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Enhanced Solubility and Dissolution by Drug-drug Cocrystals: A Comprehensive Review

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Abstract : Physicochemical properties such as stability, particle size, powder flowability, taste, hygroscopicity, solubility, and compatibility of active pharmaceutical ingredients (APIs) are critical for the therapeutic efficacy and production costs of solid dosage forms. Oral drug delivery systems largely depend on the solubility and dissolution rates of drug molecules, with many drugs exhibiting low water solubility and bioavailability. To address these issues, several solid-state strategies have been employed, including salts, polymorphs, hydrates, solvates, and cocrystals. Among these, pharmaceutical cocrystals have gained significant attention for their ability to improve the physicochemical properties of APIs without altering their pharmacological nature. Cocrystals, which consist of two or more neutral molecules in a stoichiometric ratio linked by noncovalent bonds, have shown promise in enhancing drug solubility, stability, and bioavailability. Regulatory authorities, including the FDA and EMA, have recognized the importance of cocrystals, providing guidelines for their classification and application. This review summarizes the preparation methods, physicochemical property modulation, and applications of pharmaceutical cocrystals, highlighting their role in advancing drug development.

Keywords : Pharmaceutical cocrystals, solubility, dissolution, solid-state strategies, physicochemical properties, bioavailability, drug development, FDA guidelines, EMA guidelines.

1.Introduction

Physicochemical properties such as stability, particle size, powder flowability, taste, hygroscopicity, solubility and compatibility of active pharmaceutical ingredients (APIs) are essential characteristics that influence the therapeutic effectiveness and production costs of solid dosage forms. In oral drug delivery systems, absorption from the gastrointestinal tract largely depends on the solubility and dissolution rate of the drug molecules. However, currently approximately 90% of new chemical entities and 40% of drugs currently available on the market belong to the biopharmaceutical classification system "BCS". Classes II and IV, characterized by low water solubility and low bioavailability. As a result, the absorption of drugs in the gastrointestinal tract is limited and therefore the clinical use of drugs is difficult. Of course, the physicochemical properties of pharmaceutical solids have a significant influence on the effectiveness of drugs. It is known that the stacking of atoms in the unit cell and crystal lattice directly influences the properties of a particular crystalline material. Therefore, modification of the physicochemical properties of solid dosage forms can be achieved by adjusting the crystal conditioning system. [1], [2] To date, several solid-state strategies have been used to optimize the properties of drugs such as salts, polymorphs, hydrates, solvates, and cocrystals. However, these approaches have limitations; B, only molecules with the appropriate ionizable groups are suitable for salt formation, and hydrates/solvates are often not stable because water/solvent molecules tend to be lost over time. For comparison, every API (regardless of its acidic, basic or non-ionized form) has the ability to form cocrystals with the corresponding conformer.[3]

In the last two decades, pharmaceutical cocrystals have attracted the attention of science and the pharmaceutical industry due to their ability to improve the physicochemical properties of active ingredients by modifying the crystal structure without altering their pharmacological nature. With the development of the cocrystal field, several pharmaceutical cocrystals such as Steglatro, Entresto and others have been approved and are in clinical trials.[4]Pharmaceutical cocrystals are defined as crystals consisting of two or more neutral molecules that differ in a stoichiometric ratio and are linked by noncovalent bonds (e.g., hydrogen bonds, van der Waals, where at least one of the ingredients is API and the others are pharmaceutically acceptable ingredients.

Since the early 2000s, it has been recognized that cocrystal engineering could be a potential approach to improve the physicochemical properties of pharmaceutical products, leading to the development of several representative pharmaceutical cocrystals. This groundbreaking work highlighted the role of crystal engineering and supramolecular synthons in the pharmaceutical design of cocrystals and promoted the development of a cocrystal-based approach to improve drug performance. Many robust supramolecular synthons have been identified that play an important role in cocrystal design and provide a driving force for the formation of pharmaceutical cocrystals. Several common functional groups are particularly susceptible to the formation of supramolecular cocrystalline synthons, such as carboxylic acids, amides, and alcohols. There are two different categories of supramolecular synthons, including supramolecular homosynthons and supramolecular heterosynthons. Supramolecular homosynthons form self-complementary functional groups such as dimers of carboxylic acids or dimers of amides. In contrast, supramolecular heterosynthons are organized by distinct but complementary functional groups (e.g., carboxylic acid, epyridine18, and aromatic alcoholic nitrogen hydrogen bonds.[5], [6], [7] With the rapid development and increasing application of pharmaceutical cocrystals, regulatory authorities are increasingly concerned about the importance of pharmaceutical cocrystals. In 2011, the US Food and Drug Administration (FDA) published draft guidance for the first time classifying pharmaceutical cocrystals as pharmaceutical intermediates, defining them as “molecular complexes of dissociable excipients in which the active ingredient and the excipient are present in the same crystal lattice". However, industrial and academic researchers found this definition too simplistic to clearly distinguish cocrystals. In 2016, revised FDA guidelines described cocrystals as “crystalline materials composed of two or more different molecules in the same crystal lattice and connected by non-ionic, noncovalent bonds.” In 2018, the FDA described pharmaceutical cocrystals as "crystalline materials composed of two or more different molecules, one of which is an active ingredient, in a specified stoichiometric ratio in the same crystal lattice, linked by non-ionic, noncovalent bonds.

Coformer is “a component that interacts non-ionically with the API in the crystal lattice, is not a solvent (including water), and is generally non-volatile”. The European Medicines Agency (EMA) defined a cocrystal as There are two different categories of supramolecular synthons, including supramolecular homosynthons and supramolecular heterosynthons. Supramolecular homosynthons form self-complementary functional groups such as dimers of carboxylic acids or dimers of amides. In contrast, supramolecular heterosynthons are organized by distinct but complementary functional groups (e.g., carboxylic acid, pyridine, and aromatic alcoholic nitrogen hydrogen bonds). With the rapid development and increasing application of pharmaceutical cocrystals, regulatory authorities are increasingly concerned about the importance of pharmaceutical cocrystals. In 2011, the US Food and Drug Administration (FDA) published draft guidance for the first time classifying pharmaceutical cocrystals as pharmaceutical intermediates, defining them as “molecular complexes of dissociable excipients in which the active ingredient and the excipient are present in the same crystal lattice". However, industrial and academic researchers found this definition too simplistic to clearly distinguish cocrystals.

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Agency (EMA) defined a cocrystal as homogeneous crystalline structures consisting of two or more components in a certain stoichiometric ratio, where the arrangement in the crystal lattice is not based on ionic bonds (as in salts)". Compared to the FDA definition of cocrystals, the EMA described cocrystals as valid alternatives to salts with the same API. In other words, the cocrystal is considered to be the same as the active ingredient, except that it has different pharmacokinetic properties. In this review, we summarize recent developments in the field of pharmaceutical cocrystals, including preparation methods and modulations of physicochemical properties and applications of cocrystals.[8], [9]

The solution-based method (including solvent evaporation, anti-solvent method, cooling crystallization, reaction co-crystallization and suspension conversion) and the solid-state method (clean milling, liquid-assisted milling and melt crystallization) are presented. Various modulated properties and applications of cocrystals are then discussed, including physical and chemical stability, mechanical and optical properties, and in vitro and in vivo performance. crystalline structures consisting of two or more components in a certain stoichiometric ratio, where the arrangement in the crystal lattice is not based on ionic bonds (as in salts)". Compared to the FDA definition of cocrystals, the EMA described cocrystals as valid alternatives to salts with the same API[10]. In other words, the cocrystal is considered to be the same as the active ingredient, except that it has different pharmacokinetic properties The solution-based method (including solvent evaporation, anti-solvent method, cooling crystallization, reaction co-crystallization and suspension conversion) and the solid-state method (clean milling, liquid-assisted milling and melt crystallization) are presented. Various modulated properties and applications of cocrystals are then discussed, including physical and chemical stability, mechanical and optical properties, and in vitro and in vivo performance.[11], [12], [13], [14]

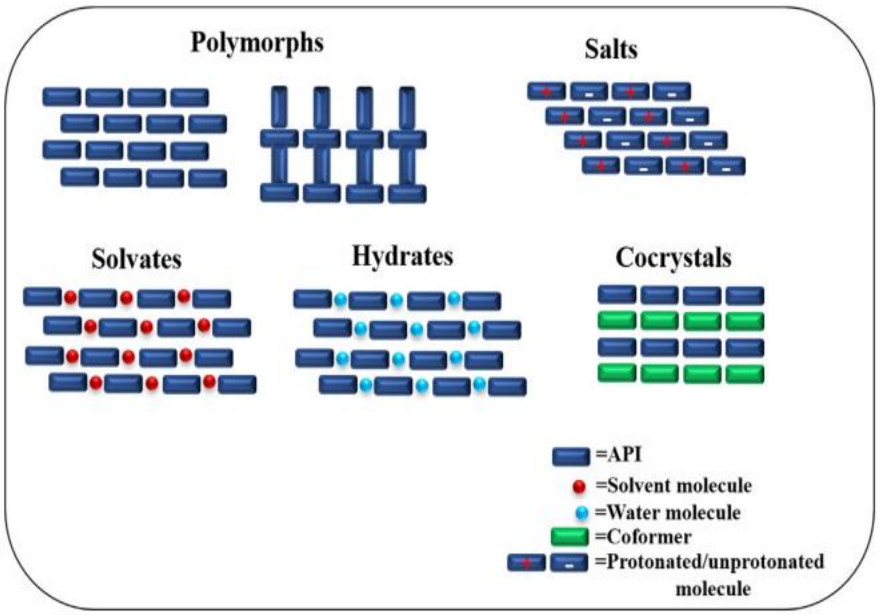

Fig 1: Different solid forms of active pharmaceutical ingredients[14]

2. Cocrystal preparation:

Various methods have been extensively documented for preparing pharmaceutical cocrystals, including solid-state grinding, solution reaction crystallization, solvent evaporation, slurry conversion, and hot melt extrusion. However, determining the most suitable method for cocrystal formation remains primarily empirical. These approaches can generally be categorized into solution-based and solid-based methods. In solution-based methods, significant solvent consumption is necessary to dissolve the cocrystal constituents. The choice of solvent is also critical as it can influence the intermolecular interactions between the active pharmaceutical ingredient (API) and the coformer, consequently impacting the outcomes of the cocrystallization process.[14]

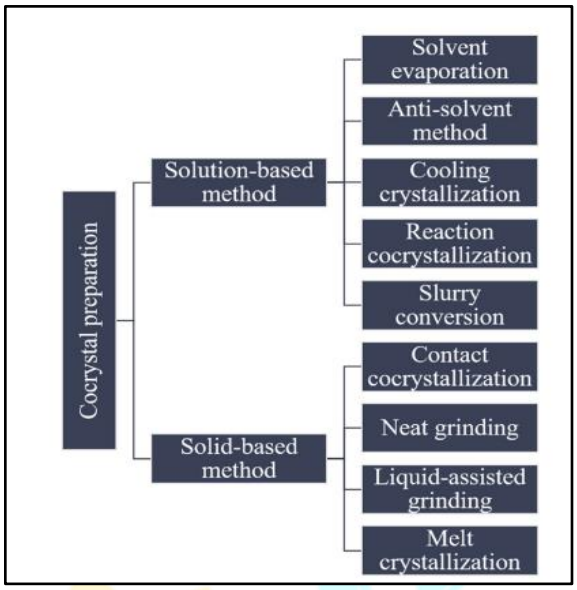

Fig 2: Common methods for cocrystal preparation[14]

2.1 Solution-based methods: The ideal scenario is to have the cocrystal in a supersaturated state while the API and coformer are saturated or undersaturated under the experimental conditions. The degree of supersaturation with respect to the cocrystal in the solution is crucial for cocrystallization and can be adjusted by the concentrations of the API and coformer. To guide the formation of cocrystals, it's important to establish a phase diagram that describes the conditions for thermodynamic stability. This ensures that the cocrystal remains in the thermodynamically stable region and prevents the crystallization of pure reactants. The location of thermodynamically stable cocrystal phase regions is primarily determined by the solubility of the reactants. Ternary phase diagrams can illustrate how to achieve the supersaturation of cocrystals when the reactants are in a saturated or unsaturated state, based on the solubilities of the reactants in noncongruently saturating solvents. By using non-equivalent reactant concentrations, the cocrystal can be generated within the stable region.[14], [15], [16].

2.2 Solvent evaporation methods: The solvent evaporation method is widely used for preparing cocrystals, especially for creating high-quality single-crystal cocrystals suitable for structural analysis through single-crystal X-ray diffraction. In this approach, the cocrystal constituents dissolve completely in an appropriate solvent at a suitable stoichiometric ratio, and then the solvent is evaporated to obtain the cocrystal. The choice of solvent significantly influences cocrystallization and may impact the solubility of the reactants. It's important that the cocrystal components are congruently soluble in the chosen solvent, as the cocrystallization process can fail if it occurs between two incongruently soluble components. This may lead to the less soluble component precipitating preferentially, resulting in a solid mixture of cocrystal and cocrystal components, or a failure to form cocrystals.[16]

2.3 The antisolvent method: The antisolvent method, also known as precipitation or solvent-antisolvent precipitation, is a technique used to produce particles or crystals from a liquid solution. In this method, a solvent containing the dissolved substance is rapidly mixed with a second liquid, known as the antisolvent, in which the solute is poorly soluble. This sudden reduction in solubility causes the solute to precipitate out of the solution in the form of particles or crystals. The antisolvent method is commonly used in various industries such as pharmaceuticals, food, and chemical manufacturing to produce fine particles with specific characteristics. It offers control over particle size, morphology, and physical properties, making it a valuable process in the production of various materials. Additionally, the antisolvent method is often utilized in the purification and isolation of compounds from a solution. The selection of solvents and antisolvents, mixing conditions, and other process parameters are crucial in determining the final characteristics of the precipitated particles. Careful consideration of these factors is essential to achieve the desired product properties.[14]

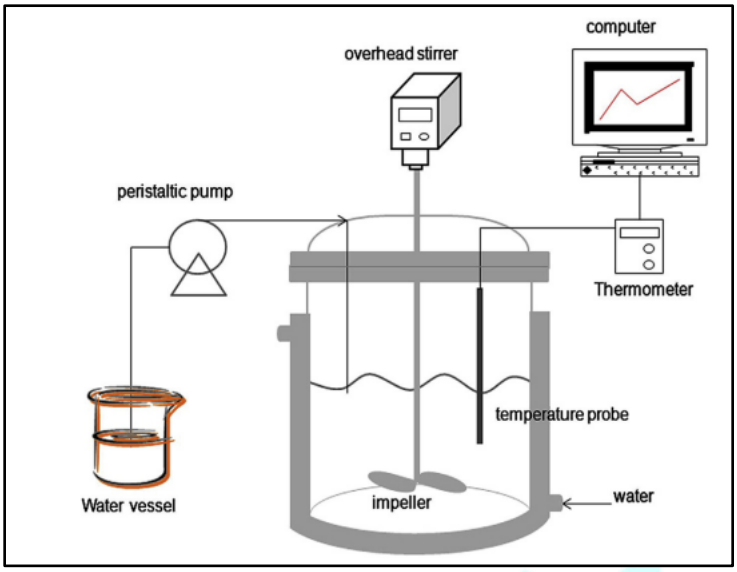

Fig 3: Experimental apparatus for the anti-solvent cocrystallization process[14]

2.4 Cooling crystallization: Cooling crystallization is a commonly used technique for producing large-scale and purified crystals. The properties of the crystals, including size distribution, purity, morphology, and polymorphism, are influenced by the local supersaturation, which is determined by process parameters such as the transformation of mass and heat. Therefore, precise control of these factors is essential, considering the multiple solid-liquid equilibria in the cocrystal preparation process. The operating region in the crystallization process is influenced by the stoichiometry of the cocrystal and the thermodynamic stability zone of the cocrystal at the initial and final temperatures. Numerous studies have demonstrated the effectiveness of this method for the scale-up manufacturing of cocrystals. When utilizing the cooling crystallization method, it's crucial to consider and control the process parameters to achieve the desired crystal properties. Additionally, understanding the thermodynamic stability and stoichiometry of the cocrystal is important for successful implementation of this technique in large-scale production.[14], [15]

2.5 Reaction cocrystallization: Reaction cocrystallization is a viable method for forming cocrystals when the cocrystal components have varying solubilities. This technique involves mixing reactants with non-stoichiometric concentrations to produce supersaturated solutions, ultimately leading to the precipitation of cocrystals. In reaction cocrystallization, the nucleation and growth of cocrystals are influenced by the capacity of the reactants to reduce the solubility of the cocrystals. By leveraging the differing solubilities of the cocrystal components, this method facilitates the controlled formation of cocrystals with specific properties. The ability to manipulate and control the solubility of cocrystals through reactant interactions makes reaction cocrystallization a valuable approach for the targeted synthesis of cocrystals. This method provides a pathway for tailoring cocrystal formation based on the unique solubility characteristics of the individual components.[14], [15]

2.6 Slurry conversion: The slurry conversion method involves a solution-mediated phase transformation process, which requires the addition of excess cocrystal components to the solvent. During the slurry, each component gradually dissolves and forms a complex, thereby promoting the nucleation and growth of cocrystals. As cocrystals begin to form, the concentrations of the reactants decrease, leading to undersaturation with respect to the reactants, which enables the continued dissolution of the cocrystal components. To effectively implement the slurry conversion method, the operational range of the component's concentration and temperature is guided by the ternary phase diagram, which facilitates the generation of cocrystal supersaturation. This approach allows for controlled cocrystal formation by strategically managing the solubility and dissolution dynamics of the cocrystal components in the solvent.

2.7 Liquid Assisted Grinding (LAG): Is a technique used in the field of mechanochemistry for the synthesis of various compounds, including pharmaceutical cocrystals. It involves the combination of solid reactants

with a small quantity of liquid (typically a solvent) during the grinding process. The addition of the liquid aids in promoting the reactivity of the solid reactants, thereby facilitating the formation of the desired compound. In the context of cocrystal synthesis, Liquid Assisted Grinding is utilized to enhance the reactivity and promote the formation of cocrystals by providing an environment that facilitates molecular interactions between the solid reactants. This method has been shown to be effective in promoting the formation of cocrystals with specific properties, such as improved stability, solubility, and bioavailability. When implementing Liquid Assisted Grinding for cocrystal synthesis, the choice of solvent, the ratio of liquid to solid reactants, and the grinding conditions play a crucial role in determining the characteristics of the resulting cocrystals. This method offers a convenient and efficient approach for the preparation of cocrystals with tailored properties, making it a valuable tool in pharmaceutical and materials science research.[14], [15]

3. Physicochemical properties of cocrystals:

2.1 Physical properties: Cocrystallization is an effective method for enhancing the physical properties and preserving the physical stability of drug substances, which can undergo unintended physical changes during manufacturing and storage. This approach proves to be a powerful strategy for improving the physical characteristics of pharmaceutical compounds, helping to maintain their stability and performance when subjected to various production and storage conditions.

2.2 Melting point: For manufacturers, solid drug forms provide a convenient way to purify, identify, transport, and store drugs. For patients, solid forms are more convenient to carry and administer than liquid forms. However, some drugs exist in a liquid state at room temperature due to their low melting points. Cocrystallization has the potential to alter the melting point of liquid drugs by incorporating a suitable coformer into the crystalline lattices.

2.3 Chemical stability: The chemical degradation of drug substances during manufacturing and storage poses a significant challenge in the development of stable pharmaceutical formulations. To address this issue, pharmaceutical cocrystals have emerged as a promising approach to mitigate the chemical instability of active pharmaceutical ingredients (APIs) in the solid state. The distance between reactive sites plays a key role in the chemical stability of crystalline solids. For example, the drug drug cocrystal of vitamin D3 and vitamin D2 with a greater distance between reactive sites in vitamin D resulted in improved chemical stability. Nicorandil (NCD) is an effective drug for cardiovascular disorders, suffering from low chemical stability under high humidity, heat and mechanical stress. In the crystal packing of NCD, the distance between lone pair electrons on pyridines (N1) and C8 of the nearby NCD molecule is 3.367 A˚ (Fig. 13B), which is shorter than the sum of the van der Waals radii of C and N (3.484 A˚). The reaction cavity refers to the space near the reaction groups in the crystal structure. A large reaction cavity causes high molecular mobility and a high probability for the occurrence of solid-state chemical reactions. Epalrestat (EPR), which is used for the treatment of diabetic neuropathy, is susceptible to the photodegradation of isomerization (E,Z to Z,Z) after exposure to ambient light irradiation. This problem not only affects the manufacturing process but also correlates to the pharmacological effect of the drug.

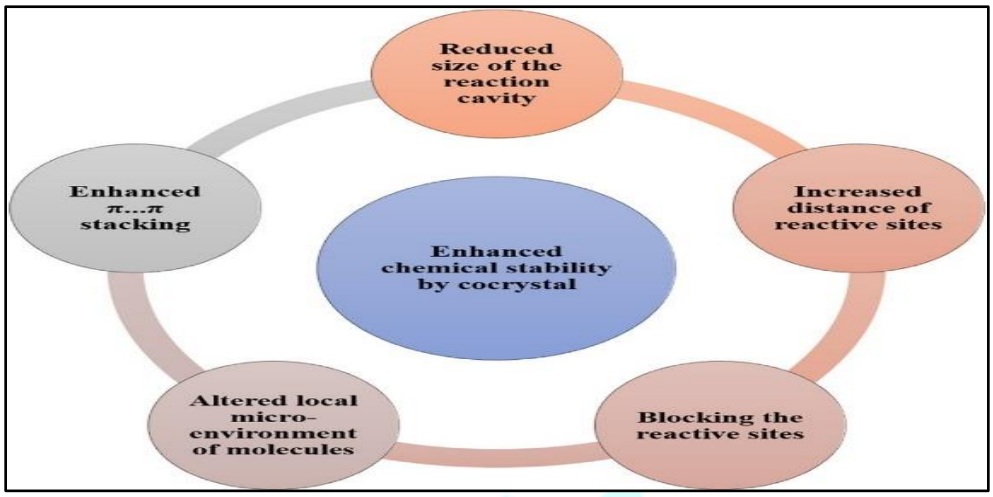

Fig 4: Diagram of the mechanisms by which cocrystals improve the chemical stability of APIs[14]

2.4 Mechanical properties: The mechanical properties of crystalline materials play a crucial role in various manufacturing processes of solid dosage forms, including blending, milling, granulation, tableting, and coating. When it comes to solid materials, mechanical deformation mechanisms include elastic, plastic, viscoelastic, and fragmentation. Typically materials with better plasticity properties may demonstrate superior compressibility, which refers to a permanent and irreversible change after the removal of stress. However, the poor mechanical properties of many organic compounds present a challenge in developing tablet formulations. Cocrystallization has been shown to effectively enhance the mechanical properties of drugs by modifying crystal packing.

2.5 Optical properties: The optical properties of drugs could be useful in biomedical applications. For example, drugs that exhibit strong fluorescence can be used as biocompatible probes for bioimaging and lipid droplet imaging in cells and in tissue slices. The molecular stacking, crystal packing arrangement and intermolecular interactions usually play important roles in the optical properties of solid materials. Recently, cocrystal engineering has shown its potential to modify the optical properties of pharmaceuticals. The following examples shows the modification of the optical behavior of drugs by introducing coformers into the crystal lattices.

2.6 Bioavailability: Bioavailability refers to the fraction of the drug that reaches systemic circulation. Numerous drug candidates failed in the preclinical stage during drug development because of the low bioavailability. In the last decade, cocrystallization has shown its potential to improve in vivo performance by enhancing the solubility, and bioavailability of poorly water-soluble drugs Ketoconazole, a broad-spectrum imidazole antifungal agent, exhibits low bioavailability because of its very low water solubility. The cocrystal of ketoconazole–p-aminobenzoic acid showed 10-fold higher aqueous solubility and 6.7-fold higher oral bioavailability than crystalline ketoconazole. Ketoconazole, a broad-spectrum imidazole antifungal agent, exhibits low bioavailability because of its very low water solubility. The cocrystal of ketoconazole–p-aminobenzoic acid showed 10-fold higher aqueous solubility and 6.7-fold higher oral bioavailability than crystalline ketoconazole.[17], [18]

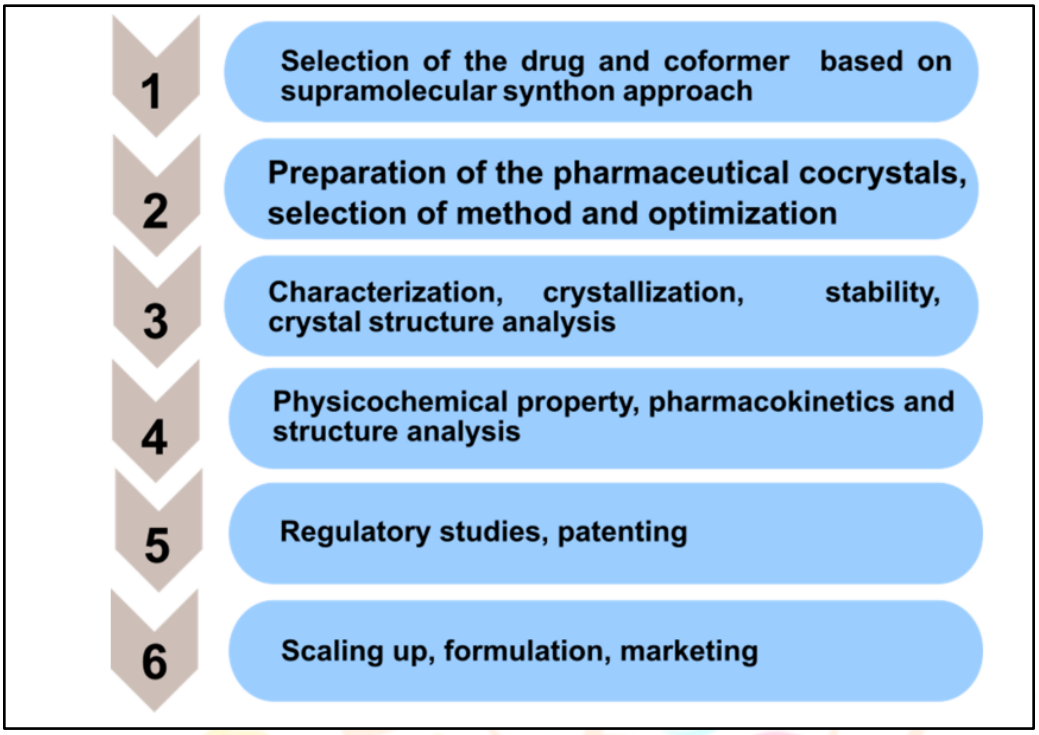

Fig 5. Key steps in the workflow of pharmaceutical cocrystals design to synthesis to drug[15]

4. Various characterization steps:

3.1 Differential Scanning Calorimetry (DSC): Instrument system used to study the thermal analysis. The hermetically sealed standard pans held samples that ranged in weight from 5 to 10 mg at a heating rate of 10°C per minute (between 30°C and 350°C). Inert nitrogen is used to provide a controlled environment for the experiments, which were run at a flow rate of 40 mL/min.

3.2 Powder X-ray Diffraction (PXRD): X-ray source Cu-K radiation (ʎ = 1.54060 Å) is utilized in conjunction with the DIFFRAC.EVA V2.1 software on a Bruker D8 advanced diffractometer to acquire PXRD. Samples needs to be mounted on sample holders and scanned with steps of 0.01 ° (2θ) and 0.1 sec per step, with a scanning interval range of 5-60 ° (2θ).

3.3 Fourier Transform Infrared Spectroscopy (FTIR): The FTIR-spectra of all the samples needs to be performed using FTIR-6100 Type A (JASCO Corporation, Tokyo, Japan) over a specific range of 4000-400 cm−1 using the KBr dispersion method.

3.4 Polarized Light Microscopy: Each sample needs to be spread on a clear glass slide and samples observed under 10X magnification using polarized light microscope (Nikon, Kanagawa, Japan).

3.5 Drug content: Precisely weighed quantity of cocrystal equivalent to 10 mg of drug dissolved in ethanol and volume is adjusted in 10 mL of volumetric flask. Absorbance can be recorded using UV-spectrophotometer (Shimadzu UV1800). All the experiments needs to be carried out in triplicate (n=3).[14], [15]

5. Micromeritic characterization:

Flow properties of powdered formulation have direct impact on particle size, shape, particle size distribution, surface texture, moisture content. Thus, variables that could provide insight into the flow of prepared cocrystals. Hence, Bulk density, Tapped density, Compressibility index, Hausner ratio, and Angle of repose were assessed.

4.1 Bulk density (BD): The BD can be checked by transferring the weighed quantity of sample into the 5mL of graduated cylinder. The mass to bulk volume ratio recorded as Bulk density.

4.2 Tapped density (TD): Tapped density (TD) determined by transferring a weighed quantity of the sample into a 5 mL measuring cylinder, which is then placed in a Tapped Density apparatus. The initial volume (V0) of the sample in the cylinder is recorded, and then the cylinder is subjected to 100 taps. The final volume (Vt) after tapping is recorded. The mass of the sample (M) to the tapped volume ratio is then calculated as the tapped density (TD) using the formula: TD = M / Vt. This process is a common method for determining the tapped density of powders or granular materials.

4.3 Compressibility index (CI): The CI is an indication of the compressibility of a powder. Calculated by using formula: CI = (TD – BD/TD) x 100

4.4 Hausner ratio (HR): HR determined using formula: HR = TD/BD

4.5 Angle of repose (AR): This is used to measure the resistance to particle movement. AR determined using equation: AR (θ) = tan-1 (h/r).[14], [15]

6. Stability study:

For three months, a stability study of prepared samples needs to be conducted at 40°C /75% RH and 25°C /60% RH. The excess sample amount needs to be stored in glass vials in a stability chamber. Solubility, % drug release, melting point, and % drug content was analyzed at 1, 2 and 3 months.

7. Dissolution Study:

The dissolution study of the size 0 capsules needs to be conducted according to USP II (Paddle) method in a temperature-controlled environment at 37 ± 2°C. The dissolution media used can be 900 mL of 0.1 N HCl, with the paddle stirring speed maintained at 75 ± 2 rpm. During the study, 5 mL samples were withdrawn from the dissolution flask at specific time intervals (5, 10, 15, 20, 30, 45, and 60 min), with the volume kept constant by replacing the same amount with fresh dissolution media. This process was repeated three times (n=3) to ensure reliability.

Following the sample withdrawal, each aliquot filtered through a 0.45µm nylon membrane filter, diluted if necessary, and then subjected to HPLC analysis. Subsequently, the f1 (difference factor) and f2 (similarity factor) were calculated using specific formulas. These factors are used to compare the dissolution profiles of the studied formulation with that of the marketed product.

$$f_1 = \left\{\left[\sum_{t=1}^{n}|R_t - T_t|\right] \Big/ \left[\sum_{t=1}^{n} R_t\right]\right\} \times 100$$

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

The f1 value indicates the difference in percentage between the two dissolution profiles at each time point, with a range of 0-15 indicating similarity. On the other hand, the f2 value is based on the logarithmic reciprocal square root transformation of the sum of squared error and provides a range of 50-100, where high values indicate greater similarity between the two dissolution profiles. Based on these calculations and comparison with the marketed product, it is possible to evaluate the similarity of the dissolution behavior of the studied formulation, providing critical insights into its performance in the dissolution media.[16], [19]

8. Application of cocrystallization in industrial application:

To effectively utilize the potential of cocrystals in enhancing drug forms, it is essential to optimize and develop cocrystallization techniques suitable for industrial application. Industrial-scale production of cocrystals necessitates methods that are scalable, robust, and environmentally friendly without compromising product

quality. The selection of cocrystallization techniques should consider criteria such as API-conformer lability, solubility, stability of components, susceptibility to forming polymorphs, amorphous states, or solvates. This selection process greatly impacts the purity, morphology, and particle size distribution of the cocrystals. Though numerous cocrystallization techniques have been reported, only a limited number of methods are scalable. Some scalable cocrystallization techniques include spray drying, spray congealing, and hot melt extrusion (HME). Their successful application in an industrial setup requires a comprehensive understanding of the underlying theory, the critical process parameters essential for achieving high yield and superior product quality, and the impact of other excipients on the cocrystal composition during manufacturing. Therefore, developing a deep understanding of these techniques, controlling essential process parameters, and considering the influence of additional excipients are crucial for the successful industrial application of scalable cocrystallization methods. Spray congealing is a relatively new cocrystallization technique in which molten API and conformer mixture is passed through an atomizer. The atomizer breaks the liquid into fine droplets, and these droplets are cooled by a cocurrent stream of cooling gas. This process leads to the solidification of liquid into fine particles, forming cocrystals. The disadvantage of the spray congealing technique is the requirement to melt the components, which limits its usage for thermolabile API.[20]

9. Commercially Available Cocrystals:

Cocrystallization has proven to be successful in the pharmaceutical sector, as demonstrated by the approval and availability of drugs based on cocrystals in the market. For instance, Suglat®, Entresto®, and Steglatro® are examples of marketed drugs containing cocrystal-based active pharmaceutical ingredients. An instance of this success is seen in the application of Suglat®, which is utilized for diabetes treatment and contains ipragliflozin as the API and L-proline as the conformer. Ipragliflozin, a sodium-glucose cotransporter 2 inhibitor, is prone to nonstoichiometric absorption of water (conversion to hydrate) when stored. Cocrystallizing it with L-Proline helps to prevent hydrate formation, ensuring stability. Astellas Pharma and Kotobuki Pharmaceutical collaborated in the development of Suglat®, which received approval for marketing in Japan in 2014.

- Entresto® is a cocrystallized medication created by Novartis, designed to reduce the risk of heart failure. It combines valsartan, an angiotensin II receptor blocker, with sacubitril, a neprilysin inhibitor, in a fixed-dose formulation. The cocrystal structure of Entresto® consists of anionic forms of valsartan, sacubitril, sodium cations, and water molecules in a specific molar ratio, along with other excipients. This represents a notable advancement in improving the pharmacokinetics of active ingredients through cocrystallization. The bioavailability of valsartan in Entresto® is 50% higher than when administered alone.
- Steglatro® is a medication for type-2 diabetes mellitus. It contains ertugliflozin, a sodium–glucose cotransporter 2 inhibitor, and L-pyroglutamic acid as a conformer. This is an example of improvement of stability of active ingredients by cocrystallization. Ertugliflozin is an unstable amorphous material. The stability and physicochemical properties of ertugliflozin are improved by cocrystal formation with L-pyroglutamic acid in a 1:1 ratio.
- Chloral betaine (beta-chlor®) is another example, which was identified as a cocrystal at a later stage (2016). Chloral is a sedative drug. The components of the cocrystal are chloral hydrate and betaine. The formation of cocrystal imparts thermal stability to the parent compound. The melting point of the cocrystal was reported to be 120°C, whereas the melting point of chloral hydrate is 60°C. In the cocrystal, chloral betaine exists as a charge-assisted diolcarboxylate heterodimer, with further Cl--O interactions forming a tetramer.[20]

10. Drug- Drug cocrystal combinations found:

Table 1: Drug- Drug cocrystal combinations found in various research projects[21]

Drug combination	Therapeutic category	Observations
Flufenamic acid with ethenzamide	NSAIDs	Increased solubility
Piroxicam with clonixin	NSAIDs	Enhanced hydration stability
Tramadol with celecoxib	NSAIDs	Optimized solubility and IDR
Aceclofenac and paracetamol	NSAIDs	Increased dissolution rate
Tenoxicam with salicylic acid	NSAIDs	Increased IDR
piroxicam with salicylic acid	NSAIDs	Pharmaceutical properties not evaluated
Meloxicam with aspirin	NSAIDs	44-fold increase in pH 7.4 phosphate buffer solubility along with improved C_{max} and bioavailability.
Metacetamol with levofloxacin	NSAIDs and antibacterial	Reduced hygroscopicity and improved photostability of levofloxacin
Ibuprofen with levetiracetam	NSAIDs and antiepileptic	Chiral resolution
Carbamazepine with indomethacin	Antiepileptic and NSAIDs	Pharmaceutical properties not evaluated
Celecoxib with nicotinamide	NSAID and skin restorative	Pharmaceutical properties not evaluated
Acemetacin with nicotinamide	NSAID and skin restorative	Increased solubility
Indomethacin with nicotinamide	NSAID and skin restorative	Pharmaceutical properties not evaluated
Naproxen with nicotinamide	NSAID and skin restorative	Increased IDR
Flufenamic acid, niflumic acid	NSAIDs and skin restorative	Pharmaceutical properties not evaluated

Aspirin with theophylline	NSAID and Antiasthmatic	Pharmaceutical properties not evaluated
Flufenamic Acid with theophylline	NSAID and Antiasthmatic	Increased solubility and enhanced hygroscopic stability
Diflunisal and diclofenac with theophylline	NSAID and Antiasthmatic	Increased solubility
Theophylline with aspirin	Antiasthmatic and NSAIDs	Pharmaceutical properties not evaluated
Sildenafil with aspirin	Erectile dysfunction and NSAIDs	Enhanced IDR

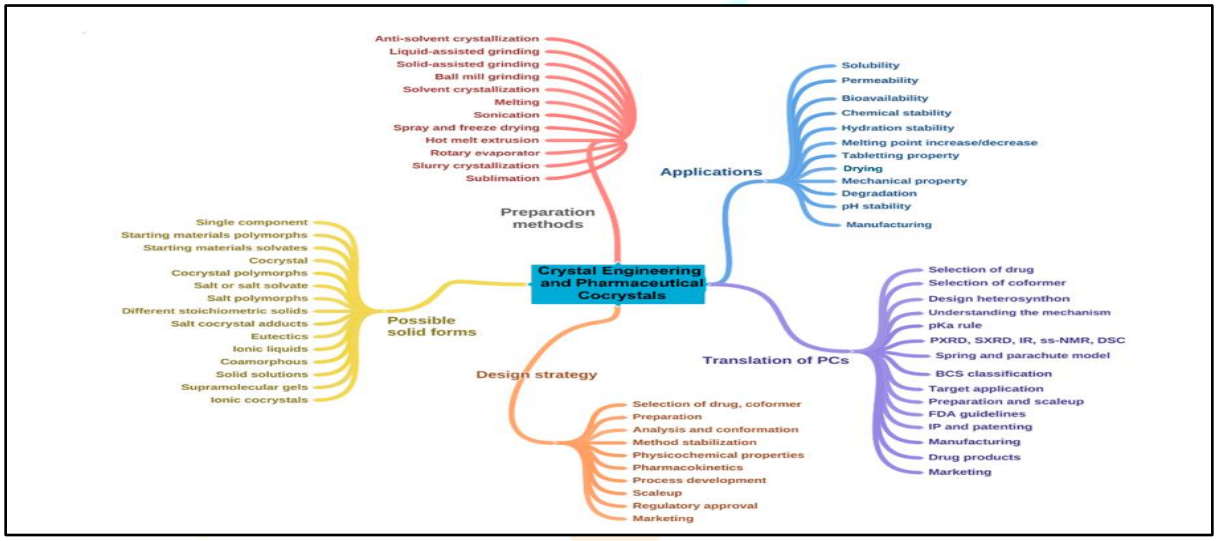

Fig 6. Design Strategy, Preparation Methods, Possible Products, and Applications of Pharmaceutical Cocrystals (PCs) and Salts [15]

10. Conflicts of interest :

There are no conflicts of interest to declare.

11. Funding :

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12. Data Availability :

All supporting data has been provided in the manuscript.

13. References:

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