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Co-Crystal: A Review on Techniques and Characterization

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ABSTRACT:-According to recent studies, achieving therapeutic excellence and gaining market economies requires more than just discovering and manufacturing novel treatments. Modified versions of presently marketed drugs are becoming increasingly important as a result. Two further problems that hinder the development of new products are an active medicinal ingredient's low bioavailability and poor water solubility. Co-crystallization with pharmaceutically acceptable molecules has no effect on the pharmacological action of the pharmaceutically active constituent, but it can enhance physical properties including solubility, stability, and rate of dissolution. Particularly, co-crystal can be used to create innovative drugs with better solubility, enhancing the effectiveness and safety of treatment. Thermodynamic stability is the most important aspect in the co-crystal fabrication process. Various techniques such as grinding, spray drying, solvent evaporation, and ultrasound assisted solution can be used to produce co-crystal formation. Among the methods employed include co-crystallization, hot melt extrusion, and the supercritical fluid atomization process. The following review paper provides further insight into the concept of co-crystals in depth by providing a brief description of co-crystal formation techniques, properties of co-crystal (solubility, tabletability, melting point, stability, bioavailability, permeability), as well as its pharmacological uses.

Keywords:- Co-crystal, Solubility ,Physiological properties, Pharmaceutical ingredient, Bioavailability

I. INTRODUCTION:-

About 60–70% of the recently identified huge number of medications are associated with BCS Classes II (low solubility/high permeability) and IV (low solubility/low permeability). [1] These pharmaceuticals produce problems with dissolution, solubility, stability, therapeutic efficacy, and other aspects of drug use. [2]The modern period requires the use of many techniques to reduce issues with the permeability and solubility of pharmaceuticals that are readily available. Multi-component crystals, such as hydrates, salts, co-crystals, and solvates, play a crucial role in the development of novel solids, primarily in the pharmaceutical industry.

COCRYSTAL:-

The term "crystallization" refers to the molecular modification of a medication that results in changes to its physical properties. Drug and coformer are needed for the co-crystallization process in order to form the cocrystal. Cocrystals are multicomponent molecular crystals made up of two or more chemically distinct molecules arranged in a stoichiometric ratio. These crystals can be created by modifying pharmaceuticals to change their solubility or other physical characteristics without affecting the drugs' pharmacological effects. [3, 4, 5]

IMPLICATION OF COCRYSTAL:-

Crystallization, which is defined as the modification of a drug's physical properties at the molecular level, allows for the customization of the drug's physicochemical properties through a variety of enlisted blow techniques, negating the need for additional additives to enhance a substance's physicochemical properties. [6]

The nature of the molecular interactions between APIs and conformers, as well as synthesis processes, play a significant role in modifying just the physicochemical aspects of substances without affecting their pharmacological characteristics. The available coformer determines the impact on the API's physicochemical characteristics. [7, 8]

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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-CRYSTAL:

1) Solubility:

The capacity of a material to dissolve as much as feasible in a given volume of solvent at a certain temperature. The solubility of medication formulations that are hard to dissolve is examined. There are several approaches to increase a drug's solubility, including salt creation, solid dispersion techniques, particle size reduction, and more. [9, 10]However, a number of studies employ the crystallization approach to increase solubility. [11, 12]

2) Stability:

For any formulation, stability is a crucial element to take into account. It is crucial to guarantee the co-crystals' thermal stability, relative humidity stability, chemical stability, and solution stability. The co-crystals' relative humidity stability can be examined by water absorption/desorption experiments [13].

3) Melting Point:

The temperature at which a co-crystal's liquid and solid phases are in balance is known as the melting point. The melting point of the API shifts and becomes intermediate between the conformer and the melting point of the API when the cocrystal is formed. [14]

4)Permeability:

According to recent research, co-crystals may alter a drug's permeability in addition to improving its dissolving characteristics. These findings might enable co-crystals to be used in class III and, more crucially, class IV BCS pharmaceuticals in addition to class II medicines. The primary factor influencing drug absorption and distribution is the drug's capacity to permeate the biological membrane. [15]

5)Tabletability:

Co-crystallization is suggested as a way to improve flow ability and good mechanical strength, two requirements for tableting. For instance, compared to pure carbamazepine, the co-crystal of saccharine and carbamazepine was shown to be denser. Paracetamol's compression qualities enhanced when theophylline, oxalic acid, naphthalene, and phenazine were present. [16]

6)Bioavailability

The rate and amount of pure medication that enters systemic circulation is known as bioavailability. One of the main obstacles in the creation of formulations is the low oral bioavailability of APIs; nevertheless, this bioavailability can be increased or improved with the aid of cocrystallization. Numerous studies have improved the bioavailability of certain medications by converting them into co-crystal form.[17]

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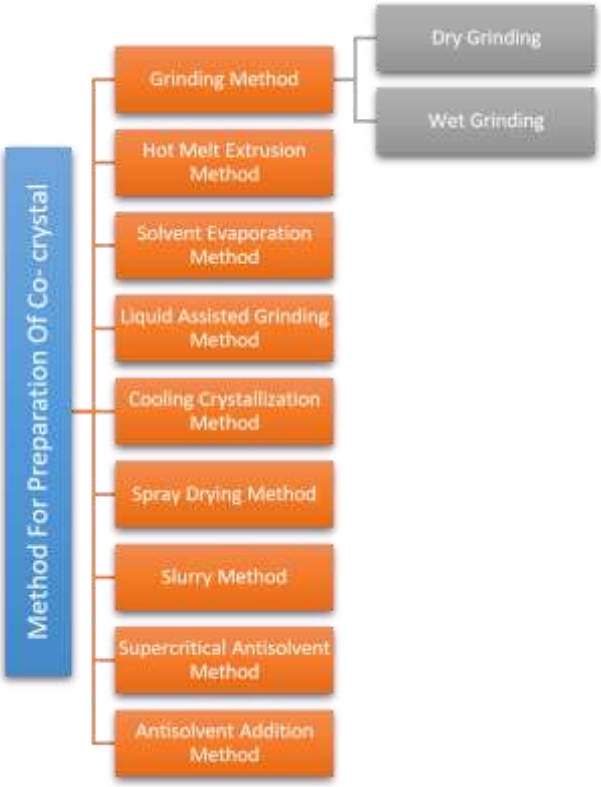
METHOD OF PREPARATION OF CO-CRYSTAL:



The discovery of drugs has led to the adoption of a variety of techniques for the manufacture of multicomponent solid forms, including cocrystals, cosolvates, co-amorphous, polymorphs, and hydrates/salts. For such preparations, the choice of solvent, API, and coformers are crucial factors. The many types of approaches that are most frequently employed include: Method based on solids. In general, melt extrusion, melt crystallization, and solid phase grinding are included. This process involves melting and combining the coformer and API to generate cocrystals in a predetermined stoichiometric ratio 1:1, 1:2. Although it is a simple, scalable, and continuous method, it is essentially not appropriate for thermo labile moiety.

1. Grinding method

It is one of the mostly used techniques for the cocrystal formation from the last few years. It is basically of 2 types: (a) Dry grinding method and (b) Wet grinding method.

a) Dry grinding method

The most popular and regularly used method for creating cocrystals involves mixing coformers and API with a mortar and pestle at a stoichiometric ratio. This process is mechanical and timeconsuming, yet it is straightforward, easy to use, environmentally friendly, and very productive. These days, laboratory-scale planetary milling devices are also offered [18]. Piracetam-citric acid, piracetam-tartaric acid, and carbamazepine-nicotine amide are a few instances of cocrystals made using this technique [19]. Compared to piracetam-citric acid cocrystal and acyclovir-succinic acid cocrystal by grinding approach [20,21],the liquid-assisted grinding method exhibited a higher cocrystal formation efficiency.

2. Hot melt extrusion method

This method involves transferring the API and coformers into a system with a set, regulated temperature, where they melt and create new moiety cocrystals [22]. Since the drug and coformer need to be combined when they are both molten, this method is not appropriate for thermolabile medicines. Using a molten mixture of API and coformer—pyrazinamide cocrystals, for example—this technique improves surface contact without the need for a solution or solvent [23].

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4. Solvent Evaporation Method:-

Another name for it is the solvent evaporation technique, which involves gradually vaporizing a solution (solvent). The functional moieties in the coformer and API trade places during the dissolving process to create new hydrogen bonds, which are most frequently utilized by researchers, such as in the case of glutaric acid cocrystals [24]. This process involves dissolving the API and coformers in a boiling solvent while stirring continuously until the final volume is tiny. In a heated air oven or outside, this boiling solution is allowed to cool gradually to generate cocrystals , such as theophylline citric acid cocrystals [25].This method involves choosing and dissolving solvent-dispersing coformers, after which the medication is dispersed into it using a dispersion homogenizer. The mixture is then combined with the appropriate solvent to precipitate the coformer into the drug's powdered indomethacin-saccharide, or carbamazepine-saccharide cocrystal.[26]

5. Liquid-assisted grinding method

Grinding with liquid assistance is another often favourabletechnique for creating cocrystals. In addition to offering a quicker rate of cocrystal formation than dry grinding, this approach is also more dependable and appropriate. Because it uses less solvent than other industrial manufacturing methods, it is recognized as an environmentally safe and ecofriendly process. More significantly, the procedure reduces the chancesof undesired solvate formation. Adefovir dipivoxil-glutaric acid cocrystal [27] and quercetin-succinic acid cocrystal increase solubility and dissipating rate upto1.62 and 1.25, respectively. These processes are independent of temperature.

6. Cooling Crystallization Method:-

This technique for the creation of cocrystals is less commonly used. In general, it is a slower and more laborious procedure than other methods, like the cocrystallization of darunavir with succinic acid. Compared to its individual medication darunavir, this has improved solubility, dissolution, and micrometric characteristics [27].

7. Solvent drop grinding

Using a suitable solvent, the coformer and API are combined in this approach. Drops of the solvent are added while swirling constantly. The solvent that is utilized acts as a catalyst to promote the production of crystals. This method can also be used to create amorphous cocrystals. Coamorphous crystals of carbamazepine and nicotinamide are one example. Crystallization cooling technique. This technique for the creation of cocrystals is less commonly used. In general, it is a slower and more laborious procedure than other methods, like the cocrystallization of darunavir with succinic acid. Compared to darunavir alone, this has improved micrometric characteristics, dissolution, and solubility [28].

8.Ultrasound-assisted solution method

This method is applied to the manufacture of nanocrystals wherein the drug and coformers are dissolved in a suitable solvent. To create turbidity, the solution is put in a sonicator, and deterioration and fragmentation are prevented by maintaining a constant temperature. For cocrystal formation and solvent evaporation, the solution is left overnight [29].

9.Spray drying method

This approach is highly frequently used to manufacture cocrystals due to its rapid, continuous, onestep process. This method involves allowing a solution containing coformer and API to evaporate over a heated air stream. This method applies to more user-friendly and scale-up applications, such as sulfadimidine/4-aminosalicylic acid cocrystals [30].

10. Slurry method

It is also among the simplest methods for the cocrystal formation phase of the crystallization process. After dissolving the chosen medication and coformer in an appropriate solvent to create a suspension, the mixture is agitated, filtered, and dried. Using a slurry method of crystallization, the medication celecoxib-venlafaxine cocrystal (NSAIDs + antidepressant) was created and patented. High solubility BCS class I drugs overcome the solubility issue with venlafaxine (BCS class I) and celecoxib (BCS class II) [31].This method involves making a slurry of API and coformer in an appropriate solvent, stirring it well with a glass rod or magnetic stirrer, and letting the solvent cool gradually at room temperature until cocrystals form, such as aspirin-4,4 dipyridyl cocrystals or acyclovir-succinic acid cocrystals [32].aspirin-4,4, dipyridyl cocrystals [33]and trimethoprim-sulfamethoxazole cocrystals.

11. Supercritical antisolvent technique

This is the most effective method for preparing crystals and preventing compound heat

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deterioration. This method forms cocrystals by dissolving a solid sample in an appropriate organic or inorganic solvent and injecting the mixture into a supercritical fluid at high pressure. This causes the solution density to drastically drop [34].Gomes de Azevedo was the one who first prepared indomethacin saccharin cocrystals. Similarly, cocrystals of piracetam-salicylic acid, diflunisal-nicotinamide, paracetamol-dipicolinic acid, and naproxen-nicotinamide are a few examples made using this technique. The best supercritical fluid used in the pharmaceutical industry is CO2 (non-polar chemical), which has the advantages of being inexpensive, readily available, non-flammable, and nontoxic. [35]

EVALUATION TEST:

1.Solubility study :

The definition of it is "the amount of drug substance that transforms into a solution in a unit of time under particular conditions of temperature, solvent composition, and liquid/solid interface." To assess the effectiveness of a drug's formulation for dissolve, an in-vitro dissolution study is conducted on any solid medication. According to official compendia, this study is conducted on the dissolving apparatus in the appropriate dissolution medium. Samples are taken at predetermined intervals and examined using a UV spectrophotometer or HPLC. Study of Solubility The solubility of cocrystals is ascertained using the Higuchi and Connors method. According to the official compendium, the solubility of cocrystals, pure API, and physical mixtures of API and coformer are measured in water and several other media.[36]

2. FTIR

It is a method that is frequently used to anticipate and determine chemical conformation, examine communion between API and coformers, and determine intermolecular interactions. FTIR analysis was conducted on the API, coformers, and cocrystals within the 400–4000 cm−1 wavelength range. This technique can identify a functional group and is fast, non-destructive, and sensitive to changes in molecular structure.[36]

3.PXRD

Using these analytical techniques, Bolla et al. analysed acemetacin cocrystals and determined the crystalline cell dimension, purity, structure, and texture of this bulk sample [37]. It deals with the investigation of crystalline behaviour of a powder or drug sample.

4.SEM

An electron beam with high intensity is scanned across a sample using a scanning electron microscope (SEM). The signals that are produced when the electrons interact with the sample's constituent atoms reveal details about the surface topography of the sample. It is employed to ascertain particle size and the cocrystal micrograph.[38,39,40]

II. CONCLUSION:-

Co-crystals are an excellent alternative for drug development to enhance solubility, bioavailability, stability and processability. However, there are several challenges including co former selection, physicochemical characterization and formulation. Careful drug conformer screening and formulation design can lead to successful Cocrystals development.. This review insight is given on the proposed mechanisms of co-crystallization in different techniques. On early development, co-crystallization processes mainly focus on traditional methods, such as solvent evaporation, grinding, and slurry method. But, every method still needs to investigatethoroughly to understand the clear co-crystallization mechanism for each method.

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