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Review On: Pharmaceutical Co-Crystals

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Abstract: Pharmaceutical co-crystals have gained significant attention recently as a new solid form due to their ability to alter the physicochemical properties of Active Pharmaceutical Ingredients (APIs). However, advancing the pharmaceutical use of co-crystals remains challenging, with the need for high-throughput screening methods and techniques capable of producing co-crystals on an industrial scale still limiting their widespread use in the industry. This review offers a comprehensive overview of pharmaceutical co-crystals, focusing on the role of supramolecular chemistry, co-crystal design strategies, preparation methods, studies on physicochemical properties, mechanisms of solubility enhancement, and evaluation techniques. The article also discusses the impact of selecting the right process design and formulation in overcoming translational challenges. Finally, it briefly covers the applications and marketed drug products involving pharmaceutical co-crystals.

Key Words- Co-Crystal Formers, Co-Crystals, Crystal Engineering, Solid-State Characterization, Supramolecular Chemistry.

INTRODUCTION

Developing a new dosage form from a new chemical entity is a complex and multifaceted process that involves strategic and exploratory research in selecting and developing medical products. The molecule must pass through several stages of development to meet the required criteria. Insufficient knowledge about its properties and pharmaceutical manufacturing capabilities before clinical trials can result in complicated and expensive issues in later stages. In many cases, improving existing molecules is considered more advantageous than developing new ones. Most solid-state Active Pharmaceutical Ingredients (APIs) exist in either crystalline or amorphous forms. Crystalline materials are typically preferred for product development due to their higher stability compared to amorphous forms, which are less stable and may undergo re-crystallization over time.

Although crystal forms are stable, reproducible, and easier to purify than other types of solids, their major drawback is low solubility. Among all biopharmaceutical properties, solubility remains a key challenge for most Active Pharmaceutical Ingredients (APIs). Solubility and dissolution rates are critical factors in determining a drug's performance. Enhancing these properties without altering the molecular structure is one of the biggest challenges in the successful development of new drug products. To address this, various strategies have been employed to improve solubility and, consequently, the absorption and bioavailability of drugs. These strategies include milling techniques, hot melt extrusion, self-emulsification, solid dispersion, inclusion complexes, liposomal formulations, and the use of nanoparticles.

GENERAL ASPECTS OF CO-CRYSTAL FORMATION

One key characteristic of co-crystals, compared to other crystalline forms of Active Pharmaceutical Ingredients (APIs), is their ability to be manipulated through crystal engineering. Crystal engineering refers to the process of modifying the crystal packing of a solid material by altering the internal arrangement of molecules that govern the formation and breaking of noncovalent bonds, such as hydrogen bonding, van der Waals forces, π-stacking, and electrostatic interactions. In multicomponent systems, the co-crystallizing agent introduces additional diversity into the crystallization process, enhancing the variety of possible solid-state forms of APIs.

For example, as shown in Figure 1, the crystal packing of caffeine can be altered by co-crystallizing it with different excipients, like nicotinamide and saccharine. Since the properties of materials are influenced by their solid-state structures, the characteristics of APIs can be tailored systematically by choosing different co-crystal formers. Therefore, selecting the right co-crystallizing agent is a crucial first step in the design of co-crystals.

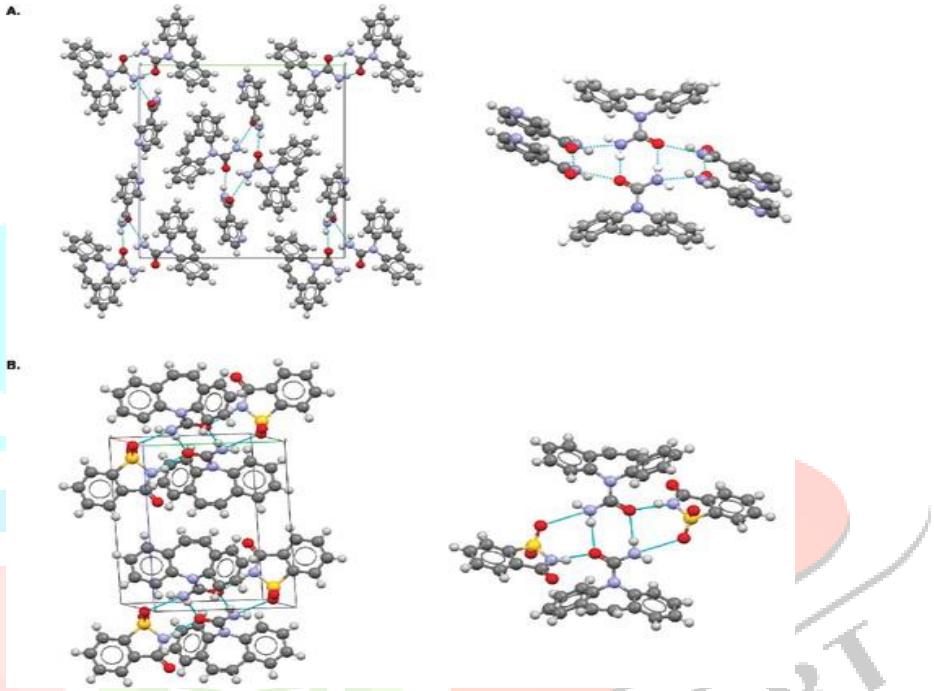

figure1: co-crystal structures of carabamazepine with nicotinamide and with saccharine.[1]

CO-FORMER SELECTION STRATEGIES

The design of pharmaceutical co-crystals is a multi-stage process, as illustrated in Figure 2. The key step in this process is the formation of supramolecular synthons—non-covalent bonds between self-complementary functional groups. This concept highlights the importance of understanding the supramolecular chemistry of the functional groups present in the API as the first step in designing a co-crystal. After examining the functionality of the API, a search of the Cambridge Structural Database is typically conducted to identify common, stable supramolecular synthons within related structures.

Following this, potential co-crystal formers are selected based on their ability to complement the functional groups of the API. As a general guideline, the hierarchy of supramolecular synthons within common functional groups—such as carboxylic acids, amides, and alcohols—can be utilized, as these are particularly favorable for forming supramolecular heterosynthons (intermolecular bonds involving different functional groups).

However, recent literature emphasizes the need to go beyond the expected supramolecular synthons to explore unexpected interactions. High-throughput crystallization offers a more thorough approach to discovering both expected and unexpected co-crystal formation events.

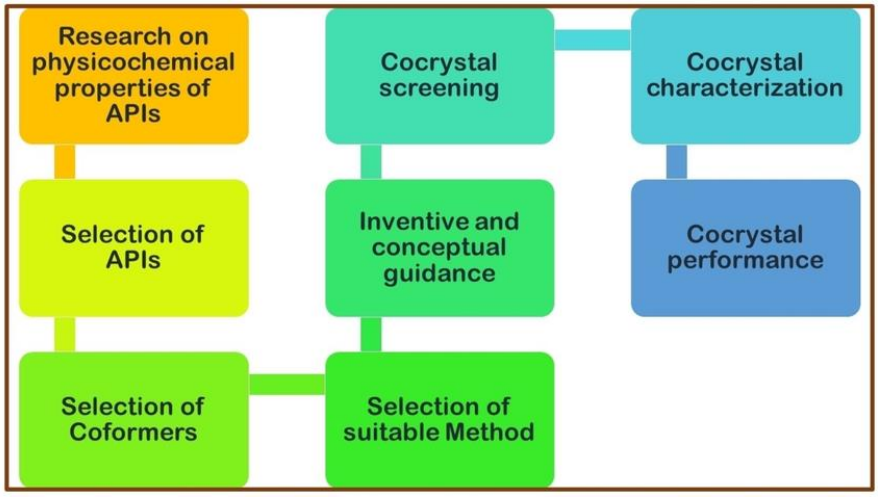

figure 2:schematic of steps for co-crystal design. [1]

CO-CRYSTAL SCREENING METHODOLOGIES

Co-crystal screening methodologies are primarily divided into two categories: solution-based crystallization methods and solid-based techniques.

1. **Solution-Based Crystallization Methods**: These include techniques such as solvent evaporation, slurry conversion, cooling crystallization, and precipitation. Solution-based methods are the most commonly applied in co-crystal screening. However, a significant drawback of these methods is the requirement to know the solubilities of the starting components. A suitable solvent must be identified for all the materials involved before beginning the screening experiment.
2. **Solid-Based Techniques**: These include crystallization from the melt, dry co-grinding, and wet co-grinding. These solid-state methods offer alternative approaches but may come with their own set of challenges compared to solution-based techniques.

In general, while solution-based crystallization is widely used for co-crystal screening, the need for careful selection of solvents based on solubility is a key consideration in these processes.

DIFFERENCES BETWEEN CO-CRYSTALS, SALTS, SOLVATES, AND HYDRATE

The USFDA has provided definitions for co-crystals, salts, and polymorphs in its guidelines. Polymorphs are substances that can exist in multiple crystalline forms, including solvates, hydrates (also known as pseudopolymorphs), and amorphous forms. These polymorphs exhibit different physicochemical properties due to variations in their crystal lattice structures.

Salts are formed when there is a complete proton transfer between two substances. This complete transfer distinguishes salts from co-crystals. While salts are formed by transferring a proton from an acid to a base, co-crystals are held together by non-covalent interactions, such as hydrogen bonds, van der Waals forces, and other interactions, without a complete proton transfer. The pKa value can be a useful predictor for whether a co-crystal or a salt will form. Co-crystals typically form when the pKa value is less than 0, while salts are more likely to form when the pKa value is greater than 3. Between pKa values of 0 and 3, predicting co-crystal formation becomes less reliable, though as the pKa increases, the likelihood of salt formation rises.

Co-crystals and solvates can be distinguished based on the physical state of the co-formers. Solvates contain a liquid (such as a solvent) at room temperature, whereas co-crystals remain solid. When the solvent in a solvate is water, the term hydrate is used. Solvates and hydrates are less stable than co-crystals, as the solvent's presence in the crystal lattice can make these forms more sensitive to changes in temperature and humidity. This instability arises because solvates and hydrates may lose their solvent or water under certain conditions, such as high temperatures or slight humidity changes, which can result in altered physicochemical properties between the hydrated and dehydrated forms. For example, solvated forms of spironolactone have been shown to increase the drug's dissolution rate. Liquid-assisted grinding (LAG) techniques have been employed to synthesize various polymorphic forms of co-crystals and solvates.

In summary, while co-crystals are held together by non-covalent interactions between two or more components, salts result from a complete proton transfer between an acid and a base. Solvates and hydrates involve the inclusion of solvent or water molecules in the crystal structure, but solvates are less stable due to the volatility of their solvent content, while co-crystals remain solid and stable under similar conditions.

ADVANTAGES OF CO-CRYSTALS

Co-crystals offer several advantages when compared to other methods like salt formation, solid dispersions, amorphous drugs, and encapsulation for modifying the physicochemical properties of medications. One significant advantage is that co-crystals remain in a stable crystalline state, eliminating the need for additional excipients or additives in formulations. This stability makes co-crystals particularly appealing for pharmaceutical applications.

The physicochemical properties of active pharmaceutical ingredients (APIs) can be significantly enhanced through their interactions with coformers, which are components that modify properties when incorporated into the crystal structure. The overall effect on the API's properties is largely dependent on the choice of coformer, as different coformers can lead to different outcomes in terms of solubility, stability, and bioavailability. However, co-crystals formed with sensitive coformers might not be stable under harsh conditions, such as exposure to strong acids or bases.

One key advantage of co-crystals is their ability to improve the physicochemical properties of non-ionizable APIs without altering their pharmacological activity. This gives co-crystals an edge over traditional salts, which often require proton transfer.

In addition to their stability and versatility, co-crystals can help speed up the drug development process, reducing both time and costs, which is particularly beneficial for pharmaceutical companies. Co-crystal synthesis methods, which can be categorized as green chemical processes, are environmentally friendly because they typically have high yields, do not require solvents, and produce minimal by-products.

Another benefit is that pharmaceutical co-crystals, with their unique structures, can be patented as new crystal forms in combination with existing APIs. This provides opportunities for intellectual property protection and innovation. Notable co-crystal formulations already on the market include Entresto (Novartis) for chronic heart failure and Viagra (Pfizer) for erectile dysfunction and pulmonary arterial hypertension.

Below, Figure illustrates the various physical characteristics of co-crystals and provides suitable examples of their applications.

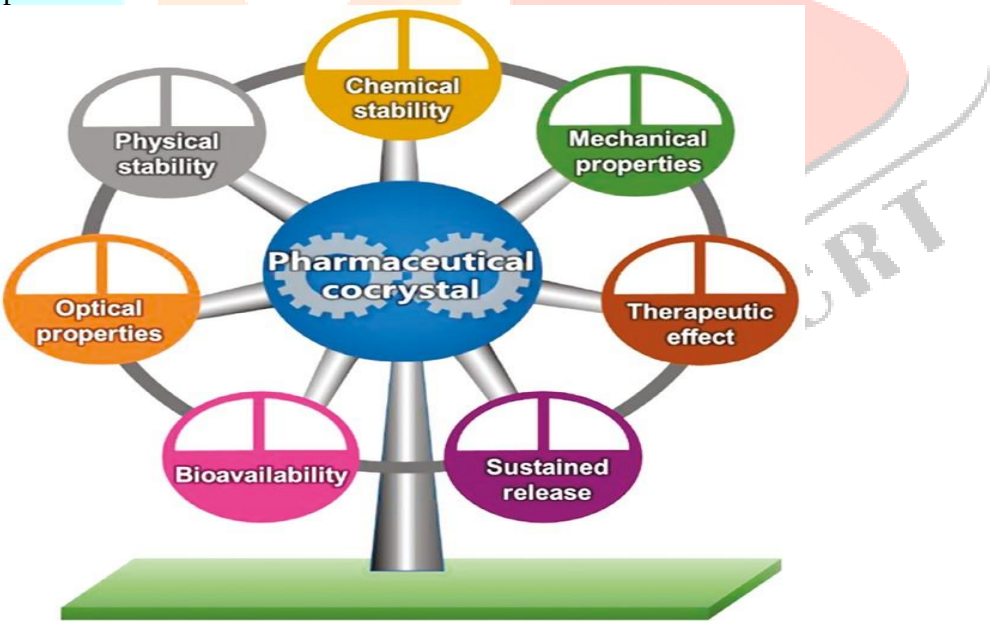

figure 3: different applications of pharmaceutical co-crystals to modulate the performance of pharmaceuticals API.

SOLID-STATE CHARACTERIZATION OF CO-CRYSTALS

Single-crystal X-ray diffractometry (XRD) is a powerful method for determining the solid-state structure of co-crystals at the atomic level. However, growing single crystals of many Active Pharmaceutical Ingredients (APIs) can be time-consuming or even unfeasible. As a result, the formation of co-crystals is typically verified using X-ray powder diffractometry (XRPD).

One limitation of XRPD is that it cannot differentiate between solvates, hydrates, polymorphs, or co-crystals. Moreover, pharmaceutical co-crystals are particularly prone to forming isostructural phases, which can further complicate the interpretation. For instance, multiple isostructural co-crystals of piroxicam have been reported, highlighting the need for a multi-technique approach to co-crystal characterization.

Raman spectroscopy has proven to be an especially effective tool for distinguishing between isostructural phases. Additionally, other spectroscopic techniques, such as Infrared (IR), Raman, and Near-Infrared (NIR)

spectroscopy, are commonly used during co-crystal screening to provide complementary structural information.

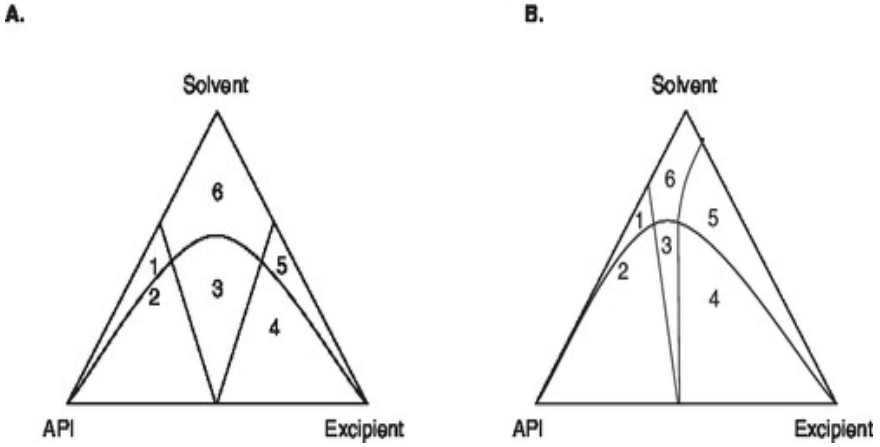

figure 4: schematic ternary phase diagrams showing the regions of thermodynamic stability in a multicomponent system with either similar or dissimilar solubility co-crystallizing agents.[1]

SUPRA-MOLECULAR CHEMISTRY AND CRYSTAL ENGINEERING

The scientific community has had some differences in opinions regarding the definitions of co-crystals in the past. The European Medicines Agency (EMA) defines a co-crystal as a crystalline structure that is homogeneous and contains two or more components arranged in a crystal lattice with a specific stoichiometric ratio (EMA, 2015). Co-crystals are created through intermolecular interactions, including halogen bonding, electrostatic interactions, π stacking, hydrogen bonding, and van der Waals forces, all of which are non-covalent interactions between the active pharmaceutical ingredient (API) and the co-former.

PROPERTIES OF CO-CRYSTALS

1) SOLUBILITY

The ability of a material to dissolve is crucial, as it determines how much can dissolve in a specific volume of detergent at a certain temperature. The solubility of drug formulations that are difficult to dissolve is a key area of study. Various methods are used to improve solubility, such as altering the form of the product, modifying the dissolution system, reducing particle size, and other techniques. One notable approach that has enhanced solubility is cocrystallization. For example, compared to ketoconazole, the antifungal drug's solubility shows a 53-fold increase in its pure form and a 100-fold rise in its cocrystal form. Cocrystals generally exhibit greater solubility than the pure substance, and they also improve dissolution rates due to the increased solubility of the material.

2) STABILITY

A key factor to consider when developing lozenge formulations is stability. Co-crystallization alters the molecular structure, which in turn affects the mechanical properties of the solids. Therefore, it is essential to examine the stability of polymorphic co-crystals. Stability studies typically cover aspects such as chemical stability, product stability, thermal stability, photostability, and various moisture stress conditions, all of which are crucial in the development of pharmaceutical co-crystals. Chemical stability studies, in particular, provide insights into any chemical changes that may occur in the drug product. Chemical stability is vital for both the creation of pharmacological lozenge formulations and the process of drug discovery.

3) MELTING POINT

The melting point of a solid is a key characteristic used to assess the stability and purity of a product's thermodynamic system. This property is particularly important during the co-crystal formation process. The thermal properties of the active pharmaceutical ingredient (API) depend on the selection of the coformer. In other words, choosing a coformer with a high melting point can enhance the thermal stability of the API. On the other hand, low melting point co-crystals can be beneficial for thermolabile compounds. The melting point and thermal properties are typically analyzed using techniques like Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). While high melting point co-

crystals may face issues with water solubility, low melting point co-crystals can present challenges in drying, processing, and stability.

4) PERMEABILITY

The permeability of an active pharmaceutical ingredient (API) across a biological membrane plays a key role in the drug's distribution and absorption. A major factor influencing drug permeability is the n-octanol/water partition coefficient, which can be calculated using log P and (C log P) for the drug in its unaltered form. By forming co-crystals with multiple coformers, the permeability of the BCS Class III drug, 5-fluorouracil, was found to be higher than that of the pure drug. The permeability of the co-crystals improved as the drug and coformer formed a heterosynthon, enhancing their interaction.

5) BIOAVAILABILITY

Oral administration is the most efficient method for drug delivery, but low oral bioavailability remains a significant challenge in the development of new API formulations. Bioavailability refers to the rate and extent to which the active ingredient is absorbed into the systemic circulation. To improve this, pharmaceutical co-crystals with enhanced oral bioavailability and water solubility are developed using crystal engineering. For example, the meloxicam-aspirin co-crystal shows improved onset of action and superior oral absorption compared to the pure drug.[16]

METHODS OF PREPARATION OF CO-CRYSTALS

1. GRINDING METHOD

Co-crystal formation through grinding methods is often considered superior to other techniques and is commonly used.

a) Dry (Neat) Grinding

The drug and coformer are combined in a specific ratio and then ground mechanically in a ball mill for dry grinding,or manually using a mortar and pestle.

b) Wet Grinding

This method is similar to dry grinding, except that during the grinding process, a few drops of solvent are added to the API and coformer mixture.

2. SPRAY DRYING METHOD

Spray drying is considered the best method because it is fast, continuous, and involves only one step. This technique creates a unique environment using spray dryers. During the spray drying process, a stream of hot air is applied to an API and coformer mixture or suspension to evaporate the solvent. This method is particularly effective for producing co-crystals of drugs that are poorly soluble in water.

3. SOLVENT EVAPORATION TECHNIQUE

This is the most commonly used and reliable method for producing co-crystals. The API and coformer are dissolved in a chosen solvent using an appropriate system to form the co-crystal. The solvent is then allowed to gradually evaporate at room temperature to achieve the desired stoichiometric ratio and produce the co-crystals. When selecting a solvent, it is crucial to consider the solubility of both the coformer and the API. The quality of the co-crystal is greatly influenced by the solvent used during co-crystal formation. This method relies on the principle that the functional groups of the drugs and the coformers interact through intermolecular forces, such as hydrogen bonding, resulting in co-crystal formation.

4. ULTRASOUND ASSISTED SOLUTION CO-CRYSTALS

This method is used to produce small co-crystals, or nanocrystals. During ultrasound-assisted co-crystallization, the coformers and API are dissolved in an appropriate solvent and placed in a sonicator at room temperature. After applying 6 to 12 ultrasonic pulses in the sonicator, a cloudy solution is formed. Cold water is used during sonication to maintain a constant temperature in the sonicator and prevent excessive heating. The mixture is then left to dry overnight. Pure co-crystals are formed through this process, and their purity can be evaluated using X-ray diffraction techniques.

5. SUPERCRITICAL FLUID AUTOMIZATION TECHNIQUE

In this method, the drug and coformers are mixed using a high-pressure supercritical fluid, such as CO2, and the resulting mixture is atomized to produce co-crystals. The supercritical fluid's antisolvent effect is utilized to form co-crystals in the Supercritical Antisolvent (SAS) process. Various techniques based on supercritical fluids have been developed to produce microparticles by leveraging the unique properties of these fluids. Recent research shows that

polymorphs and other solid forms of APIs can also be produced using supercritical fluid-based systems, particularly through the SAS process.

6. HOT MELT EXTRUSION METHOD

This method can only be used with chemicals that are thermodynamically stable. It is a one-step process that eliminates the need for a solvent during co-crystal formation. In this approach, heat and high-intensity mixing are applied to make the drug and coformer miscible in the molten state, ensuring better surface contact and efficient mixing. For this process to work, the drug and API must be miscible in molten form, which means thermolabile substances should not be used. Compared to previous methods developed by the pharmaceutical industry to improve the physicochemical properties of drugs (such as bioavailability, solubility, and stability), this method offers a more streamlined approach.[16]

A comparison between FDA and EMA guidelines of Pharmaceutical co-crystals was discussed in table

table 1: comparison between FDA and EMA guidelines of pharmaceutical co-crystals.

REGULATORY GUIDELINES	EMA (2015)	FDA (2016)
Regulatory category	Active pharmaceutical ingredient	Polymorph of active pharmaceutical ingredient
Composition	Active pharmaceutical ingredient and co-former in fixed stoichiometric arrangement	Active pharmaceutical ingredient and a food or drug grade co-former
Co-former role	Reagent	Excipient
Interaction in crystal	Non – ionic / no covalent interaction	Non – ionic / no covalent interaction
New active substance registration	Possible if shown dissimilar in efficacy/safety	No
Classification	Salt of Active pharmaceutical ingredient	Polymorph of Active pharmaceutical ingredient

API solid form classification based on structure and composition.

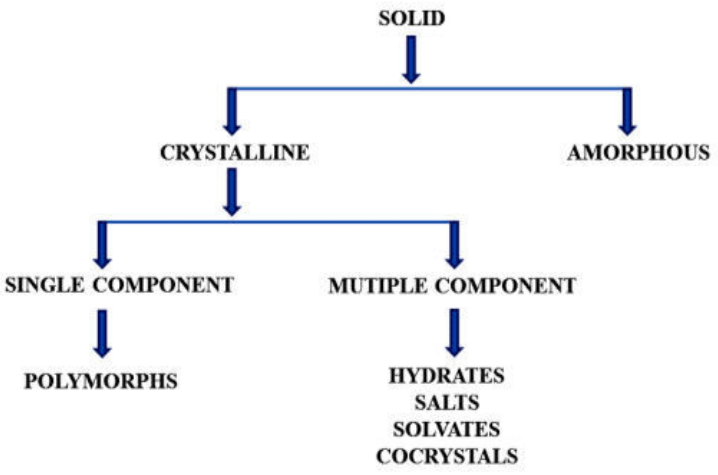

figure 5: API solid form classification based on structure and composition[6] .

Co-crystals present new opportunities for generating a broader range of solid forms of drug substances that exhibit the ideal balance of critical properties needed for the development of viable and effective drug products. Additionally, exploring co-crystallization options for a particular Active Pharmaceutical Ingredient (API) can enhance intellectual property protection for the drug product. This added protection helps mitigate the risks of expensive litigation and market erosion, making co-crystals a valuable strategy in pharmaceutical development.

A molecular-level mechanism for two cases of mechanochemical co-crystallization via halogen bonds has been described, based on the observation and structural analysis of intermediates formed during the early stages of the reaction. This mechanism involves the competition between strong and weak intermolecular halogen bonds of the N...I and S...I types. It begins with the formation of finite molecular assemblies connected by N...I bonds, which then polymerize into infinite chains through cross-linking via S...I bonds. Co-crystallizations of exemestane and megestrol acetate showed improved initial dissolution rates compared to the original crystals. The dissolution enhancement mechanism differed: for the exemestane/maleic acid co-crystal, the improvement was due to the formation of fine particles, while for the megestrol acetate/saccharin co-crystal, the enhancement resulted from the preservation of the co-crystal form and rapid dissolution before transformation occurred.

The mechanisms involved in converting crystalline drugs to co-crystals and the factors influencing co-crystal stability have been discussed. The concentration of the coformer solution plays a key role in controlling the formation and stability of co-crystals with different stoichiometries. Studies on 1:1 and 2:1 carbamazepine-4-aminobenzoic acid co-crystals revealed that co-crystals with a higher coformer content were more stable at higher coformer concentrations. Co-crystallization also took place in solid mixtures of co-crystal reactants. Co-crystals of carbamazepine with nicotinamide, saccharin, and various carboxylic acid coformers were formed through moisture absorption and deliquescence in the reactant mixtures. In the solid-state, co-grinding carbamazepine with saccharin or nicotinamide led to the formation of co-crystals.

CO-CRYSTAL CHARACTERIZATION

In some instances, the formation of a co-crystal is easily identified by the physical properties of the resulting material. For example, when acetaminophen and 2,4-pyridine dicarboxylic acid form a co-crystal, the red color of the new substance is immediately noticeable, even though both components are white solids (Figure 6). This red color is due to the conversion of the pyridine dicarboxylic acid into its zwitterionic form within the co-crystal, a result of the hydrogen bonding in the crystal structure. This transformation also leads to a reduction in the π-π energy gap.

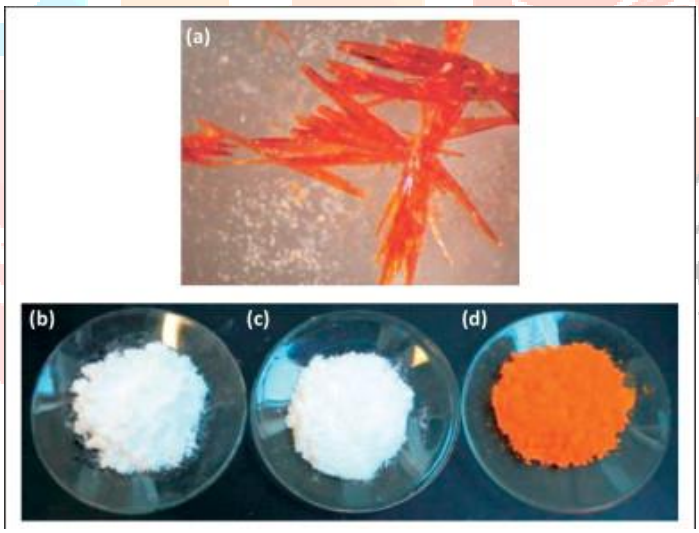

figure 6: a coloured co-crystal formed from white component solids[6] .
(a)single crystals of the 1:1 acetaminophen and 2,4-pyridine dicarboxylic acid co-crystal, (b) powdered acetaminophen, (c) powdered 2,4-pyridine dicarboxylic acid, and (d) powdered co-crystal

Co-crystal formation can often be identified through a comprehensive set of techniques commonly used to analyze crystalline molecular solids. These methods, extensively discussed in various authoritative texts, include single crystal and powder X-ray diffraction (SC-XRD and PXRD), thermal analysis methods like differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), polarized optical hot-stage microscopy (useful for determining precise melting points), vibrational spectroscopy (IR and Raman), and solid-state magic angle spinning nuclear magnetic resonance (MAS-NMR) spectroscopy. The most definitive method for structural characterization of a co-crystal is single crystal X-ray diffraction.

EVALUATION OF PHARMACEUTICAL CO-CRYSTALS

The methods employed to assess pharmaceutical co-crystals made using supercritical carbon dioxide (scCO2) are similar to those used for co-crystals created through traditional techniques. Many co-crystals produced with scCO2 have already been synthesized using conventional methods, and the existing characterization data in literature helps guide the evaluation of co-crystals obtained via the supercritical method. The characterization techniques focus on examining the crystal size and morphology, purity, structure, interactions, and physical properties, such as dissolution rate, which are important for the co-crystal's pharmacological application. Crystal size and morphology are typically analyzed using scanning electron microscopy (SEM), with optical microscopy also being employed. Particle size distribution can be determined from SEM images or through separate laser diffraction measurements. Although micronization is not the main goal of scCO2 co-crystallization, the particle size remains an important factor, especially for poorly soluble active pharmaceutical ingredients (APIs), where smaller particles could improve solubility. The dissolution profiles of co-crystals should be determined and compared to those of the active pharmaceutical ingredient (API). For APIs with poor solubility, an enhancement in the dissolution rate is seen as an advantage of the new formulation. Additionally, physical and chemical stability studies are conducted, including relative humidity stability tests if hygroscopicity causes form changes or degradation. Lastly, the yield should be assessed to determine whether the process is feasible for industrial application.

APPLICATIONS

The application of co-crystals has been explored in several therapeutic contexts, as outlined in the challenges of translational development discussed earlier in this paper.

Apixaban (AXP, trade name Eliquis), used for thromboembolic treatment after knee or hip replacement surgery, has poor solubility and low oral bioavailability. Despite attempts to improve solubility by increasing the dose beyond 25mg, no significant improvement in oral bioavailability is observed. To address this, Chen and colleagues prepared apixaban-oxalic acid (APX-OXC) co-crystals, which exhibited better solubility compared to the anhydrous form of apixaban. Pharmacokinetic studies showed a 2.7 times greater area under the curve (AUC0-24h) for the APX-OXC co-crystals, indicating enhanced bioavailability.

Adefovir dipivoxil (AD, trade name Hepsera) is used to treat hepatitis B virus but is thermally unstable, with accelerated degradation under various conditions. The marketed formulation remains stable at room temperature but converts to a dehydrated form under 75% relative humidity (RH). Jung S and colleagues prepared AD co-crystals with suberic acid and succinic acid, which enhanced both the thermal stability and aqueous solubility of the drug. AD-saccharine co-crystals also maintained stability under storage conditions (1 month at 60°C), demonstrating the potential of co-crystallization to improve the stability and shelf life of unstable drugs.

Paracetamol (P-Hydroxyacetanilide, PA) is a widely used analgesic with poor solubility and limited compatibility, classified as a BCS Class-III drug. Co-crystals of paracetamol with various co-formers, such as PA-pherazine, PA-trimethylglycine, and PA-citric acid, have shown improvements in its physicochemical, mechanical, and pharmaceutical properties.

Ethenzamide (ET), a non-steroidal anti-inflammatory drug (NSAID) belonging to BCS Class-II, has low water solubility. Several studies have demonstrated that co-crystals of ethenzamide with various co-formers significantly improve its solubility and other physicochemical properties.

These examples highlight the potential of co-crystallization to enhance the solubility, stability, and bioavailability of drugs, especially for those with challenging physicochemical properties.

CONCLUSION

The growing interest in co-crystals is largely driven by the need to modify drug properties. Significant improvements in dissolution rate, bioavailability, solubility, and other physicochemical characteristics have been reported. Future research should focus on addressing real-world industry challenges, such as developing scalable methods that meet industrial standards and improving high-throughput screening techniques. The choice of method is crucial and must be tailored to each specific system.

While co-crystallization holds great potential for improving drug properties, considerable effort is still required to make it a routine practice in the pharmaceutical industry. Preclinical and clinical studies have demonstrated proof-of-concept for the advantages of co-crystals. However, several challenges remain in translating co-crystals into final drug products. These include concerns about the safety of co-formers, polymorphism, solubility limitations, the behavior of co-crystals in formulations, and difficulties in establishing in vitro-in vivo correlation (IVIVC).

Increased scientific understanding of crystal engineering and the biopharmaceutical performance of co-crystals will be key to the successful introduction of co-crystal-based drug products in the future.

The successful delivery of a drug to a patient—ensuring safety, efficacy, and cost-effectiveness—relies heavily on the physicochemical properties of the drug in its solid state. Modifying the material properties of drugs has significant therapeutic, manufacturing, and commercial implications. Therefore, it is crucial to focus on understanding and optimizing the fundamental material properties during drug product development in order to create medicines with the desired and optimal characteristics.[2]

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