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OVERVIEW ON PHARMACEUTICAL CO-CRYSTALLIZATION TECHNIQUES

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ABSTRACT

One of the most promising techniques for improving the physicochemical characteristics of APIs – solubility, bioavailability, and stability – is pharmaceutical co-crystallization. This method relies on non-covalent interactions to create a crystalline complex of an API with one or more co-formers, which are tiny organic molecules. Co-crystallization is an alternative to the widely used conventional solid-state modification methods, such as particle size reduction. The method makes it possible to create engineered materials with enhanced drug performance while maintaining the API's therapeutic action. A number of co-crystallization processes, including solvent evaporation, grinding, and slurrying, as well as the fundamental ideas behind their production, are described in the overview that follows. The most common characterization methods used to evaluate co-crystals are X-ray diffraction. The review paper presents spectroscopic and thermal analysis. In keeping with the timeframe of this work, this paper addresses the difficulties and future directions of pharmaceutical co-crystallization, including scalability and regulatory concerns as well as more general issues. The main goal was to advance our knowledge of co-crystallization.

KEY WORDS:

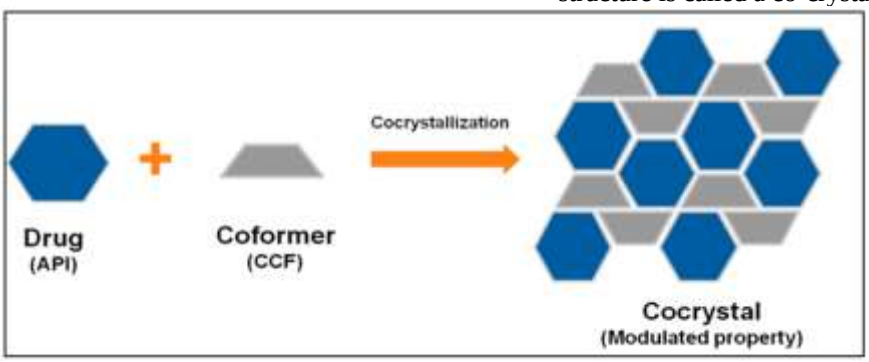
- *Pharmaceutical Co-Crystallization.*
- *Selection of Co-formers.*
- *Formulation methods.*
- *Evaluation methods.*
- *Solubility Enhancement.*

INTRODUCTION

Significant analysis, experimental research, candidate drug selection, experimental development, and fully created drug are the five separate stages that make up the intricate process of drug discovery or development. Drug design and development, wherein the "Research and Development" department employs collaborative teams to enhance drug understanding [(1)]. Many potentially promising drug candidates are discarded from late-stage development throughout the research and development process, primarily due to their low bioavailability [(2)].

Pharmaceutical scientists have been more interested in the co-crystallization process over the past ten years because they want to modify the physicochemical properties of active pharmaceutical ingredients without changing their pharmacological activity. This makes them a better choice for patents and for developing these medications into new, marketable formulations [(3)].

Pharmaceutical Co-crystallization is a process that involves combining two or more chemical substances to form a crystalline structure with unique properties. The resulting structure is called a co-crystal.



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Co-Crystal

A co-crystal is a crystalline structure made up of two or more substances, which could be molecules, atoms, or ions. To increase a drug's bioavailability in the human body, its physicochemical characteristics—such as its melting point, solubility, dissolution, and stability—are improved. Which results in the drug's optimal therapeutic impact with fewer side effects. While co-crystallization with pharmaceutically acceptable chemicals can enhance physical qualities, it has no effect on the pharmacological action of active pharmaceutical components [(4)]. Drugs are categorized into four main groups by the Biopharmceutics Classification System (BCS) according to their permeability and solubility characteristics. Drugs in BCS Class II and Class IV have limited solubility in water. Hydrophobic medications with poor aqueous solubility may have reduced bioavailability and poor absorption [(5)].

Design of Co-Crystal

The design and preparation of pharmaceutical co-crystals is a multi-step procedure. Finding the functional groups that can form intermolecular interactions with appropriate co-formers requires first studying the structure of the target API molecule. A co-former is a substance that interacts with the API in the crystal lattice in a nonionic manner; it is usually non-volatile and is not a solvent, including water.Van der Waals contacts, π-π stacking interactions, and hydrogen bonding—the most prevalent interaction in co-crystal structure—are examples of these intermolecular interactions. Selecting a co-crystal former is the next step. Being pharmaceutically acceptable—for instance, pharmacological excipients and chemicals categorized as generally as safe (GRAS) for use as food additives—is the main need for a co-former. A single crystalline phase of several components in a specific stoichiometric ratio, where the various chemical species interact through hydrogen bonds or other non-covalent bonds, is what makes up co-crystals. The hydrogen bond has been the most significant interaction in co-crystal formation due to its strength and directionality. As seen in Figure 1, strong and weak hydrogen bond synthons are frequently the basis for supramolecular configurations in pharmaceutical crystals. N–H... O, O–H... O, N–H... N, and O–H... N are examples of strong hydrogen bonds, whereas C–H... O–N and C–H... O=C[(6)] are examples of weak hydrogen bonds.

Co-Former

Co-former is a co-crystallizing agent that interacts nonionically with the API (active pharmaceutical ingredient) in the crystal lattice. Co-formers are mainly non-volatile and they are highly water soluble agent.

IDEAL PROPERTIES FOR SELECTION OF CO-FORMER.

- Low molecular weight.
- Pharmaceutically acceptable.
- Non-toxic.
- Multiple API-binding sites.
- Form strong intermolecular interaction.

Selection of Co-Formers

One of the most important and significant steps in creating co-crystals is choosing a co-former. Depending on how well the co-former works, co-crystals' physicochemical characteristics can change. The physico-chemical characteristics of co-crystals are enhanced by appropriate co-former selection, but they can also be deteriorated by biased co-former selection. The final co-crystals' physicochemical characteristics are also influenced by the drug-to-co-former ratio. To filter out appropriate co-formers for certain medicinal molecules, a variety of selection techniques are employed. Currently, there are seven distinct techniques for co-former preliminary screening [(7)].

PKa Based Model

A molecule's acidity or basicity is gauged by its acid dissociation constant, or Pka. A pka-based model is a mathematical representation used in pharmacy that forecasts the actions of ionizable medications by using the value of the acid dissociation constant (pka). To predict different pharmacokinetic and pharmacodynamic outcomes, it combines pka with other molecular characteristics. Solubility, permeability, bioavailability, and drug-target interactions are all improved by PKA.

By being aware of the acid-base characteristics of possible co-formers and API. The possibility that stable co-crystals may develop is easily predicted.

Step to select co-former by pka model

1. Determine the pka of API.

2. Identify potential co-formers.

For Acidic API  Choose Basic Co-former.

For Basic API  Choose Acidic Co-former.

Cambridge Structural Database

The Cambridge Structural Database (CSD) can be used to evaluate the likelihood of hydrogen bonds forming between molecules. A compound's crystal structure can be described using CSD single crystal x-ray crystallography. Information can be searched, accessed, and used from the database at any

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moment, and the resolved structure can be saved in CSD. Two examples of software that may be used to visualize the structure using the data gathered from the CSD are "atoms" and "powder cell" [8].

CDS is used in selecting a co-former
1. Examining molecular structures might help determine which kinds of molecules might interact effectively with a medicine by examining how particular molecules fit together in a crystal.
2. Finding Similarities: Look for molecules that resemble the drug of interest in terms of form or functional groups. This aids in their prediction of the co-formers that could create stable pairings.
3. Examining interactions: It is crucial to examine how molecules interact with one another within a crystal. Because they affect the stability and characteristics of the drug-co-former complex, these interactions are essential when choosing a co-former.
4. Identifying appropriate co-formers: co-formers can be chosen based on their desirable qualities, as well as their track record of increasing medication delivery or solubility when combined with other similar pharmaceuticals.

Hansen Solubility Parameter (HSP)
In pharmaceutical research, Hansen Solubility Parameters (HSP) are a useful tool, especially for predicting stability, formulation, and solubility. HSP measures the intermolecular forces between a solvent and a solute using three parameters: δD, δP, and δH. It improves poorly water soluble substances' solubility, permeability, and bioavailability.
Components:
1. δD (Dispersion): measures London dispersion forces (non-polar interactions)
2. δP (Polar): measures dipole-dipole interactions (polar forces)
3. δH (Hydrogen Bonding): measures hydrogen bonding interactions.

Hydrogen Bonding
The contact between the target molecule and co-former during co-crystal formation is caused by non-covalent interactions such as hydrogen bonds and van der Waals forces. Hydrogen bonding is one of these factors that is crucial to the creation of co-crystals [64,65]. Knowledge-based prediction strategies for choosing co-formers include hydrogen bond propensity (HBP) and hydrogen bond energy (HBE). The likelihood of a particular hydrogen bond forming is known as HBP, and it is influenced by the structural features of the particular functional group. [9].

Supramolecular Synthon Approach
A regular and distinct liner relationship between molecular building blocks is known as a supramolecular synthon. Two molecules are brought together by molecular functions that interact with one another in a predictable way through non-covalent interactions to generate synthons. Because they have both a donor and an acceptor for hydrogen bonds, self-complementary functional groups like alcohols, amides, and carboxylic acids can form supramolecular homosynthons. This ability is not present in the functions of other functional groups, which solely contain donors or acceptors of hydrogen bonds. However, all functions can combine with additional complementary functional groups to generate supramolecular heterosynthons [10].

AIM: To enhance the solubility of poorly-water soluble drugs by co-crystallization techniques.

OBJECTIVES
To evaluate the potential of co-crystallization to enhance solubility, bioavailability and stability of poorly-soluble drugs.
To review co-crystallization techniques, including solution-based, solid-state, and solvent-free methods.
To examine the analytical techniques used to characterize co-crystals, such as PXRD and DSC.
To discuss the role of co-formers in co-crystallization and their selection.

FORMULATION OF CO-CRYSTALLIZATION
Co-crystals can be made in a variety of ways, but the traditional crystallization process included cooling, evaporation, and the addition of substances that decreased solubility in a solution with the right amount of super saturation.The solvent evaporation approach did not produce favorable results for CCs. Two strategies are commonly used for CCs: solution-based and grinding-based techniques.The development of CS may qualify the testing with a single XRD (SXRD), hence solution-based methods are usually preferred. Solvent drop grinding and neat-grinding are two of the grinding-based techniques [11].

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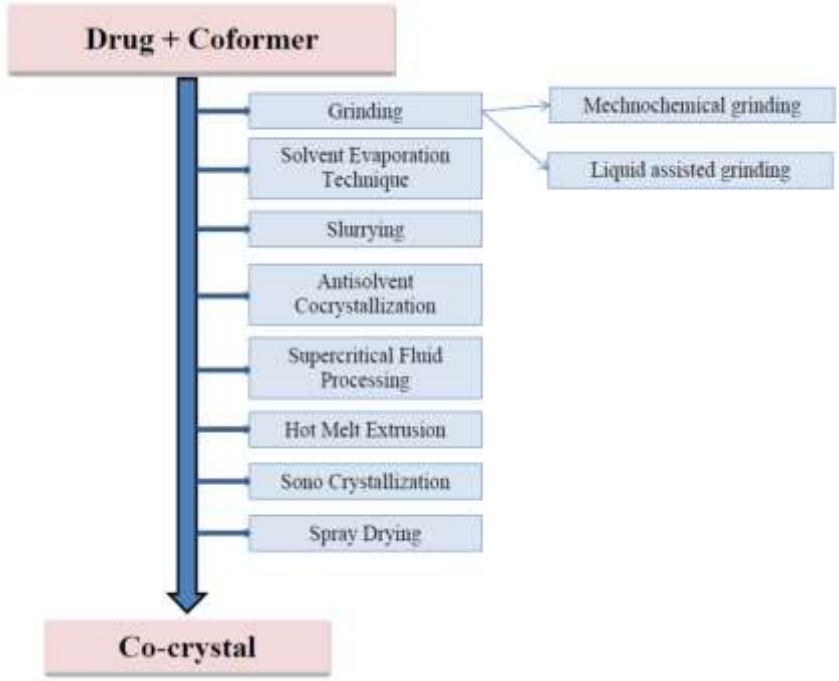

Solvent Evaporation

The most straightforward method of co-crystallization is solvent evaporation, which involves adding a solvent or chemical that changes solubility, chilling, and supersaturating the solution through evaporation [12].

Procedure:-

DRUG (API) + COFORMER

↓

MIXED WITH SOLVENT

↓

THIS SOLUTION IS EVPORATED BY USING THE HEAT.

↓

AT THE TIME OF EVAPORATION THE MOLECULES OF THE SOLITION

START FORMING HYDROGEN BOND WITH DIFFERENT FUNCTIONAL

GROUP.

Anti-Solvent Crystallization

In order to promote the precipitation of the particles, a solvent that is less soluble in the chemical is frequently added to the solution. After filtering the resultant suspension, XRPD can be used to characterize the solid that has been collected. This method's drawbacks include its poorer performance as compared to grinding and the considerable amount of solvent required [13].

Cooling Crystallization

A reactor is typically used to mix the components and solvent in cooling co-crystallization, which is dependent on temperature variations. After that, the system is heated to cause the disintegration of both components. The temperature is lowered to obtain saturation. This method can be used in conjunction with phase diagrams to anticipate the possible development of co-crystals and identify thermodynamic stable zones [14].

Grinding Method

This is a solvent-free co-crystallization technique. Using a mortar and pestle, a ball mill, or a vibrator mill, the solid ingredients that will form the co-crystal are combined in the proper stoichiometric quantities, then compressed and crushed. The typical grinding time is between 30 and 60 minutes [15].

Procedure:-

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Select the Active Pharmaceutical ingredient (drug) & co-former.

⬇

Both the drug and co-former are ground into fine powders.

⬇

Place the powder in a grinding jar (mortar & pestle) and grind the powder together.

⬇

The grinding process creates mechanical energy that can promote the formation of Co-crystal.

⬇

Grind the both the powder together for a period of time (normal milling time is 60mint.).

⬇

Grinding help to break the crystal and rearrange into a new structure, where the drug & Co-former form a co-crystal.

Slurrying Technique

By dissolving two or more separate substances—typically a medication and a co-former—in a liquid, the slurrying method of co-crystallization creates co-crystals before the solid co-crystals are produced. By allowing the components to interact in a controlled setting, this approach induces the development of solid co-crystals.

- Prepare the solid materials.
- Mix with a solvent.
- Stir the mixture.
- Co-crystal formation.
- Separation and drying.

Solvent Drop Technique

Another name for this method is liquid-assisted kneading or grinding. This entails using a tiny amount of liquid to help grind stoichiometric amounts of co-formers. This technique was created to speed up the generation of co-crystals, but it has benefits over solid state grinding, including higher yield, greater product crystallinity, and control over polymorph synthesis [16].

Supercritical fluid atomization technique.

In the supercritical atomization procedure, high pressure supercritical fluid, such as CO2, is used to combine the medication and co-formers. This solution is atomized using an atomizer to create co-crystals [17].

EVALUATION OF CO-CRYSTALLIZATON

Co-crystal evaluation is the process of identifying and characterizing co-crystals as well as figuring out their physical and chemical characteristics using a variety of procedures.

X-ray diffraction (XRD) Studies – Single Crystalline and Powder (XRD).

This analytical method is used to identify the phase of the unit cells that are connected to the co-crystal. Single and powder X-ray crystallography can yield complete structural information on co-crystals. While single crystal XRD is primarily used for structural recognition using software like "DIFFRAC.SUITE TOPAS," powder XRD is frequently used to identify different co-crystals by detecting changes in the crystal lattice because different characteristic peaks are associated with different co-crystals [18].

Differential Scanning Calorimetry

In DSC, samples are heated at a steady rate, and the energy required to do so is measured. It is possible to identify the temperatures at which thermal events take place using DSC. Thermal events include crystallization, melting, deterioration, and the transition from glass to rubber. It is also possible to quantify the energy required for melting and (re)crystallization. The amount of crystalline material can be determined using the melting energy. [19].

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Spectroscopy- Vibrational, Nuclear Magnetic Resonance.
The structural behavior of co-crystals is identified using vibrational spectroscopy (infrared and raman), where the energy absorbed or dispersed by the co-crystals' chemical bonds differs from that of the pure components [20].

Field Emission Scanning Electron Microscopy (FESEM).
The surface morphology of co-crystals is investigated using topography or FESEM. For the comparison, component and co-crystal micrographs from the FESEM investigations are used [21].

Hot Stage Microscopy
When two chemicals are heated together, the total phase number shown by the system can be visualized using hot stage microscopy or the Kofler contact method. A zone of mixing is created when compounds with a high melting point begin to melt and recrystallize before other melted compounds come into contact with them [22]. The hot stage microscopy study incorporates both thermal analysis and microscopy. A solid's physicochemical properties are examined in relation to temperature and time [23].

CONCLUSION

Co-crystallization methods provide a flexible and effective way to improve the characteristics of materials and medicinal molecules. These techniques can solve common issues in drug formulation by promoting the creation of co-crystals, which can enhance solubility, stability, and bioavailability. Researchers are able to customize their strategy according to particular requirements because different processes, such as solvent evaporation and grinding methods, each have their own advantages and considerations. Co-crystallization techniques will be further refined as the area develops thanks to developments in characterisation and predictive modeling, creating new opportunities for materials science and drug development innovation. All things considered, incorporating co-crystallization processes has a lot of potential to improve the effectiveness and functionality of a variety of applications.

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