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A Review on Co-Crystallization: A Novel Technique for Enhancement of Solubility and Bioavailability

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Abstract:- Drugs' poor oral bioavailability and poor solubility are the main issues throughout the design and development of new products. Although they have significant drawbacks, traditional approaches have been used to increase the solubility of medications that are weakly soluble in water, such as solvates, salts, and polymorphs. The co-crystallization strategy is utilised as an alternate method to modify the physicochemical properties of an active pharmaceutical ingredient without changing its pharmacological action, such as solubility, bioavailability, permeability, flowability, and melting point. Drug and co-former are both included in co-crystals, which are multi-component crystalline systems with the same crystal lattice. A comprehensive overview of pharmaceutical co-crystals is provided in this review article. This page provides a summary of the benefits, co-crystal formation processes, evaluation, and characterisation testing.

Keywords- *co-crystals, solubility, bioavailability, physiochemical, crystal lattice.*

I. INTRODUCTION

The most common dosage forms include tablets, capsules, and other solid objects. There are various states outside solid state that enable transmitting the API more quickly. Nevertheless, this state provides API in the most portable, storable, and useful format. Consequently, comprehending and managing solid-state chemistry becomes a crucial component of medication development. Often times, because of several instability problems, an API cannot be created in its purest form. As a result,they are transformed into solid forms such co-crystals, polymorphs, salts, solvates, and hydrates. Eachone contributes a unique physiochemical property and influences the drug's stability, bioavailability, purity, and manufactureability in their own unique way. Given this, it is crucial to comprehend the connection between a compound's specific solid structure and its functional characteristics. Pharmaceutically active compounds have poor water solubility, which restricts their pharmacological effect. However, the solubility parameter cannot be compromised; hence several methods are being employed to improve bioavailability. [1]Several methods have been developed by researchers to make medications more soluble, which increases their bioavailability. Size reduction, solid dispersion complexation, salt formation, nanoparticles, self-emulsifying drug delivery systems (SEDDS), addition of co-solvents, nano-suspension and emulsion, and cocrystal formation are some of the methods that can be used to increase the solubility of poorly water-soluble drugs. Each methodology has advantages and disadvantages, and the choice of technique should take into consideration elements like the qualities of the active pharmaceutical ingredient (API), the nature of the selected excipients, the process of development, and the nature of the dosage form. The cocrystals approach stands out from the rest of these methods because it does not alter the drug's pharmacological properties while potentially enhancing its bioavailability and a number of physicochemical properties, including melting point, tabletability, solubility, stability, bioavailability, and permeability. [2]

The choice of solvent is based on choosing a coformer that is more soluble than the API and cocrystal. The selection of solvent was based on the equilibrium diagram of the solid-liquid phase of a multicomponent system, which distinguished between the critical concentration and the solubility of the coformer. The first step yields a greater cocrystal productivity rate, whilst the second step offers the greatest window for phase-pure crystallisation. Both of these steps are sufficient to drive cocrystallization. In terms of the kinetics of crystal nucleation and growth, the link between super-saturation and coformer concentration is investigated. As a result, the general design of the cocrystallization experiment can be summarised as follows: preparing a saturated coformer solution at the ideal temperature in the specific solvent, selecting a specific temperature at which to dissolve the API with heat so as to ensure that a point is reached where the coformerconcentration is just above the critical coformer concentration in order to obtain the maximum throughput that results in nucleation in a controlled manner in order. A coformer solution is created utilising low solubility solvents for coformers and cocrystals in order to separate the cocrystals from the residual solution and lessen the likelihood that they will be converted into pure components. [3]

As a novel technique for changing the physical, chemical, and pharmacological properties of medications, the cocrystallization process in pharmaceuticals has drawn considerable attention. Over other types, cocrystallization offers a few advantages. The possibility of the cocrystals that can be synthesised for an API is increased firstly by the wide range of APIs for which cocrystallization can be used, and secondly by the wide range of potential coformers that are accessible. Pharmaceutical salts and cocrystals have a similar analogy: for salts, the difference between the pKa of an acid and a base must be at least 2 units, whereas for cocrystals, the difference must be between 0 and 1 unit. The properties of a non-ionizable API could be altered is the additional advantage of cocrystallization [4, 5]

A. Advantages

- Co-crystal formation can be used to change the solubility, bioavailability, stability, hygroscopicity, shape, filtration, and flowability of medicinal compounds, among other crucial properties.
- A co-former that is enantiomerically pure can be used to create selective diastereomeric co- crystallization.
- Co-crystals can be a viable purification choice, especially for non-ionisable compounds, reducing the need for pricey chromatographic procedures in the process.
- Co-crystallization is a technique that turns liquids, pastes, and greasy goods into solids, enabling more reliable and effective manufacturing procedures. [6]

B. Physiochemical properties of co-crystals

- Solubility
- Maximum wavelength
- Stability
- Intrinsic dissolution
- Bioavailability
- Melting point
- Selection criteria for the conformer
- Tabletability

METHODS

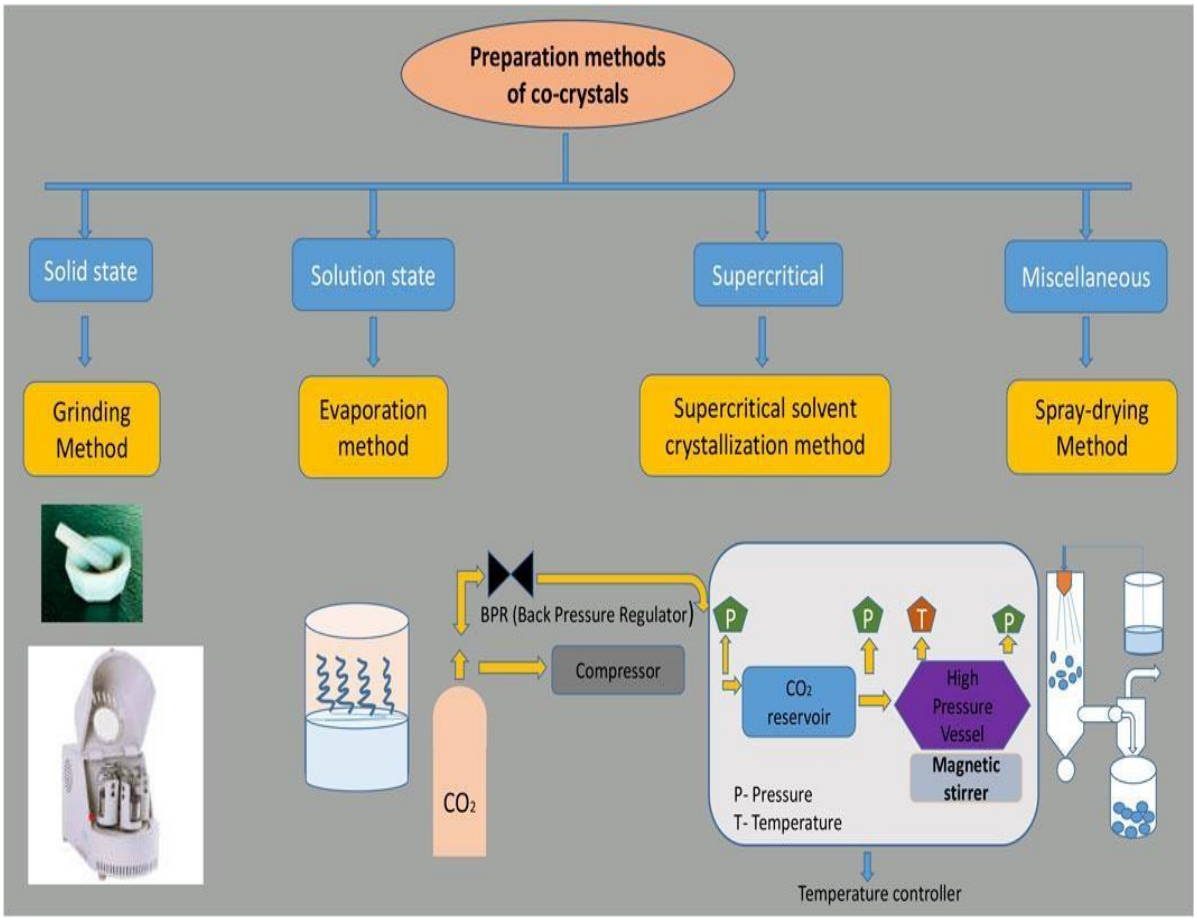

Fig. 1: Preparation Methods of co-crystals

A. Solvent Evaporation

The most practical approach for crystallisation is solvent evaporation. This method involves combining the material with a common solvent and allowing it to totally evaporate. The molecular solution is projected to undergo a number of hydrogen bonding events throughout the evaporation. The API and conformer co-crystal components are prepared in a solution using this method using a volatile solvent. The mixture is maintained at room temperature. The solute components achieve their super saturation concentration as a result of the slow solvent's evaporation, which causes nucleation and crystal formation [7]

B. Cooling Crystallization

Temperature is an important factor in crystallisation; for some substances, such as supersaturated solutions, a rise in temperature increases solubility, while a decrease in temperature causes the precipitation of co-crystals. The main advantage of this method is the production of the most uniform co-crystal size with the least amount of energy. [8]

C. Supercritical Solvent Crystallization

The supercritical solvent crystallisation method does not require the addition of organicsolvents because CO2 acts as a solvent. This process causes crystal nucleation, growth, and formation by inducing intermolecular interactions. This approach has the benefit of not requiring drying processes for

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elimination. [9]

D. Hot melt extrusion

Extrusion has following advantages such as highly effective mixing, improved surface contacts. The cocrystallization process doesn't require use of solvents. The thermodynamic stability of compound is the main factor influencing the choice of this method. With the help of pressure and heat above their melting points, the API and conformer are combined simultaneously in this method. Extrusion is useful method for cocrystals synthesis. [10]

E. Sonocrystallization Method:

A sonochemical approach has been devised to create organic cocrystals of finite size. The main goal of this procedure was the synthesis of nanocrystals. The process of forming caffeine-maleic acid crystals was initiated using ultrasound. [11]

F. Anti-solvent Co-crystallization

In order to increase co-crystal formation and reduce the solubility of co-formers in the solvent, an anti-solvent is employed in anti-solvent co-crystallization. Solvent and antisolvent must be miscible in order to prepare a single phase. The most used solvent-antisolvent combination is water and organic solvent. For co-crystals with lower solubility, anti-solvent cocrystallization is a correct alternative for cooling and evaporative co-crystallization. Additionally, the procedure can run at room temperature, using less energy than cooling and solvent evaporation. [12]

G. Slurry Co-crystallization

An alternate method for creating co-crystals with incongruent solubilities in the co-formers is slurry co-crystallization. A small amount of solvent is used to make slurry, which is then usedto suspend one or both of the co-former crystals. The single component crystals dissolve into the polymorphic transformation process mediated by solution as the stable co-crystal nucleates and grows. [13]

H. Laser irradiation technique

In order to encourage recrystallization into a cocrystal framework while using a powder formof the coformer, a high-power CO2 laser is used in the laser irradiation approach. This method is innovative for the synthesis of cocrystals. [14]

I. Reaction crystallization

The reaction crystallisation method is used to rapidly create cocrystals at microscopic and macroscopic scales at room temperature. Cocrystallization is reliant on the cocrystal components and their solubility. The more soluble component (co-former) is added in a quantity that is just below its solubility threshold after the less soluble component (drug) has first been formed into a saturated solution in methanol and filtered. [15]

J. Grinding

For the production of cocrystals, grinding procedures have been used extensively over the past severalyears, and they have shown to be superior to alternative methods (solution or melt). Wet grinding andtidy grinding are two different types of grinding techniques. In dry grinding, the coformer and drugare mixed in a stoichiometric ratio and pulverised in a ball mill or mortar and pestle. [16] Wet grinding was accomplished similarly to neat grinding by adding a few drops of solvent to the mixture. [17, 18]

K. Spray Drying.

In spray drying, cocrystals are created by spraying a hot air stream onto a solution or suspension of medicine and coformer to evaporate the solvent. This method is the mostwidely used since it is a quick, continuous procedure. In order to prepare and scale upcocrystals, a special environment will be provided via the spray drying method. [19, 20]

II. CHARACTERISATION OF COCRYSTALS

A. Melting point

The melting point is the temperature at which the solid and liquid phases are in balance. The melting points of pure API, co-formers, and cocrystals are calculated using the capillary method using liquid paraffin. [21, 22]

B. Single X-ray diffraction (SXRD)

Single X-ray diffraction (SXRD) is a technique for identifying the solid-state structure of cocrystals at the atomic level. The problem is that producing a single pharmaceutical crystal that is appropriate for SXRD testing is not always feasible. More often, powder X-ray diffraction (PXRD) is utilised to validate the creation of cocrystals. [23, 24]

C. Powdered X- Ray Diffraction

PXRD is frequently used for cocrystal structure evaluation and screening. The PXRD patterns generated by diffractometers were contrasted to evaluate the structure of cocrystals. When a cocrystal's PXRD pattern is different from that of its constituent parts, cocrystallization has occurred.[25]

D. Raman Spectrocopy

Vibrational, rotational, and other low frequency modes in a system are studied using Raman spectroscopy. Raman spectroscopy is used in a wide variety of applications to find characteristic peaks of cocrystals. [26]

E. SEM Analysis

The scanning electron microscope, or SEM, uses a high-energy electron beam to view a material. The interactions between the electrons and the sample's constituent elements produce signals that provide information about the sample's surface topography. It is utilised in cocrystal microscopy and to measure particle size. [27]

F. Solid-state NMR (SSNMR)

SXRD cannot study solid phases, hence characterising solid phases is necessary. In order to determine the complexity of a complex by measuring the proton transfer, SSNMR is employed. SSNMR is therefore a crucial technique for identifying salt or cocrystals. It can also be utilised to analyse hydrogen bonds and local conformational changes brought on by couplings to assess the cocrystal structure. [28]

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G. Stability Study

The information on drug product shelf life under various storage conditions is provided bystability studies. Drugs need to be kept in glass vials with a range of environmental factors(such humidity, temperature, and light) for varying lengths of time. The samples are nextsubjected to thermal analysis, drug release study, XRD analysis, and FTIR analysis; theoutcomes are then contrasted with those from the preliminary stability study analysis. [29]

H. TGA Analysis

The temperature of sublimation or breakdown can also be calculated using the TGA. The existence of volatile components or the hydrates/solvates forms of cocrystals can also be ascertained using this technique. TGA analysis helps to predict cocrystal purity, thermal stability, and compatibility. The sample mass lost weight during the TGA analysis, which is a sign of cocrystal breakup or volatile component loss. [30]

I. FTIR studies

FTIR spectroscopy is used to anticipate the intermolecular interactions and compatibility of medicines and coformers. The chemical structure of molecules is routinely predicted using this method. FTIR is used to assess pure pharmaceuticals, coformers, physical mixes, and cocrystals in the 400–4000 cm-1 range. [31]

J. DSC

Screening for cocrystal formation has been done by using DSC. The DSC spectrum can be used to check for the development of cocrystals by looking for an exothermic peak followed by an endothermic peak. These peaks in the physical mixing of components demonstrate the potential for cocrystal formation. Using a corresponding empty pan as a reference, pure drug, coformer, physical mixture, and cocrystals were weighed out (1.5-2.5 mg) and tested in aluminium pans with heating speeds of 5-30°. The inert atmosphere was maintained by nitrogen gas flowing at a 50 ml/min rate. DSC can be used to determine endothermic or exothermic behaviour, melting point, glass transition temperature, polymorphic nature, heat of fusion, and more. [32, 33, 34]

III. MARKETED FORMULATIONS OF COCRYSTALS

- Co-crystals of theophylline
- Co-crystals of aceclofenac
- Co-crystal of 5-nitrouracil
- Co-crystals of indomethacin
- Pharmaceutical co-crystals of carbamazepine and saccharin(Tegretol®)
- Pharmaceutical co-crystals of fluoxetine hydrochloride (Prozac®)
- Pharmaceutical co-crystals of itraconazole(Sporanox®)
- Pharmaceutical co-crystals of sildenafil (Viagra®)
- Co-crystal of melamine and cyanuric acid
- Co-crystals of Sacubritil and Valsartan (Entresto®)

IV. CONCLUSION

Pharmaceutical Cocrystals are an area of study that is now undergoing rapid development due to its significant possibility of improving the physical and biological properties of APIs. Combining knowledge-based and experimental techniques for coformer selection ushers in a new era in cocrystal formation. Cocrystallization is a useful technique for enhancing the physicochemical properties of drugs while preserving their pharmacological effects on the active pharmaceutical ingredient (API). Owing to enhanced pharmacological advantages they display and a shortened drug development process, pharmaceutical cocrystals are gaining industrial attention.

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