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A Review on Pharmaceutical Cocrystals

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ABSTRACT

Pharmaceutical cocrystals are crystalline materials composed of two or more different molecules, at least one being an active pharmaceutical ingredient (API), in a fixed stoichiometric ratio, held together by non-covalent interactions.Cocrystal can be prepared by cocrystallization method. Thus it improves the performance of solubility,stability and dissolution profile.This review article gives an overview on Pharmaceutical cocrystal including preparation method, physicochemical properties, evaluation and applications.

Key words: Cocrystallization,Coformer, Crystalline,Solubilty, Pharmaceuticals

I. INTRODUCTION

Pharmaceutical cocrystals are multicomponent systems in which at least one component is an active pharmaceutical ingredient and the others are pharmaceutically acceptable ingredients.Cocrystallizaton of a drug substance with a coformer is a promising and emerging approach to improve the performance of pharmaceuticals, such as solubility, dissolution profile, Pharmacokinetics and stability.

According to the definition by the US Food and Drug Administration (FDA), cocrystals are crystalline materials composed of two or more different molecules, typically drug and cocrystal formers ("coformers"), in the same crystal lattice. Pharmaceutical cocrystals have presented opportunities for engineering solid state forms beyond conventional solid-state forms of an active pharmaceutical ingredient (API), such as salts and polymorph. This includes modification of drugs to alter physical properties of a drug, especially a drug's solubility, without altering its effect .[1]

There are two main classifications of cocrystals, ionic cocrystals (or charge assisted) and molecular cocrystals. There are important differences. First, molecular cocrystals generally comprise two components, a biologically active molecular compound and a pharmaceutical acceptable molecular coformer. Ionic cocrystalscocrystals must have an additional variable because they comprise at least three moieties: an anion, a cation, and a neutral component, one of which is biologically active.The second one ionic cocrystals are sustained by charge-assisted supramolecular synthons, which are less likely to be impacted by solvent and more likely to afford large property variations.

Importance and design of Pharmaceutical Cocrystals

Cocrystals are important because the cocrystal solid can be designed to have superior physical properties to either of the pure starting molecules. Physical property improvement via cocrystal formation has been reported for many agrochemicals, pigments, solid explosives and particularly for pharmaceuticals. The physical property of the solids contained within a pharmaceutical drug product will have a direct effect on the processing, delivery and finally performance of the product.

Cocrystal formation with a suitable coformer offers the potential of improved solubility via modification of the underlying crystal structure, thus potentially rendering the compound bioavailable.Ascocrystal research has expanded, it has available a range of application areas for physical property manipulation through cocrystal formation. Improvements in solubility, stability, bioavailability, dissolution rate, melting point, hydroscopicity, bulk density, friability. [2]

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ADVANTAGES:

- **Improved Solubility and dissolution**:

Cocrystals can enhance the solubility and dissolution rate of poorly soluble drugs, leading to better absorption and bioavailabil-ility.

- **Enhanced Stability:**

Cocrystals can provide improved chemical and physical stability compared to the pure API, especially for sensitive compounds.

- **Targeted Delivery:**

Cocrystals can be used to create sustained release formulations

- **Increased Bioavailability:**

By improving solubility and dissolution, cocrystals can increase the bioavailability of drugs, leading to higher plasma concentrations and better therapeutic effects.

- **Potential for New Intellectual Property:**

Cocrystals can be patented as new drug formulations, potentially extending the lifecycle of existing

DISADVANTAGES

- **Coformer Selection:**

Finding suitable coformers that enhance the desired properties while maintaining stability can be challenging.

- **Stability Concerns:**

Some cocrystals may not be stable in the presence of excipients or under harsh conditions, such as strong acids or bases.

- **Scale-Up Challenges**:

Scaling up the production of cocrystals can be difficult, requiring optimization of product- ion methods and conditions.

- **Thermodynamic Stability:**

The true cocrystal solubility is not readily measurable for highly soluble cocrystals because they can transform to the most stable drug form in solution.

COCRYSTAL PREPARATION

The methods have been documented for cocrystal preparation,such a solid state grinding, solutionreaction crystallization, slurry conversion and hot melt extrusion. The selection of a suitable cocrystallization method remains empirical. Generally, the most widely used cocrystal formation approaches can be classified as solution-based methods and solid-based methods. In addition, the choice of the solvent affects the results of cocrystallization, as it can change the intermolecular interactions between API and coformer.solid-state methods offer the potential to eliminate the requirement of solvent use in cocrystal synthesis, where no or less solvent is required.[3]

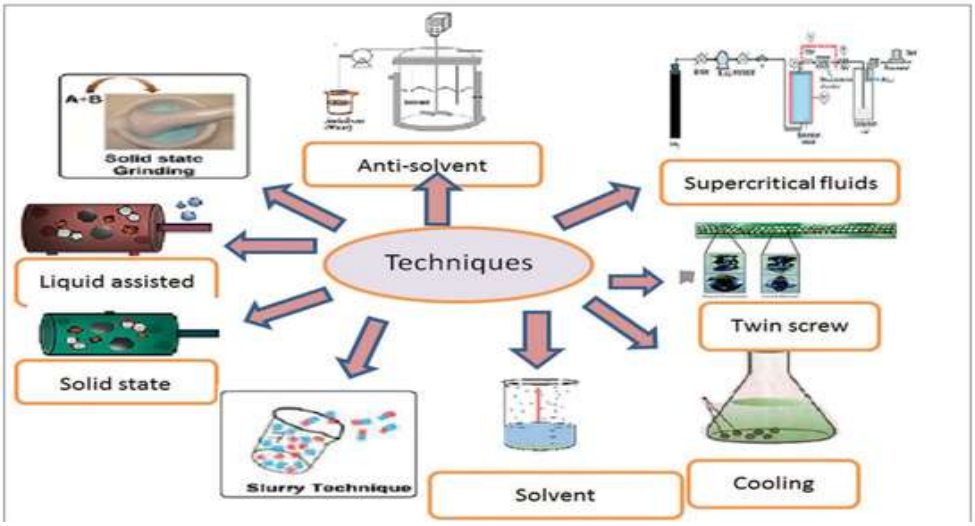

Fig no.1 Preparation Techniques

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A. SOLUTION BASED METHOD

A large no. of methods exists for cocrystallization from solution, and each will be discussed in the following section. The major driving force for crystallization is supersaturation. With a cocrystal system, there are two concentrations to be consider: (1) target molecule and (2) coformer. The concentrations of both relative to the solubility of the cocrystal decided the extent of supersaturation for cocrystallization. A eutectic point will exist where at one fixed solution concentration, a mixture of cocrystal and the target molecule is the stable solid phase for the system; Similar way a second eutectic point exists for a mixture of the cocrystal and coformer.It has been suggested that it may be useful to consider polymorphic compounds, which exist in more than one crystalline form as co- crystallizing components.

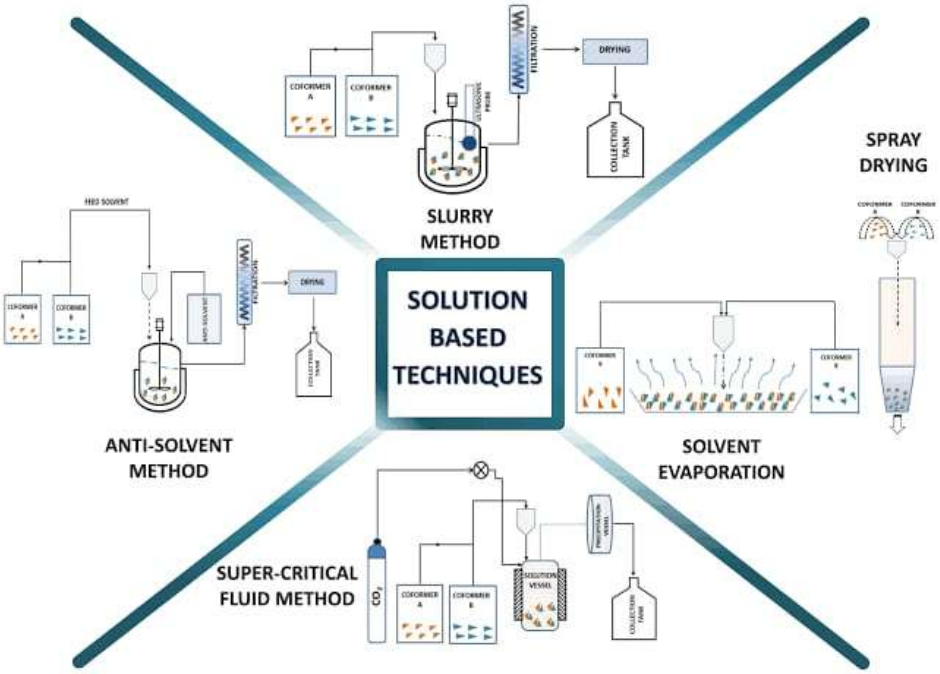

Fig 2:Solution based techniques

1. SOLVENT EVAPORATION METHOD

Solvent evaporation is the most common method for preparing cocrystals and is typically applied for synthesizing high-quality single-crystal cocrystals that suitable for structural analysis by single-crystal X-ray diffraction. In this approach, the cocrystal constituents completely dissolve in a suitable solvent at an appropriate stoichiometric ratio and then evaporate the solvent to obtain the cocrystal. The selection of solvent influences the cocrystallization, which potentially impacts the solubility of the reactants. [4]

2. ANTISOLVENT METHOD

Antisolvent crystallization has been considered an effective approach to control the quality, particle size and properties of cocrystals, in which crystallization is conducted in semi batch or continuous manufacturing process.The antisolvent method in pharmaceutical cocrystals formation involves dissolving the drug and coformer in a suitable solvent and then adding an antisolvent to induce precipitation of the cocrystal. This method relies on creating supersaturation by reducing the solubility of the cocrystal in the solvent/antisolvent mixture, leading to crystal formation.

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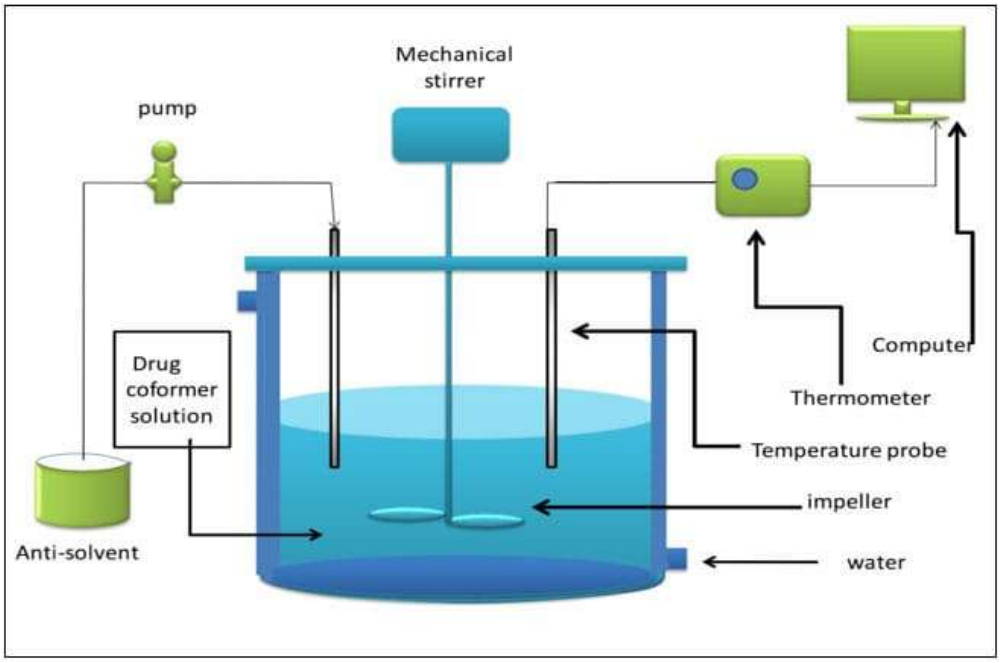

Fig 3 :Apparatus for antisolvent method

3. SLURRY CONVERSION

This technique involves the suspension of the target molecule and coformer, usually in a fixed molar ratio, in a solvent with the solid fraction always remaining in excess. In practical terms, the technique can also operate by adding the target molecule to a solution or suspension of coformer in solvent. While this is a solution based method, it does not require generation of a clear (fully dissolved) starting solution.The rate at which slurry conversion occurs will differ based on the solubility driving force, the relative concentrationof the target molecule and coformer, and the nucleation and growth kinetics of the system. There have been limited kinetic accounts of isothermal slurry conversion for Cooling any cocrystal system.

4. COOLING CRYSTALLISATION

Crystallization is a widely used method to prepare large-scale and purified crystals. In this method, the crystal properties of distribution size, purity, morphology and crystal polymorphism depend on the local supersaturation, which is determined by the process parameters, such as the transformation of mass and heat.In the crystallization process, the operating region depends on the stoichiometry of the cocrystal, as well as the thermodynamic stability zone of the cocrystal at the start and end temperature. [4]

REACTION COCRYSTALLIZATION

Reaction cocrystallization is suitable for cocrystal formation when the cocrystal components possess different solubilities; the reactants with nonstoichiometric concentrations are mixed to generate cocrystal supersaturated solutions, leading to cocrystal precipitation. In this method, the nucleation and growth of cocrystals are controlled by the ability of reactants to decrease the solubility of cocrystals.[5]

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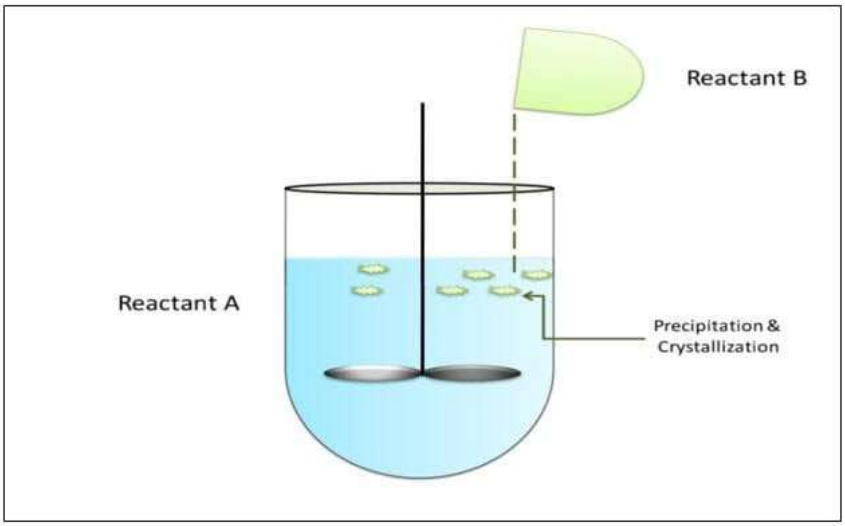
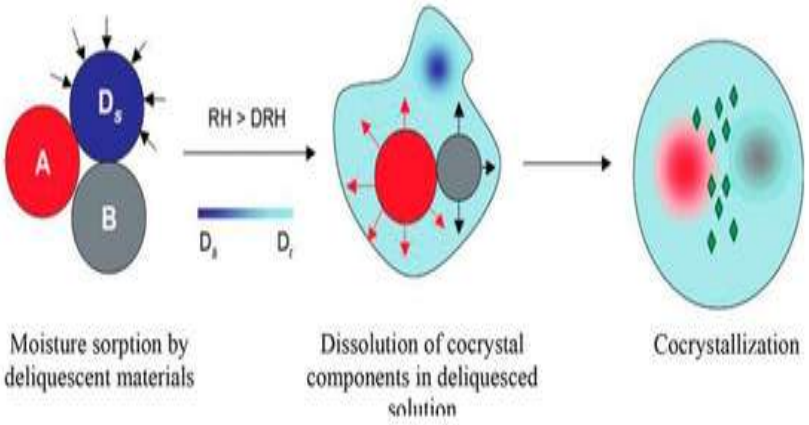


Fig 5: reaction cocrystallization

SOLID BASED METHOD

Solid-state crystallization methods are effective and environmentally friendly in cocrystal formation as they need less or no solvent; the cocrystal forms spontaneously through direct contact or grinding with higher energy inputs. They are reasonable alternatives to solution-based cocrystallization methods, which might generate environmental hazards due to the large solvent consumption. Numerous pharmaceutical cocrystals have been synthesized by solid-based methods. [6]



SOLID STATE GRINDING

The solid-state grinding method, which includes neat grinding and liquid-assisted grinding, is popular for producing cocrystals. The neat grinding method requires energy input to form the cocrystal by manual grinding (mortar and pestle) or mechanical milling (ball milling or vibratory mill) without the addition of a solvent. For liquid-assisted grinding, the cocrystal is formed by grinding with the assistance of a small amount of solvent. [7]

LIQUID ASSISTED GRINDING

The liquid-assisted grinding (LAG) method is useful for generating cocrystal products with high yields and high crystallinity compared to neat grinding. In addition, this method is suitable for rapid cocrystal screening, which is independent of the solubility of the raw materials. Enhanced molecular diffusion can be achieved by the addition of a small amount of liquid, which acts as a catalyst for accelerating cocrystal formation. The selection and amount of liquid play a key role in the mechanochemical reaction, influencing the formation of different solid products and the quality of crystals.

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This method can be used to prepare high-purity cocrystals with a significant reduction in the preparation time. It also allows the synthesis of selective polymorphic forms of cocrystals. This allows interconversion between crystalline forms of polymorphic organic components, according to polarity of the solvent. Limitations of liquid-assisting grinding include the fact that it is a small-scale technique, requires high energy consumption, and has a low performance in terms of product purity. [8]

HOT MELT EXTRUSION METHOD

Hot-Melt Extrusion (HME) method is a method that combined cocrystal formation and drug-formulation process, exhibit a simpler way to manufacture a drug product. In the hot melt extrusion (HME) technique, the cocrystals area unit is prepared by heating the drug and coformers with intense intermixture, which improved the surface contacts without using solvent. The heat that used for HME method is set at a specific temperature, where only the matrix is softened/ melted. Cocrystal formation using HME method requires a catalyzing agent to improve cocrystal formation played by softened/melted matrix. Suitable matrices for HME method must have several qualities; (1) have low glass transition (Tg) temperature, lower than melting point of cocrystal to ensure a lower processing temperature, (2) have limited noncovalent interaction with drug or conformer, (3) exhibit a rapid solidification step. [9]

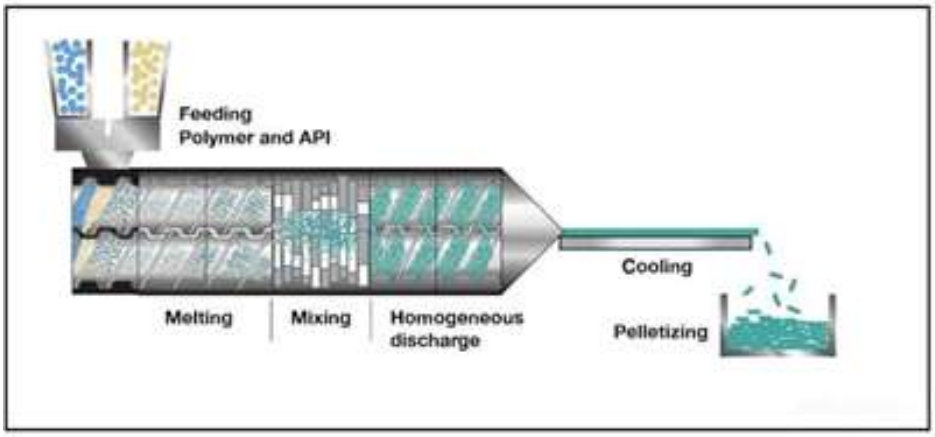

Fig 6: Hot melt extrusion method

Physicochemical properties of Pharmaceutical cocrystals

1. Melting Point
2. Stability
3. Photo stability
4. Solubility
5. Bioavailability

1.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.

Propofol is applied to induce and maintain general anesthesia and sedation. It is formulated as an oil-in-water emulsion because of its low melting point (18 °C), resulting in associated problems including instability, pain on injection . The propofol–isonicotinamide cocrystal is a stable solid at room temperature due to the increased melting point.

2.Solubility

The enhanced solubility of cocrystals increases the rate of dissolution, which is the rate limiting step in gastrointestinal absorption. Cocrystals can overcome the limitation of traditional methods of solubility enhancement such as configuration of salt, solid dispersion and micronisation, etc. by thermodynamic and kinetic approaches. [10]

3.Photo stability

The photostability of drugs is a function of inter ring distance in the crystal lattice. Higher the ring distance more is the expected photo stability. In this manner, cocrystals of carbamazepine-

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saccharin and carbamazepine-nicotinamide found to overcome degradation, by repositioning the molecules in the crystal grid by the virtue of its longer ring distances.

4.Bioavailability

Bioavailability refers to the rate and quantity of a medication that enters the systemic circulation. Developing new formulations of drugs faces a significant challenge when it comes to their low oral bioavailability. Crystal engineering plays a crucial role in designing and synthesizing pharmaceutical co-crystals that offer improved oral bioavailability and aqueous solubility.[11]

5.Stability

The stability of a pharmaceutical co-crystal usually covers four elements: relative moisture stress, heat stress and chemical and solution stability. The presence of relative moisture asses the product's best storage state as water in the cocrystals causes the loss of its quality.[12]

EVALUATION OF COCRYSTAL

1.Spectroscopic Analysis:

- Fourier-Transform InfraredSpectroscopy:

It is widely used process for the prediction and determination of chemical conformation, intermolecular interactions, and communion study between API and coformers. Analysis of the API, coformers, and cocrystals has been performed by FTIR in the wavelength range of 400–4000 cm^{-1}. This method is quick, nondestructive, prone to changes in molecular structure and can also detect a functional group.[13]

2.Thermal Gravimetry Method:

This method is useful for determining the sample weight under the influence of temperature for a specific period of time. Differential scanning calorimetry (DSC): It is used for the determination of cocrystal formation, determined by the existence of exothermic crest followed by endothermic crest in the DSC spectra. The cocrystal formation is determined by the presence of crest (peaks) present in the compound.

3.Hansen Solubility Study:

Hansen solubility parameter is one of the important tools to predict the miscibility of a drug and coformer in crystal formation or with excipients/carriers. It can also predict compatibility of pharmaceutical materials and its study is also useful for the pre- formulation and formulation of tablets. The cohesion energy that is used to predict physiochemical properties such as melting point and solubility of a compound

4.Dissolution Study:

It can be defined as "the quantity of drug substance that changes into a solution in a unit time in specific conditions of liquid/solid interface, solvent composition, and temperature." In-vitro dissolution study of any solid drug is carried out to evaluate the dissolution efficacy of formulated drug. This study is performed on the dissolution apparatus in the suitable dissolution medium as per official compendia. The samples are collected at specified time interval are analyzed by HPLC or UV spectrophotometer.

5.Stability Study:

It is also one of the potent parameters for the evaluations of cocrystals as it gives information about different climatic storage conditions and shelf life of the drug or drug products. There are various parameters that affect the stability of drug such as humidity, light, and temperature. Stability studies are performed at particular temperature and humidity conditions for predetermined time intervals which gives an idea about cocrystal product shelf life at various storage conditions.[14]

APPLICATIONS OF PHARMACEUTICAL COCRYSTALS

Pharmaceutical Applications:

- Improved Solubility &Dissolution:

Cocrystals can significantly enhance the solubility and dissolution rate of poorly soluble drugs, leading to better bioavailability and absorption.

- Enhanced Stability:

Cocrystals can improve the stability of APIs against degradation, especially in storage or during processing.

- Controlled Release**:**

Cocrystals can be used to create formulations that provide controlled or sustained release of drugs.

- Taste Masking**:**

Cocrystals can help mask the unpleasant taste of certain drugs, improve patient compliance

- Drug-Drug Interactions**:**

Cocrystals can be used to modulate the pharmacokinetic and pharmacodynamic effects of drugs by altering their absorption, distribution, metabolism, and excretion.

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- Targeted Drug Delivery**:**

Cocrystals can be designed to target specific tissues or cells, improving the effectiveness of drug therapy.

- Scale-Up and Cost-Effectiveness**:**

Cocrystals can assist in scaling up production and may offer cost advantages compared to traditional salt formation.

- Materials Science:

Cocrystals can be used to create materials with specific properties, such as enhanced mechanical strength or improved thermal stability.

Benefits of Cocrystals:

- Enhanced Drug Properties:

Cocrystals can improve the physicochemical properties of drugs, making them more suitable for formulation and delivery.

- Improved Bioavailability**:**

By enhancing solubility and dissolution, cocrystals can lead to better bioavailability of drugs.

- Novel Drug Formulations**:**

Cocrystals allow for the development of new drug formulat-ions with improved properties.

- Versatility:

Cocrystals can be tailored to meet specific needs, offering a wide range of possibilities.

II. CONCLUSION & FUTURE ASPECTS

Cocrystals especially Pharmaceuticallyhave become an important solid form in pharmaceutical space. It is evident from the number of research papers, review articles which are published in various journals as well as organization of conferences, symposiums and workshops in last decade. From the industrial point of view the number of patents filed throughout the world by various pharmaceutical industries and research groups are also increasing at a fast rate, since there is both regulatory and intellectual property relevance. Cocrystals are an excellent alternative for drug development in order to enhance solubility, bioavailability, stability and processability.

This review insight is provided on the proposed mechanisms of cocrystallization to be formed by different techniques. During development, cocrystallization processes mainly focus on traditional methods, such as solvent evaporation, grinding and the slurry method. However, as time has gone by and the field has progressed, scientists in this field have developed newer methods which are increasingly simple to enable the cocrystallization processes to overcome their previous limitations.

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