design principles for hydrogen bonding in organic cocrystals [18, 19]. Desiraju subsequently pioneered the concept of supramolecular synthons, elucidating the formation of hydrogen bonds in crystal structures [20]. Cocrystals are defined as crystalline materials composed of two or more different molecules within the same crystal lattice that are associated by nonionic and noncovalent bonds. Additionally, if the solid form in a drug product is a new cocrystal entity, it is considered a new

polymorph (solvate/hydrate) of the active pharmaceutical ingredient (API). [21] The scientific community defines cocrystals as solids that are 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. [22]This definition excludes simple salts, hydrates, and solvates. However, from a supramolecular perspective, solvates or hydrates could be considered cocrystals in the case of "solvated/hydrated salt cocrystals. [23]" Cocrystals are multicomponent solids composed of two or more neutral molecules, solid at room temperature, in a stoichiometric ratio within the same crystal lattice.[24] They consist of an API and a cocrystallizing agent (coformer), typically a small organic compound generally regarded as safe, which may be another drug or a non-toxic molecule. Cocrystals of poorly aqueous soluble APIs combined with highly soluble coformers have demonstrated a solubility advantage that is orders of magnitude higher than the parent drug, as well as improved dissolution and increased bioavailability. [25, 26] Multicomponent solid forms include both crystalline and amorphous systems, with crystallinity providing a stability advantage over amorphous materials. Unlike salts that rely on ionic interactions, cocrystals are formed by reversible and non-covalent interactions between the functional groups of the drug and coformer. Unlike solvates, cocrystal components are solid at room temperature.[27] Due to their significant potential for the pharmaceutical industry and the fact that a few are now on the market, the US Food and Drug Administration (FDA) Research and Evaluation Center has issued guidance on the regulatory classification of pharmaceutical cocrystals.[28] In this document, the FDA defines cocrystals as crystalline solids composed of two or more molecules within the same crystal lattice, forming a molecular complex that is dissociable from the API-excipient, with the coformer being the excipient. [29,30]To characterize a cocrystal, the FDA requires evidence that both the API and the coformer exist in their neutral states and that no ionic interaction is involved in associating the two substances. [31]Similarly, the European Medicines Agency (EMA) has published a discussion paper on the use of cocrystals in medicinal products, describing cocrystals as homogeneous crystalline structures composed of two or more components in a definitive stoichiometric ratio, where the arrangement in the crystalline lattice is not based on ionic bonds. The EMA also requires that the formation of cocrystals be demonstrated using appropriate analytical techniques. [32, 33]

The USFDA's draft guidance defines cocrystals, salts, and polymorphs, highlighting their differences. Polymorphs are compounds that exist in different crystalline forms, such as solvates or hydrates (also known as pseudo polymorphs) and amorphous forms. These different forms have distinct lattice arrangements, leading to varying physicochemical properties due to their unique crystal lattice structures. [34]Salts are compounds formed by the complete transfer of a proton from one compound to another. The differentiation between salts and cocrystals hinges on this proton transfer: in salts, a complete proton transfer occurs between acid-base pairs, whereas in cocrystals, no proton transfer takes place. Instead, the two components in cocrystals are bound to each other by noncovalent interactions such as hydrogen bonding, π-π stacking, and van der Waals forces.[35]

3. METHODS FOR OBTAINING COCRYSTALS

Numerous methods have been documented for cocrystal preparation, including the reaction crystallization method, solid-state grinding, solution reaction crystallization, solvent evaporation, slurry conversion, and hot melt extrusion. However, selecting a suitable crystallization method remains largely empirical. Generally, the most widely used cocrystal formation approaches can be categorized into solution-based methods and solid-based methods. In solution-based methods, a considerable amount of solvent is needed to dissolve the cocrystal constituents. Moreover, the

choice of solvent significantly influences the outcome of cocrystallization, as it can modify the intermolecular interactions between the active pharmaceutical ingredient (API) and the coformer.

3.1.REACTION CRYSTALLIZATION METHOD

The Reaction Crystallization Method (RCM) was initially detailed by Rodríguez-Hornedo et al. This technique operates by diminishing the solubility of the molecular complex responsible for cocrystal formation, thereby creating favorable conditions for nucleation and crystallization. The driving force behind cocrystallization is supersaturation, generated by the surplus addition of individual components (drug and coformer) in solution, resulting in non-stoichiometric concentrations. [36] In the preparation of cocrystals using RCM, saturated solutions of the coformer are utilized, to which an excess amount of the drug is added beyond its solubility limit. These solutions can be prepared by dissolving the drug and coformer in a pure solvent, in a solvent containing solid components, or by blending two solutions where the drug and coformer are already dissolved. As the drug is introduced to the saturated coformer solution, it dissolves until reaching its solubility threshold, leading to the precipitation of the cocrystal from the solution. The resultant solution or slurry is then agitated for the requisite duration for the reaction to take place before being filtered.[37]

3.2.SOLUTION-BASED METHODS

In these methods, ternary phases (API, coformer, and solvent) coexist in the solution, with the ideal condition being for the cocrystal to be supersaturated while the reactants (API and coformer) are either saturated or undersaturated under the experimental conditions. Hence, the degree of supersaturation concerning the cocrystal in solution becomes the crucial parameter for cocrystallization and can be adjusted by varying the concentrations of the API and coformer. [38] To facilitate the pathway of cocrystal formation, establishing a phase diagram becomes essential, delineating the conditions for thermodynamic stability. This ensures that the cocrystal remains within the thermodynamically stable region and prevents the crystallization of pure reactants. The positioning of thermodynamically stable cocrystal phase regions is predominantly determined by the solubility of the reactants.[39] In solvents where the reactants can be congruently saturated, cocrystals form with equivalent reactant concentrations. However, in non-congruently saturating solvents where the reactants exhibit different solubilities, cocrystals are generated using nonequivalent reactant concentrations to reach the stable cocrystal region.[40]

3.3.SOLVENT EVAPORATION METHOD

Solvent evaporation is the most common method for preparing cocrystals and is typically used to synthesize high-quality single-crystal cocrystals suitable for structural analysis by single-crystal X-ray diffraction. In this approach, the cocrystal constituents are completely dissolved in a suitable solvent at an appropriate stoichiometric ratio, and then the solvent is evaporated to obtain the cocrystal. [41,42]The choice of solvent significantly influences cocrystallization, potentially impacting the solubility of the reactants. In a given solvent, the cocrystal components should be congruently soluble. If cocrystallization occurs between two components with incongruent solubilities, the less soluble component precipitates preferentially, resulting in either a solid mixture of cocrystal and cocrystal components or a failure to form cocrystals.[43] This technique has been successfully used to synthesize many cocrystals. For instance, a block-shaped single crystal of a 1:1 febuxostat–piroxicam cocrystal, which interacted via a carboxylic acid-azole synthon, was formed by slow evaporation of acetonitrile at room temperature over 3 to 5 days.[44] The resulting cocrystal exhibited higher solubility and better tabletability than the corresponding components. Similarly, cocrystals of nebivolol hydrochloride–nicotinamide with improved dissolution rates were obtained by solvent evaporation. [45]

3.4.COOLING CRYSTALLIZATION

Cooling crystallization is a widely utilized method for preparing large-scale and purified crystals. In this process, the properties of the crystals, including size distribution, purity, morphology, and polymorphism, depend on the local supersaturation, which is influenced by process parameters such as mass and heat transfer. Therefore, precise control of these factors is essential, considering multiple solid-liquid equilibria in the cocrystal preparation process. [46,47]During crystallization, the operating conditions are determined by the stoichiometry of the cocrystal and the thermodynamic stability zone of the cocrystal at the starting and ending temperatures. Numerous studies have demonstrated the effectiveness of this method for the scale-up manufacturing of cocrystals.[48] For example, α-Lipoic acid–nicotinamide cocrystals were produced with kilogram yields, 99% purity, and uniform particle sizes using a continuous oscillatory baffled crystallizer. To induce cocrystal nucleation, a 10% w/w seeding suspension was introduced into the crystallizer for 10 seconds at 10°C.[49,50]

3.5.ANTISOLVENT METHOD

Antisolvent crystallization is considered an effective approach for controlling the quality, particle size, and properties of cocrystals. This method is employed in both semi-batch and continuous manufacturing processes.[51] For example, Chun et al. utilized the antisolvent technique to prepare indomethacin-saccharin cocrystals. They mixed a solution containing 0.034 mol/L indomethacin and 0.05 mol/L saccharin in 150 mL methanol, to which 75 mL water (antisolvent) was added to the solution vessel using a peristaltic pump with a stirring speed of 300 rpm at 25°C for 1 hour.[52] This resulted in the formation of rod-like or columnar cocrystals with improved dissolution rates.

During antisolvent crystallization, the solubility of the cocrystal decreases due to the addition of the antisolvent, leading to supersaturation and subsequent precipitation of cocrystals. Therefore, selecting the proper combination of miscible solvents is crucial, ensuring that the cocrystal has low solubility in the poor solvent. The ratio of the cosolvent can significantly influence the yield of cocrystals, as the solvent composition can impact the solubility of both the cocrystal and its individual components.[53,54]

3.6.SLURRY CONVERSION

The slurry conversion method represents a solution-mediated phase transformation process wherein excess cocrystal components are introduced into a solvent. Throughout the slurry process, each constituent gradually dissolves, facilitating the formation of a complex structure that catalyzes the nucleation and growth of cocrystals. As cocrystals emerge, the concentrations of the reactants diminish, inducing undersaturation and prompting further dissolution of the cocrystal components. The operational parameters, including component concentrations and temperature, are meticulously controlled based on the ternary phase diagram, which serves as a roadmap for achieving optimal cocrystal supersaturation.[55]

In their study, Huang et al. observed a significant impact of initial component concentrations and operating temperature on the formation rate of the theophylline–benzoic acid cocrystal, assessed via in-line Raman spectroscopy. They noted a positive correlation between higher initial concentrations of the reactants and temperatures with the cocrystal formation rate. This relationship stems from the increased likelihood of component collisions and augmented total contact surface area associated with higher initial concentrations. Furthermore, elevated temperatures expedite the transition of reactants to the activated state, further facilitating cocrystal formation.[56,57]

3.7.SOLID-STATE GRINDING

The solid-state grinding method, which encompasses both neat grinding and liquid-assisted grinding, stands as a widely utilized approach for cocrystal production. Neat grinding entails applying energy to generate the cocrystal through manual grinding (utilizing a mortar and pestle) or mechanical milling (employing ball milling or vibratory milling) without the incorporation of a solvent. Conversely, liquid-assisted grinding involves forming the cocrystal by grinding with the aid of a small quantity of solvent [58,59]

3.8.CONTACT COCRYSTALLIZATION

Interactions between the Active Pharmaceutical Ingredient (API) and coformer have been observed to spontaneously occur following "soft" mixing of the raw materials.[60] Potential mechanisms elucidating spontaneous crystallization upon contact encompass vapor diffusion of the two solids, moisture sorption, eutectic phase formation, amorphization, and long-range anisotropic molecular migration. Factors such as increased humidity, elevated temperature, and smaller particle sizes of raw materials have been determined to facilitate cocrystal formation.[61,62] For instance, MacFhionnghaile et al. detailed the formation of caffeine–urea cocrystals within 3 days by premilling raw materials separately at room temperature and 30% relative humidity. They identified interparticle surface contact between the solids as a pivotal factor influencing caffeine–urea cocrystal formation. Similarly, Ervasti et al. showcased the phase transformation of theophylline–nicotinamide physical mixture to cocrystal occurring sans the assistance of mechanical grinding.[63,64] Another example of spontaneous crystallization is the cocrystallization of isoniazid and benzoic acid, wherein the rearrangement of cocrystals on the isoniazid surface was accelerated in the presence of moisture, thereby promoting interaction with benzoic acid vapor.[65,66] Furthermore, premilling of cocrystal physical mixtures was observed to diminish the induction time of cocrystal nucleation while augmenting the cocrystal formation rate.[67,68]

3.9.MELTING CRYSTALLIZATION

Melting crystallization presents an environmentally friendly approach to pharmaceutical cocrystal preparation, as it obviates the need for solvents.[69] However, meticulous assessment of the thermal stability of both the drug and coformer is imperative.[70] For instance, Yan et al. synthesized melatonin–pimelic acid cocrystals via melt crystallization, forming within the temperature range of 50 to 70°C. Similarly, the carbamazepine–nicotinamide cocrystal was prepared by melting a physical mixture of the drug and coformer at 160°C, followed by cooling the melt to ambient temperature for crystal growth.[71,72] Rodrı´guez-Hornedo and colleagues explored the crystallization pathways of the carbamazepine–nicotinamide cocrystal from the melt upon heating. They discerned two distinct pathways at varying heating rates:[73]

1. At a slow heating rate (3°C/min), a metastable phase of carbamazepine–nicotinamide cocrystal initially nucleated, subsequently transitioning into the stable form.
2. At a rapid heating rate (10°C/min), the individual components of the cocrystal first crystallized, melted, and then the stable form of the cocrystal emerged from the melt.

4. PHYSICOCHEMICAL PROPERTIES OF COCRYSTALS

4.1.MELTING POINT:

The melting point is a key physical property of solids, used to determine product purity, with sharp melting points and narrow ranges indicating high purity. A high melting point

demonstrates the thermodynamic stability of new materials, meaning that the thermal stability of an API can be increased by selecting a coformer with a higher melting point. [74, 75] Conversely, cocrystals with low melting points can be advantageous when dealing with thermolabile drugs.

Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) are the most commonly used techniques for determining melting points and conducting thermal analysis. [76]The melting point of pharmaceutical cocrystals can be tailored by the judicious selection of coformersthe melting point of cocrystals is directly related to the coformers used. [77]

4.2.SOLUBILITY:

Solubility stands as a critical parameter in the formulation of poorly soluble drugs, prompting the exploration of various strategies such as salt formation, solid dispersion, particle size reduction, and cocrystallization to enhance drug solubility. Among these, cocrystallization has garnered significant attention from researchers. For instance, the solubility of the antifungal drug ketoconazole saw a remarkable increase of 53 times through salt synthesis and 100 times through cocrystal formation compared to the pure drug. [78] This suggests that cocrystals can achieve superior solubility enhancements compared to salt formation. Similarly, the solubility of apixaban cocrystals saw an approximate twofold increase, with these cocrystals exhibiting faster dissolution rates compared to the pure drug. A theoretical method based on Keu (the ratio of solution concentrations of cocrystal components at the eutectic point) has emerged as a valuable tool for determining the solubility of cocrystals in a pure solvent.[79] This method streamlines cocrystal selection and formulation without the material and time requirements of traditional methods. Serajuddin utilized Keu to describe the solubility ratio and solution chemistry of cocrystals, examining over 40 cocrystals and solvent combinations.

4.3.BIOAVAILABILITY:

Bioavailability refers to the rate and extent to which a pure drug enters systemic circulation. Low oral bioavailability of Active Pharmaceutical Ingredients (APIs) poses a significant hurdle in new formulation development. Crystal engineering emerges as a crucial approach for designing and synthesizing pharmaceutical cocrystals with augmented aqueous solubility and oral bioavailability.[80,81] For instance, a pharmacokinetic study of apixaban-oxalic acid cocrystals in beagle dogs illustrated a 2.7-fold increase in oral bioavailability compared to the pure drug. Similarly, the oral bioavailability of baicalein notably surged by forming cocrystals with nicotinamide, yielding 2.49 times higher peak plasma concentration (Cmax) and 2.80 times higher area under the curve (AUC) compared to the pure drug in rats.[82] Moreover, meloxicam cocrystals with aspirin displayed enhanced oral bioavailability relative to the pure drug, manifesting a 12-fold faster onset of action in rats. Cocrystals of 6-mercaptopurine, a BCS Class-II drug, also showcased significantly heightened oral bioavailability (168.7%) compared to the pure drug in rats. These examples underscore the potential of cocrystals to amplify the solubility and bioavailability of poorly soluble drugs, thus augmenting their therapeutic efficacy.[83]

4.4.TABLETABILITY

Cocrystallization of a drug with a coformer can profoundly impact crystal packing, tabletability, and compaction, pivotal parameters in preformulation studies.[84] The compaction behavior of paracetamol cocrystals with trimethylglycine and oxalic acid surpassed that of the pure drug. Similarly, the tabletability of resveratrol was augmented by forming cocrystals with 4-aminobenzamide and isoniazid, showcasing superior tabletability compared to either the pure

drug or the coformers alone.[85] Altering crystal packing through cocrystallization can modify the mechanical properties of APIs. For instance, cocrystals of vanillin isomers with the same coformer exhibited enhanced tabletability compared to the individual isomers and the coformer. These findings underscore how cocrystallization can ameliorate the mechanical properties of drugs, facilitating improved tablet formulation and compaction, vital for the development of effective pharmaceutical products.[86]

4.5.STABILITY

Ensuring stability is paramount in the development of new dosage formulations, particularly in the realm of pharmaceutical cocrystals. Various stability assessments, including examinations of relative humidity stress, chemical stability, thermal stability, solution stability, and photo stability, are imperative.[87] Relative humidity stress testing involves automated water sorption/desorption studies to evaluate moisture's impact on the formulation. Researchers have extensively investigated cocrystal behavior under such conditions. For example, cocrystals of glutaric acid and 2-[4-(4-chloro-2 fluorophenoxy)phenyl]pyrimidine-4-carboxamide exhibited 0.08% moisture content at a high relative humidity of 95% and remained stable across different conditions. Similarly, indomethacin-saccharin cocrystals demonstrated minimal water sorption during relative humidity studies, with no dissociation or transformation observed under experimental conditions.[88] Moreover, the relative humidity stability of theophylline cocrystals with various coformers (oxalic acid, malonic acid, maleic acid, and glutaric acid) was assessed at different relative humidity levels (0%, 43%, 75%, and 98%) over various time intervals (1 day, 3 days, 1 week, and 7 weeks). The findings revealed enhanced physical properties and stability, particularly through the prevention of hydrate formation.[89,90]

4.6.PERMEABILITY:

Drug absorption and distribution pivot significantly on permeability across biological membranes, a factor profoundly influenced by the n-octanol/water partition coefficient, typically assessed using log P and (C log P) for the unchanged form of the drug. For example, the permeability of a BCS class-III drug, 5-fluorouracil, saw notable enhancement through cocrystallization with various coformers such as 3-hydroxybenzoic acid, 4-aminobenzoic acid, and cinnamic acid. [91]Moreover, the permeability of hydrochlorothiazide and its cocrystals with diverse coformers underwent investigation using Franz diffusion cells. In all cocrystals, the drug flux surpassed that of the pure drug, except for succinamide cocrystals. This enhancement in cocrystal permeability can be attributed to the formation of a heterosynthon between the drug and the coformer.[92]

5. APPLICATIONS OF COCRYSTALS

The choice between cocrystals and salts hinges on the active pharmaceutical ingredient (API) and the specific project requirements. While salts may exhibit superior physicochemical properties in certain cases, such as higher intrinsic solubility in water compared to cocrystals, the decision ultimately depends on the desired outcome.[93] Cocrystals with a negative ΔpKa value yield non-ionized drug molecules upon dissolution, whereas salts produce ionized APIs, which are more water-soluble. When the dissolution rate of the drug is crucial, cocrystals may outperform the salt form.[94] Cocrystallization serves as an alternative method to enhance the solubility and bioavailability of poorly water-soluble drugs, particularly those that are neutral or

weakly ionized. Moreover, cocrystallization offers the possibility of improving various characteristics such as melting point, tabletability, solubility, stability, bioavailability, and permeability, as discussed.[95]

6. BENEFIT OF COCRYSTALS

Several approaches, such as salt formation, micronization, solid dispersion, amorphous drugs, and encapsulation, can be employed to customize the physicochemical properties of drugs. Among these, cocrystals offer distinct advantages as they exist in a stable crystalline form and do not necessitate additional excipients or additives in formulations. [96]The physicochemical properties are influenced by factors such as the properties of the active pharmaceutical ingredients (APIs) and coformers, the nature of molecular interactions between them, and the synthetic procedures employed. [97]

Formulating cocrystals enables the enhancement of the APIs' physicochemical properties without altering their pharmacological properties, owing to the presence of the coformer in the crystal structure, which acts as a property-modifying component. The impact on the API's physicochemical properties is contingent upon the available coformer.[98] Another unique advantage of cocrystals over salts is their applicability to non-ionizable APIs and complex drugs with sensitive functional groups that may not withstand the harsh conditions of strong acids or bases.Additionally, cocrystals offer several other significant advantages. They have the potential to expedite the drug development timeline for APIs, thereby reducing costs, which is appealing to pharmaceutical companies.[99]The solid-state synthesis techniques for cocrystals align with green chemistry principles, offering high yields, minimal solvent usage, and few by-products. Moreover, pharmaceutical cocrystals differ structurally from their bulk forms, allowing for the patenting of cocrystals of existing APIs as new crystal forms. Various formulations of pharmaceutical cocrystals are available in the market, including Viagra (Pfizer) for erectile dysfunction and pulmonary arterial hypertension, Entresto (Novartis) for chronic heart failure treatment, and several others currently in clinical development.[100]

7. FUTURE PERSPECTIVES AND CHALLENGES

Cocrystallization presents a promising avenue for enhancing the physicochemical properties of drugs while preserving their pharmacological attributes. However, selecting suitable coformers for an active pharmaceutical ingredient (API) remains a significant challenge in pharmaceutical cocrystal formation. [101] Various approaches have been employed for coformer selection and cocrystal screening, each with its own limitations. Ideally, coformers should be Generally Recognized As Safe (GRAS) by the USFDA and listed in the EAFUS database, but their GRAS status does not guarantee suitability as cocrystal-forming agents. Additionally, stability in the presence of excipients poses an unresolved issue in cocrystal development, and scaling up production to yield high-purity cocrystals remains a challenge, making cocrystals less appealing to the industry. [102] in 2011, the US-FDA issued guidelines regarding the patenting of cocrystals, classifying them as "API excipient" molecular complexes rather than new APIs. Conversely, the EMA suggests that cocrystals should undergo similar documentation principles as salts. Despite differing regulatory perspectives, both agencies' interest underscores the growing recognition of pharmaceutical cocrystals as potentially marketable drugs. While the

development, screening, and evaluation of new cocrystals demand significant time and resources, researchers have employed knowledge-based approaches for coformer selection, design, and cocrystal screening, as highlighted in earlier sections. [103] As advancements in cocrystal research continue to emerge, pharmaceutical cocrystals are expected to play an increasingly significant role in drug development. In the realm of oral formulations, addressing poor aqueous solubility and low bioavailability represents a major challenge. [104]Among the various strategies for overcoming these challenges, the cocrystal approach offers unique advantages by maintaining the drug's pharmacological properties while leveraging the physicochemical properties of the coformer. Unlike salts, cocrystals can be employed for drugs that are non-ionizable or weakly ionizable in nature. Therefore, cocrystals hold potential for improving melting point, tabletability, solubility, stability, bioavailability, and permeability, alongside offering simple formulation approaches. While cocrystal formation remains relatively unexplored, a combination of knowledge-based and experimental methods for coformer selection heralds a new era in cocrystal research and development. [105]

10. CONCLUSION

Pharmaceutical cocrystals are emerging as a highly promising avenue for enhancing the physical and biopharmaceutical properties of active pharmaceutical ingredients (APIs), making this field of study one of rapid development. Various methods exist for the formation and physicochemical characterization of cocrystals. Efforts are underway to develop both theoretical and empirical methods for predicting cocrystal formation. As our comprehension of the factors defining cocrystal formation and stability deepens, theoretical prediction methods could become invaluable tools for assisting in the design of cocrystal-based dosage forms. Furthermore, the advancement of industrially applicable production methods for cocrystals, coupled with the establishment of a clear and favorable regulatory framework, is anticipated to elevate their significance as alternative approaches to salt formation or API polymorph selection in the near future**.**

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