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Exploring Cocrystals: Preparation Tactics, Advantages, And Formation Mechanisms

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ABSTRACT

The low solubility profile of drugs is one of the most demanding characteristics in drug dosage development, restraining the bioavailability of any drug. Based on solubility and permeability profiles, drugs are categorized into four different groups by the biopharmaceutical Classification system (BCS), which provides guidance optimization of dosage form for any drug. Many formulation methods for solubility enhancement of drugs having low solubility have been prepare. While they have shown fruitful results in enhancing drug bioavailability effectively, outcomes of these methods are based on certain physicochemical conditions of that molecule. Some of these methods have been discussed in this article. The preferred drug formulation for the majority of APIs continues to be oral dosage forms. Pharmaceutical co-crystals are a cutting-edge approach for increasing the bioavailability of low-solubility drugs in oral dosage form by boosting solubility, micrometric properties, dissolution rate, and stability. Co-crystals are the combination of an active pharmaceutical ingredient and one or more pharmaceutically accepted guest molecules called coformer in a stoichiometric ratio in a crystal lattice. In the current scenario, the solubility profile of drugs is a leading concern in drug development in pharma industry. This review paper offers a thorough examination of pharmaceutical cocrystals, encompassing preparation techniques, physicochemical characteristics, and practical uses. It serves as a valuable resource for improving the design and production of pharmaceutical cocrystals with specific physicochemical traits and intended applications, providing valuable insights for their efficient development.

Keywords: Co-crystallization, Co-crystals, coformer, Biopharmaceutical Classification system, solubility enhancement.

1. INTRODUCTION

One of the key challenges in drug development process for hydrophobic drugs is to enhance the solubility of the drug, which raises bioavailability at the target site of action. One of the most crucial factors in a drug's screening for drug development is its poor solubility[1,2]. A solute solubility in a solvent is controlled by the selected solvent and specific pressure and temperature conditions. Solubility is a vital criterion to attain the required drug concentration in the bloodstream to reach a desired site of action. For oral drug delivery, drugs having low solubility mainly require higher doses to reach the bloodstream. Most drugs are weak acids and weak bases having poor solubility [3,4]. The release profile of a drug is a vital parameter in the case of oral drug delivery. The Biopharmaceutical Classification System (BCS), a method for measuring permeability and solubility, categorizes drugs into four groups. Drugs in BCS class II shows low solubility and high permeability are the ideal candidates for solubility enhancement with a minimal side effect, resulting in improved bioavailability.

The way atoms are arranged in the crystal lattice and unit cell of a substance directly affects its properties. Altering the packing of crystals can change the physical and chemical characteristics of solid drug forms. There are several methods to adjust the properties of Active Pharmaceutical Ingredients (APIs), such as creating different crystal forms (polymorphs), forming salts, solvates, hydrates, and cocrystals. However, these methods have their limitations. For example, salt formation is only possible for molecules with specific ionizable groups, and hydrates/solvates can be unstable as they may lose water/solvent molecules over time. On the other hand, cocrystals offer a versatile solution since they can potentially be formed with any API, whether it is acidic, basic, or nonionized, by pairing it with a compatible coformer. In recent decades, pharmaceutical cocrystals have gained significant attention from both the academic and pharmaceutical sectors. They can enhance the physicochemical properties of APIs by altering the crystal structure without changing their pharmacological characteristics. As a result, several pharmaceutical cocrystals have been approved, such as Steglatro® and Entresto®, and more are currently in clinical trials.

Pharmaceutical cocrystals represent a specialized category of crystalline materials with a significant role in the development and formulation of drugs. These cocrystals are composed of two or more distinct molecules or compounds, often comprising a drug molecule and a coformer, arranged in a specific stoichiometric ratio through non-covalent interactions like hydrogen bonding[5,6]. They are engineered to tackle several critical challenges encountered in the pharmaceutical sector. One of the primary benefits associated with pharmaceutical cocrystals is their capacity to improve

the solubility of poorly soluble drug compounds[7,8]. By forming cocrystals, drug molecules can be combined with other substances that enhance their solubility, ultimately leading to improved bioavailability and therapeutic effectiveness[9,10]. Furthermore, cocrystals have the potential to augment the chemical and physical stability of drug compounds, extending their shelf life and reducing the necessity for specialized storage conditions[11,12]. In this comprehensive review, we will provide an overview of recent advancements in pharmaceutical cocrystals. This will encompass various aspects, such as the techniques employed for their preparation and the methods used to modify their physicochemical characteristics, as well as their diverse applications[13,14].

PREPARATION OF PHARMACEUTICAL CRYSTALS AND PHARMACEUTICAL DEVELOPMENT ASPECTS

The development of pharmaceutical cocrystals involves the identification of suitable coformers and the prediction of their potential to form stable cocrystals (Table 1). Here are some common prediction and coformer selection strategies for cocrystal development:

Crystal Structure Prediction (CSP): It is a computational approach crucial for cocrystal development. It employs advanced algorithms to predict potential crystal structures of cocrystals by analyzing the molecular interactions between the active pharmaceutical ingredient (API) and coformers. CSP calculates the thermodynamic stability and energy landscapes of various crystal structures, helping researchers identify the most favorable API-coformer combinations. By simulating and exploring a wide range of potential cocrystal structures, CSP guides experimental efforts, significantly reducing the trial-and-error process in cocrystal development and accelerating the discovery of stable and pharmaceutically relevant cocrystals with improved properties, such as solubility, stability, and bioavailability[15].

Thermodynamic Considerations: In cocrystal development, thermodynamic considerations are crucial for assessing the stability and feasibility of cocrystal formation. Thermodynamics examines factors like Gibbs Free Energy (ΔG), which quantifies cocrystal stability compared to its individual components. A negative ΔG indicates favorable cocrystal formation. Phase diagrams illustrate the temperature and pressure conditions where cocrystals are stable. Solubility product (Ksp) informs about cocrystal solubility, with lower values indicating greater stability. Experimental techniques and the influence of temperature and pressure on cocrystal stability are also important. These considerations help researchers predict, design, and select suitable cocrystals with improved properties for pharmaceutical and materials applications. Supramolecular Interactions: Analyze the intermolecular interactions between the API and coformers using computational chemistry techniques. Identify hydrogen bonding, π-π interactions, and other non-covalent forces that can facilitate cocrystal formation[16].

Experimental Screening: By conducting various experimental screening of various coformers with the API, potential of various cocrystals can be identified. Techniques like solvent-drop grinding, slurry conversion, and co-crystallization are used to test different combinations[17].

Physicochemical Properties: Physicochemical properties, such as solubility, melting point, pKa, and crystallinity, plays a crucial role in cocrystal development. Coformers with complementary properties can improve drug stability, bioavailability, and dissolution rates. Understanding and optimizing these properties are essential for designing successful cocrystals with enhanced pharmaceutical characteristics[18].

Crystal Engineering Principles: Crystal engineering principles involve designing cocrystals based on molecular interactions and crystal packing. It requires choosing coformers that interact with the active pharmaceutical ingredient (API) via strong hydrogen bonds or other supramolecular interactions. The development of stable cocrystals with desirable features, such as increased medication solubility and stability, is guided by these concepts.

Database and Literature Searches: By consulting existing databases and literature to identify known cocrystals or coformers that have previously demonstrated success with similar APIs. This can provide valuable insights and starting points for cocrystal development[19].

High-Throughput Screening: High-throughput screening involves rapidly testing numerous API-coformer combinations to identify potential cocrystals. It accelerates cocrystal development by systematically exploring a wide range of conditions, reducing the time and resources required for discovery. This approach enhances the likelihood of finding promising cocrystal candidates with improved properties[20].

Table 1: Tabular summary prediction and coformer selection strategies for cocrystal development:

Strategy	Description
Crystal Structure Prediction (CSP)	Computational methods to predict possible cocrystal structures.
Thermodynamic Considerations	Evaluate ΔG for various API-coformer combinations to assess thermodynamic stability.
Supramolecular Interactions	Analyze intermolecular forces like hydrogen bonding to predict cocrystal formation.
Experimental Screening	Conduct lab experiments to test different API-coformer combinations.
Physicochemical Properties	Consider coformers' solubility, melting point, and pKa for compatibility.
Crystal Engineering Principles	Apply crystal engineering knowledge to predict API-coformer compatibility.
Database and Literature Searches	Search existing data and literature for known cocrystals or coformers.
High-Throughput Screening	Efficiently test numerous combinations to accelerate coformer selection.

METHODS OF CO-CRYSTALS DEVELOPMENT

There are some methods of preparation of cocrystal given below (Figure 1):

Solvent Evaporation Methods: The solvent evaporation method is a frequently used cocrystal production technique. It entails mixing a solvent to dissolve both the coformer and active pharmaceutical ingredient (API). Stoichiometric ratios must be exact. Under carefully regulated circumstances, the solution is allowed to slowly evaporate, which promotes the growth and nucleation of cocrystals. Slower evaporation rates typically result in larger, well-formed crystals. Cocrystals can be collected, purified, and characterized using various analytical tools. This method offers versatility and simplicity, making it popular for cocrystal development. The choice of solvent and crystallization conditions can be optimized to tailor cocrystal properties, such as particle size and purity, to meet specific pharmaceutical and material needs[21].

Slurry Conversion Method: It is a commonly employed technique in cocrystal development. It entails mixing the active pharmaceutical ingredient (API) and coformer in a minimal amount of solvent to create a thick slurry. The slurry is then aged under controlled conditions, allowing for the gradual evaporation of the solvent. During this process, cocrystals form within the slurry due to reduced solvent concentration. The stirring helps maintain uniform conditions for cocrystal growth. Once formed, cocrystals can be isolated, purified, and characterized. This method is advantageous for compounds with limited solubility in common solvents and offers a controlled approach to tailor cocrystal properties for specific pharmaceutical and material applications[22].

Solvate and Desolvate Method: The solvate and desolvate method is a valuable approach in cocrystal development. The active pharmaceutical ingredient (API) and the coformer are first dissolved in a solvent that promotes the formation of solvates. After that, solvate crystals are produced by allowing the solution to gradually crystallise. Subsequently, the solvent molecules are removed from the solvate crystals through processes like evaporation, anti-solvent addition, or gentle heating, leading to the formation of cocrystals. This method allows for precise control over cocrystal formation and offers the advantage of tailoring cocrystal properties. Characterization techniques confirm cocrystal identity and quality, making it a valuable technique in pharmaceutical and materials science for optimizing product properties[3].

Cooling Cocrystalization

Cooling crystallization is a method used in cocrystal development. It begins with dissolving the active pharmaceutical ingredient and coformer in a suitable solvent, forming a solution. Then, either at room temperature or using a controlled cooling system, the solution is gradually cooled. As the temperature decreases, cocrystals nucleate and grow within the solution. The slow cooling rate helps produce high-quality cocrystals with well-defined properties. Once formed, the cocrystals are isolated, washed, dried, and characterized. Cooling crystallization is advantageous for systems where temperature plays a critical role in cocrystal stability, and it is widely employed in pharmaceutical and materials science to tailor cocrystal properties for specific applications[4].

Wet Grinding Method

Wet grinding is a solvent-free method employed in cocrystal development. It involves meticulously grinding the active pharmaceutical ingredient and coformer together in the presence of a minimal amount of liquid or solvent. This mechanical process disrupts the crystal lattices of the compounds, facilitating cocrystal formation. The grinding is typically carried out under controlled conditions using equipment like ball mills or mortars and pestles. Optionally, a small quantity of solvent may be added to improve grinding efficiency. After grinding, the resulting cocrystals are isolated, characterized, and stored. Wet grinding offers a solvent-free approach to produce cocrystals, making it suitable for substances with limited solubility and is valuable in pharmaceutical and materials science applications[5].

Neat Grinding Method

Cocrystal development uses a procedure called "neat grinding" that is solvent-free. It entails mixing the coformer and active pharmaceutical ingredient without the use of any liquids or solvents.. This mechanical grinding process disrupts the crystal lattice of the compounds, promoting intermolecular interactions and cocrystal formation. Neat grinding is typically performed using mortar and pestle or specialized grinding equipment under controlled conditions. The resulting cocrystals are isolated, characterized, and stored. This method is advantageous as it eliminates the need for solvents, making it environmentally friendly and suitable for compounds with poor solubility. Neat grinding is valuable in pharmaceutical research and materials science for optimizing cocrystal properties[6].

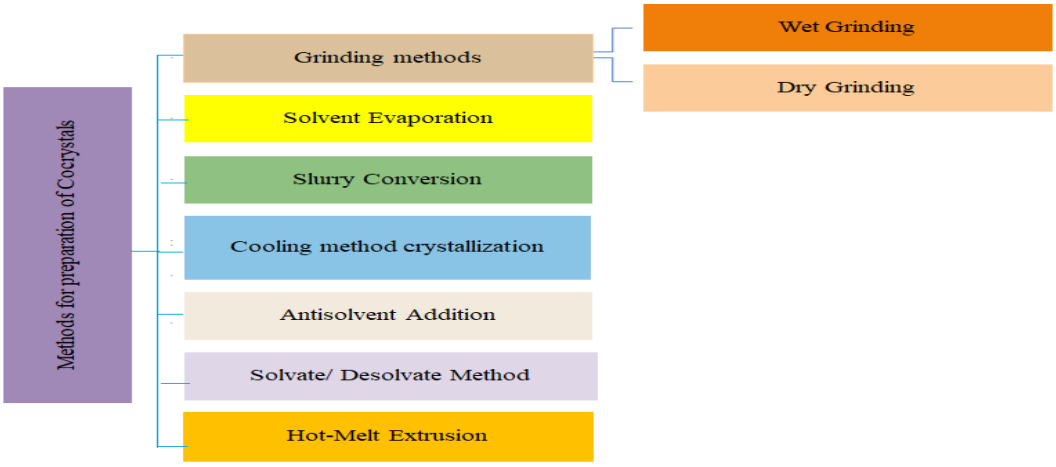

Figure 1: Methods of Preparations of Cocrystals

CHARACTERIZATION OF COCRYSTALS

Cocrystals characterization is a multifaceted process involving a combination of analytical techniques (Figure 2). Each method offers unique insights into the structural, thermal, and morphological aspects of co-crystals. Together, these techniques provide a comprehensive understanding of co-crystals, facilitating their development for various applications, including drug formulation, materials design, and chemical synthesis. Accurate characterization is essential for harnessing the full potential of co-crystals and advancing their contributions to science and industry.

The thermal behaviour of co-crystals is investigated using thermal analysis techniques such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). DSC measures heat flow as a function of temperature, revealing phase transitions, melting points, and decomposition temperatures. TGA, on the other hand, measures weight changes as a function of temperature, providing information about the stability and composition of co-crystals under different thermal conditions. These techniques help determine the suitability of co-crystals for various applications, especially in pharmaceuticals where stability at different temperatures is critical. One of the most powerful methods for co-crystal characterization is X-ray crystallography. This technique involves shining X-rays onto a crystal and measuring the resulting diffraction pattern. By analyzing the diffraction pattern, scientists can determine the three-dimensional arrangement of atoms within the crystal lattice. X-ray crystallography provides precise structural information, including bond lengths, angles, and molecular packing in the co-crystal. This data is invaluable for understanding the nature of interactions between co-former molecules[27,28].

Similarly, various spectroscopic methods, such as infrared spectroscopy, nuclear magnetic resonance spectroscopy, and Raman spectroscopy, are employed for co-crystal characterization. IR spectroscopy identifies functional groups and intermolecular interactions within the co-crystal, while NMR spectroscopy elucidates the structural details, including the spatial arrangement of atoms. Raman spectroscopy provides information about molecular vibrations and crystal symmetry, aiding in the identification of co-crystal phases. Solid-state NMR spectroscopy is another specialized technique used to probe the atomic-level structure and dynamics of co-crystals in their solid state. It provides valuable information about the local environments of nuclei within the crystal lattice, revealing intermolecular interactions, conformational changes, and mobility of co-former molecules[29,30].

Similarly, Powder X-ray diffraction is a non-destructive method for figuring out if co-crystals are crystalline or not. PXRD, as opposed to single crystal X-ray diffraction, is appropriate for powdered samples. It generates a diffraction pattern that can be analyzed to identify the crystal structure, phase purity, and crystallinity of co-crystals. PXRD is particularly useful for quality control and assessing the reproducibility of co-crystal synthesis[31].

Scanning Electronic Microscopy is employed to visualize the surface morphology and particle size of co-crystals. This technique provides high-resolution images of co-crystals, allowing researchers to assess their physical characteristics, such as shape, size, and surface texture. SEM is crucial for understanding the external features of co-crystals and can be used to investigate their agglomeration behavior[32].

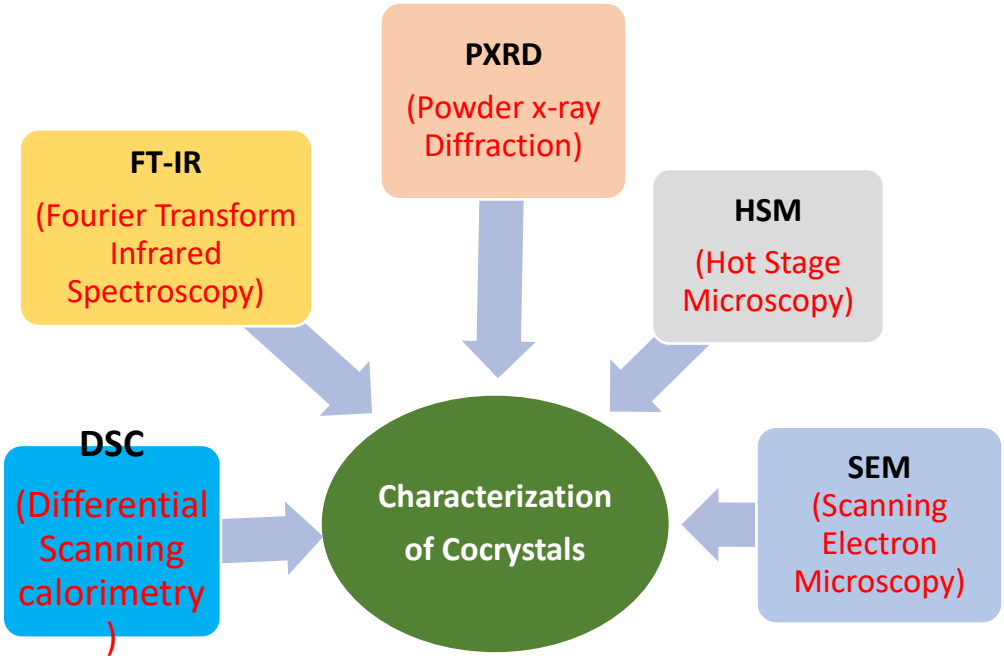

Figure 2: Characterization Technique of Cocrystals

ADVANTAGES OF COCRYSTALS

Cocrystallization offers several advantages in various fields, including pharmaceuticals, materials science, and chemistry:

Improved Solubility: Active pharmaceutical ingredients (APIs) that aren't very soluble can have their solubility increased by cocrystals. which can lead to improved bioavailability and more effective drug formulations. For example, theophylline, a poorly soluble drug used to treat asthma, forms a cocrystal with caffeine. The cocrystal structure increases theophylline's solubility by facilitating hydrogen bonding between the two compounds, making it more readily dissolvable in bodily fluids. This enhanced solubility leads to quicker absorption and improved therapeutic effectiveness. Thus, cocrystals serve as a valuable strategy to overcome solubility challenges, ensuring better bioavailability and more efficient drug delivery for a wide range of pharmaceutical compounds[18.33].

Tailored Properties: Cocrystals allow for the modification of API properties such as melting point, stability, and hygroscopicity, making it possible to customize drugs for specific applications. Cocrystals enhance tailored properties by combining two or more distinct molecular components to create a new crystalline material with precisely engineered characteristics. For instance, saccharin and sodium saccharin can form a cocrystal, enhancing sweetness while reducing bitterness. By selecting the appropriate coformer, cocrystals can modify physical properties like melting points, stability, and solubility, offering desirable attributes for pharmaceuticals, agrochemicals, and materials science. The deliberate design of cocrystals allows for fine-tuning properties to meet specific requirements, making them valuable in creating custom materials with improved performance and functionality for a variety of applications[34].

Patent Extension: Developing cocrystals can extend the patent life of a drug by creating a new crystalline form with improved properties, providing companies with market exclusivity for a longer period. cocrystals enable companies to secure additional patents. These patents protect the unique cocrystal formulations, extending market exclusivity beyond the original API patent. This extra protection can significantly prolong a drug's commercial life, providing more time for pharmaceutical companies to recoup research and development investments and generate revenue. Furthermore, cocrystals often improve drug properties, enhancing therapeutic efficacy, which can further justify their market presence. In essence, cocrystals are a powerful tool for maintaining a competitive edge and maximizing returns on pharmaceutical innovations[35].

Reduced Toxicity: By modifying the properties of its components cocrystallization has the ability to decrease toxicity. When drugs or chemicals form cocrystals their toxicity levels may be reduced due, to changes in solubility, bioavailability and release rate within the body. This results in a controlled delivery method ultimately decreasing the likelihood of adverse effects and toxicity associated with these compounds. Utilizing co crystallization is therefore an approach, in the field of pharmaceuticals as it helps enhance both drug safety and efficacy[36].

Regulatory Approval: Cocrystallization plays an important role in obtaining approval for pharmaceuticals. It has the potential to enhance the stability and bioavailability of ingredients ensuring performance of the drugs. By improving these aspects co crystals increase the likelihood of meeting safety and efficacy standards set by regulators. Moreover co crystallization can also assist in securing patent protection thereby extending market exclusivity, for drug manufacturers. Overall co crystallization contributes significantly to a drug development process enabling companies to obtain regulatory approval and compete effectively in the market (Table 2)[37.]

Enhanced Stability: Co-crystals enhance stability by forming a crystalline lattice where the active pharmaceutical ingredient (API) interacts with another molecule, stabilizing it. This interaction can protect the API from degradation due to factors like moisture, heat, or light. Co-crystals can also alter the dissolution rate and solubility of the API, which can lead to more controlled release and improved stability in formulations. By reducing the propensity for degradation, co-crystals help ensure that the API maintains its potency and effectiveness over a longer shelf life[38,39].

Intellectual Property: Co-crystallization provides significant advantages in intellectual property rights. It allows pharmaceutical companies to secure new patents by creating novel crystalline forms of existing compounds, extending exclusivity and preventing generic competition. These patented co-crystals can enhance the market value of a drug, attract potential investors or partners, and create formidable barriers to entry for competitors. Licensing and collaboration opportunities also arise, enabling revenue generation. In essence, co-crystallization is a potent strategy for protecting and maximizing the intellectual property rights associated with pharmaceutical compounds. Moreover, Co-crystallization is an emerging technique in the pharmaceutical industry that has acquired interest for the scientist to work in this field. Some examples of USFDA and EMA approved pharmaceutical drug products are mentioned below[6].

Table 2: Marketed formulations of co-crystal[40-43]

Sr. No.	Drug Name	Brand Name	Use
1	Co- crystals of carbamazepine	Tegretol	Anticonvulsant or Anti-epileptic
2	Co-crystals of fluoxetine Hydrochloride	Prozac	Antidepressant
3	Co-crystals of Itraconazole	Sporanox	Antifungal
4	Co-crystals of Sildenafil	Viagra	Erectile disfunction
5	Co-crystals of Escitalopram oxalate- oxalic Acid	Lexapro	Antidepressant
6	Co-crystals of Sacubitril-disodium valsartan	Entries	Chronic heart failure
7	Co-crystals of Ertugliflozin-L-Pyroglutamic acid	Steglatro	Antidiabetic
8	Co-crystals of Tramadol-celecoxib	E-58425	Acute postoperative pain
9	TAK -020	Gentisic acid	Rheumatoid arthritis
10	Ipragliflozin with L-Proline	Suglat	Antidiabetic

CONCLUSION AND FUTURE PROSPECTIVES

The potential of co crystallization techniques, in academics and industries is highly promising for the future. In the field of pharmaceuticals, co crystals have the potential to revolutionize drug development by overcoming issues related to solubility and bioavailability. This enables the creation of patient friendly medications. As regulatory agencies increasingly recognize the value of co crystals in improving drug properties we can expect an increase in their integration into pipelines. In chemistry co crystallization will continue to play a role in understanding interactions and supramolecular chemistry. Utilization of cocrystals to design molecules with properties for purposes such as catalysis, sensing and other applications. Additionally, co crystallization aligns with the growing emphasis on chemistry and friendly processes due to its sustainable nature. It reduces waste and energy consumption compared to methods. Moreover, Co crystallization techniques are expected to drive innovation across fields in the years. Their versatility and ability to address standing challenges position them as technologies with a bright future ahead. As research progresses, in this area we can anticipate a range of applications that will impact our daily lives while contributing to scientific advancements and industrial progress. Co-crystallization appeared as a convenient revolutionary tactics for new drug discovery as compared to other methods of solid-state moderation utilizes in the pharmaceutical industry for the synthesis of new molecules, in nutraceutical co-crystals and enhanced solubility resulting in increased bioavailability and chiral resolution. In conclusion, this review offers a thorough exposition, complete with illustrative instances, of the techniques for preparation, physicochemical attributes, and diverse uses of co-crystals. The development of pharmaceutical co-crystals for use in healthcare applications will be accelerated by the use of ground-breaking technology and stringent regulatory guidelines. In the upcoming years, it is projected that more therapeutic products based on co-crystals would be available to patients.

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