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EXPLORING CO-CRYSTALS: TECHNIQUES AND CHARACTERIZATION OVERVIEW

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ABSTRACT:
Recent studies emphasize that achieving therapeutic efficacy and economic viability requires more than just discovering and developing novel drugs. Modified versions of existing drugs are increasingly crucial. Two major challenges hindering new product development are the low bioavailability and poor water solubility of active pharmaceutical ingredients (APIs). Co-crystallization with pharmaceutically acceptable molecules offers a solution without altering the pharmacological activity of the API but improving its physical properties such as solubility, stability, and dissolution rate. Co-crystals, particularly, enable the creation of innovative drugs with enhanced solubility, thereby improving treatment efficacy and safety. Thermodynamic stability is critical in the co-crystal formation process, achieved through techniques like grinding, spray drying, solvent evaporation, and ultrasound-assisted solutions. Methods such as co-crystallization, hot melt extrusion, and supercritical fluid atomization contribute to co-crystal production. This review provides an in-depth exploration of co-crystals, covering formation techniques, properties (solubility, tabletability, melting point, stability, bioavailability, permeability), and pharmacological applications.

KEYWORDS: Co-crystal, Solubility, Physiological properties, Pharmaceutical ingredient, Bioavailability.

INTRODUCTION:

Approximately 60–70% of newly identified drugs belong to Biopharmaceutical Classification System (BCS) Classes II (low solubility/high permeability) and IV (low solubility/low permeability). These drugs pose challenges related to dissolution, solubility, stability, therapeutic efficacy, and other aspects of drug administration. Modern pharmaceutical development necessitates employing various techniques to address issues with drug permeability and solubility. Multi-component crystals such as hydrates[1], salts, co-crystals, and solvates are pivotal in developing novel solid forms, particularly in the pharmaceutical sector[2].

Co-crystal:

Co-crystallization refers to the molecular modification of a drug to alter its physical properties. The process of co-crystallization involves combining a drug with a coformer to

form a co-crystal. Co-crystals are molecular crystals composed of two or more chemically distinct molecules in a specific stoichiometric ratio. These crystals can modify the solubility or other physical characteristics of pharmaceuticals without compromising their pharmacological effects[3].

Implication of Co-crystal:

Crystallization enables the customization of a drug's physicochemical properties through various techniques, thereby eliminating the need for additional additives to enhance its properties. The molecular interactions between active pharmaceutical ingredients (APIs) and coformers, along with the synthesis processes, significantly influence the modification of substance characteristics without altering their pharmacological properties. The choice of coformer dictates the impact on the physicochemical properties of the API[4].

Sr. No	BCS Class	Solubility	Permeability
1	Class 1	High	High
2	Class 2	Low	High
3	Class 3	High	Low
4	Class 4	Low	Low

Table 1:-BCS Classification

Properties of Co-crystals:

1. **Solubility:** Solubility refers to the maximum amount of a substance that can dissolve in a given volume of solvent at a specific temperature. Enhancing the solubility of poorly soluble drug formulations is crucial in pharmaceutical development. Various techniques such as salt formation, solid dispersion, and particle size reduction are employed. Crystallization methods, including co-crystallization, have been explored extensively to improve drug solubility[5].
2. **Stability:** Stability is critical for any formulation. Co-crystals must exhibit thermal stability, humidity stability, chemical stability, and solution stability. Techniques such as water absorption/desorption experiments are used to evaluate the relative humidity stability of co-crystals[6].
3. **Melting Point:** The melting point is the temperature at which a co-crystal's solid and liquid phases coexist in equilibrium. When a co-crystal forms, its melting point typically shifts to an intermediate temperature between that of the API and the conformer [7].
4. **Permeability:** Recent research indicates that co-crystals can alter the permeability of drugs, in addition to enhancing their solubility. This property makes co-crystals potentially suitable for improving the bioavailability of BCS class III and IV pharmaceuticals, which have poor permeability characteristics [8].
5. **Tabletability:** Co-crystallization is recommended for improving flow properties and mechanical strength, both crucial for tablet formulation. For instance, co-crystals like saccharine and carbamazepine show denser packing compared to pure carbamazepine, enhancing compression properties.

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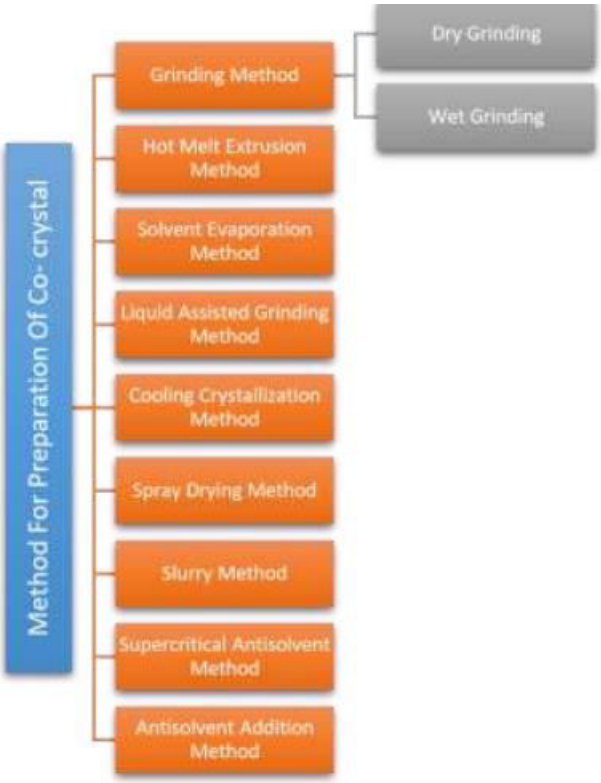
6. **Bioavailability:** Bioavailability refers to the rate and extent at which the active pharmaceutical ingredient (API) reaches systemic circulation in its unchanged form. Low oral bioavailability is a significant challenge in formulation development, which can be addressed through co-crystallization. Several studies have demonstrated improved bioavailability of drugs by converting them into co-crystal forms[9].

METHOD OF PREPARATION OF CO-CRYSTAL:



Discovery and Techniques of Multicomponent Solid Forms:

The discovery of drugs has spurred the adoption of various techniques for producing multicomponent solid forms, including cocrystals, cosolvates, co-amorphous forms, polymorphs, and hydrates/salts. Key factors in these preparations include the choice of solvent, active pharmaceutical ingredient (API), and coformers. Several commonly employed methods include[10]:

1. **Solid-Based Methods:**
   - **Melt Extrusion:** Involves melting and mixing the coformer and API at a specific stoichiometric ratio (e.g., 1:1, 1:2) to produce cocrystals. This method is scalable and continuous but may not be suitable for thermolabile compounds.
   - **Melt Crystallization:** Similar to melt extrusion, this method relies on melting the API and coformer to form cocrystals under controlled conditions.
   - **Solid Phase Grinding:** This method is widely used and involves mechanically mixing the API and coformer in a mortar and pestle or using laboratory-scale milling devices. It is straightforward, environmentally friendly, and productive. Examples

include piracetam-citric acid and carbamazepine-nicotinamide cocrystals formed via this approach.

- **Wet Grinding Method:** A variant of solid phase grinding where a small amount of solvent is added to facilitate the grinding process, enhancing cocrystal formation efficiency.

2. **Hot Melt Extrusion Method:**
   - Involves combining the API and coformers in a system at a controlled temperature where they melt and form cocrystals. This method improves surface contact between components without requiring a solution or solvent. However, it is not suitable for drugs sensitive to heat.

These techniques play a critical role in tailoring the physicochemical properties of drugs to improve their solubility, stability, and other essential characteristics, thereby enhancing their effectiveness and safety in therapeutic applications.

Methods for Cocrystal Formation:

4. Solvent Evaporation Method:

Also known as the solvent evaporation technique, this method involves gradually evaporating a solvent solution. During dissolution, functional groups in the coformer and API exchange places to form new hydrogen bonds, commonly used in creating cocrystals like glutaric acid cocrystals. The process includes dissolving the API and coformers in a boiling solvent while continuously stirring until the volume reduces significantly. The resulting solution is allowed to cool slowly in a heated air oven or outdoors to generate cocrystals, such as theophylline citric acid cocrystals. This method involves selecting and dissolving solvents dispersing coformers, followed by dispersing the medication into it using a dispersion homogenizer. The mixture is then mixed with the appropriate solvent to precipitate the coformer into the drug's powdered indomethacin-saccharide or carbamazepine-saccharide cocrystal.

5. Liquid-Assisted Grinding Method:

Liquid-assisted grinding is another favored technique for cocrystal formation. It offers a faster rate of cocrystal formation compared to dry grinding and is more reliable and suitable. This method is recognized for its environmental friendliness due to its reduced solvent usage compared to other industrial manufacturing methods. Importantly, this process reduces the likelihood of undesired solvate formation. Examples include adefovir dipivoxil-glutaric acid cocrystal and quercetin-succinic acid cocrystal, which enhance solubility and dissolution rates by up to 1.62 and 1.25, respectively, independent of temperature.

6. Cooling Crystallization Method:

This method, less commonly used, involves slower and more laborious procedures compared to other methods. For instance, cocrystallization of darunavir with succinic acid has improved solubility, dissolution, and micrometric characteristics compared to darunavir alone.

7. Solvent Drop Grinding:

In this approach, the coformer and API are combined using an appropriate solvent. Drops of solvent are added while continuously swirling, and the solvent acts as a catalyst to promote crystal formation. This method can also create amorphous cocrystals, such as coamorphous

crystals of carbamazepine and nicotinamide. The process is similar to the crystallization cooling technique.

8. Ultrasound-Assisted Solution Method:

This method is used to produce nanocrystals, where the drug and coformers are dissolved in a suitable solvent. The solution is placed in a sonicator to create turbidity, maintaining a constant temperature to prevent degradation and fragmentation. The solution is left overnight for cocrystal formation and solvent evaporation.

9. Spray Drying Method:

Highly frequent in cocrystal manufacturing, this method is rapid and continuous, performed in a single step. A solution containing the coformer and API is evaporated over a heated air stream. It is suitable for user-friendly and scalable applications, such as sulfadimidine/4-aminosalicylic acid cocrystals.

10. Slurry Method:

This simple method involves creating a slurry of API and coformer in a suitable solvent, agitating the mixture, filtering, and drying. It has been used to create cocrystals such as celecoxib-venlafaxine cocrystal (NSAIDs + antidepressant), addressing solubility issues with high solubility BCS class I drugs like venlafaxine (BCS class I) and celecoxib (CS class II) . The slurry method of crystallization involves stirring a slurry of API and coformer in an appropriate solvent with a glass rod or magnetic stirrer, allowing the solvent to cool gradually at room temperature until cocrystals form, such as aspirin-4,4 dipyridyl cocrystals or acyclovir-succinic acid cocrystals.

CONCLUSION:

Co-crystals offer a promising avenue for drug development by improving solubility, bioavailability, stability, and processability. However, challenges such as conformer selection, physicochemical characterization, and formulation remain significant. Careful screening of drug conformers and thoughtful formulation design are crucial for successful co-crystal development. This review provides insights into the proposed mechanisms of co-crystallization across various techniques. Early development efforts have primarily focused on traditional methods like solvent evaporation, grinding, and the slurry method. However, each method requires thorough investigation to fully understand the co-crystallization mechanisms involved.

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