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A REVIEW ON PHARMACEUTICAL CO-CRYSTALLIZATION

Abhale Swapnali S.[1], Loharkar Harshal S.[2], Rakibe Vaishali D.[3]

[1, 2]Student, [3]Assistant professor,

[1]Pharmaceutical Quality Assurance Department, MGV's Pharmacy College, Panchavati, Nashik-03.

[2]Pharmaceutical Quality Assurance Department, PES Modern College of Pharmacy, Nigdi, Pune.

[3]Assistant professor, Pharmaceutical chemistry Department, MGV's Pharmacy College, Panchavati, Nashik-03.

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Abstract:

Co crystal is an important and useful product in the pharmaceutical industry. In this paper included the main information about co-crystals. Polymorphism is one of the phenomena to related co-crystal which is beneficial crystallization. Crystal is prepared by various methods at the commercial level like as grinding, slurry method, Hot melt extrusion, Antisolvent method, supercritical fluid technology, Spray drying technique are used for the preparation of co-crystal. Before applying the co-crystals in any production to check for characterizing like solubility, maximum wavelength, stability, crystallographic method, different scanning calorimetry, thermal analysis, spectroscopy, scanning electron microscopy, melting point. The co-crystals are applying in the pharmaceutical industry for improving such different parameter stability, solubility, dissolution rate, hygroscopicity, or mechanical property. Earlier day regulatory market is responding to the growth of a product or needs to approval to product to in market like USFDA, EMA regulatory agencies. Now a day new advancement comes in co-crystallization production or to develop their easy application they are multi-drug nanocrystal, polymorphism, salt cocrystal, quick co former screening, etc. The main purpose of the article to know about co-crystallization and their related factors.

Keywords: *crystallization, polymorphism, method of preparation, characteristics, and properties of the co-crystal, regulatory aspect of co-crystal, new advancement*

Corresponding author:

Abhale Swapnali Sanjay,

Pharmaceutical Quality Assurance Department,

MGV's Pharmacy College, Panchavati, Nashik-03

Email address: swapnaliabhale1098@gmail.com

Phone number: 9049391829

QR code

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INTRODUCTION:

Pharmaceutical co-crystallization is an Associate with a nursing innovative technique, which might use to urge alternatives to salts, solvates, and polymorphs. It might be applied to the modification of API throughout the method of dosage type style. [1]

A recently discovered drug that squares measure 70%-90% is present in BCS category II (Low solubility/High permeability) and sophistication IV (Low solubility/low permeability) downside facing associated with dissolution, solubility, stability, efficacy, etc. Now a day's decreasing problem regarding solubility, the permeability of available drugs with various methods. Crystal play role in the design of a new solid entity[2]. Unluckily many drugs with generally excellent pharmacological will show badly bioavailability, because of unwanted physical properties. A Co crystal basically consists of two components that are API and Former; former can any other excipients, API which can be a combination to reduce the dose and side effects. Co crystallization is an effective crystal engineering approach to various properties of a drug as well as modifying crystal structure. Co crystal can be a multicomponent crystal that is formed between two components that are solid under ambient conditions where one component is an acceptable molecule [3]**.** Co crystal is classified as 0-D, 1-D, 2-D, and 3-D assembly depending upon the type of intermolecular interactions that are present within and between a collection of a certain molecule, the nomenclature of co-crystals provided based on chains, ring, and intermolecular hydrogen bonding [4].

Polymorphism:

Polymorphism is defined as the ability to reveal different unit cell structure in crystals originating from a variety of molecular conformations and packing. Is a common phenomenon of crystalline materials, it describes the ability of a sub to existing two or more crystalline phase that have different arrangements of molecule in solid-state but are otherwise identical interns of chemical contents. Polymorphism affects many different types of compounds ranging from minerals, metallurgy, and the pharmaceutical industry [5]. Crystalline solids (both single and multi-component) are known to exist in multiple forms. These forms differ in internal arrangements of molecules in the crystal structure are known as polymorphs. The solubility and dissolution property of polymorphs are directly related to the bioavailability of drugs is the prime interest of the pharma industry.

METHOD OF PREPARATION:

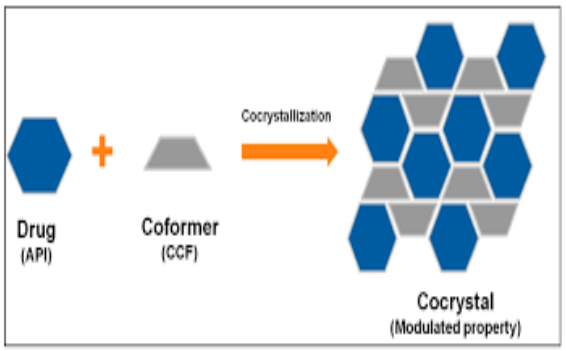

Fig 1: Formation of co-crystal

1) **Grinding:** The API and Co former components can be cocrystals by pulverizing without the addition of solvent called as grinding, or some drops of solvent drop-grinding or liquid assisted grinding. In industry, materials are pulverized in the mill. The mechanism involved in here to low molecular weight components diffuse easily into the API crystal lattice which could result in the formation of an intermediate phase that could further lead to the formation of co-crystal. The current technique of liquid assistant grinding (solvent drop grinding) has been shown to improve to kinetic and facilitate to the co-crystal formation and as lead to decreased attention of solid-state grinding as a method for co-crystallization. There are two types of grinding which are neat grinding and solvent drop grinding. The neat grinding method can be done as mechanical grinding using a ball mix, vibrating mill, or by manual grinding. Solvent drop grinding is the regular addition of solvent and should be able to dissolve compound [6].
2) **Slurry method:** In that addition of crystallization solvent in components in API along with Conformer. The selection of process mainly depends upon the physical stability of the crystallization solution to co-crystals and its solid form dissolved in a solvent to form a solution. [3]
3) **Antisolvent addition**: It is a method for precipitation or recrystallization of co-crystal former and API. The solvent includes buffers (ph) and organic solvents. [3] It is a method to prepare high-quality co-crystals due to using this process second liquid such as organic solvents/ buffer to add into drug the co former to achieve supersaturation. The added liquid should be miscible with solvent to precipitation to co-crystal.[1]
4) **Hot-melt extrusion:** it is to be used for the preparation of co-crystals as a continuous manufacturing process in a single step. Hot-melt

extrusion drugs and conforms as heated with intense mixing without the addition of solvent. [2] The selection of the method depends on the thermodynamic stability of the compound. Hot-melt extrusion was used in the synthesis of carbamazepine - nicotinamide co-crystal with polymer as former. [3]

5) **Sonocrystallization method:** Sonoreactor can be used for the preparation of cocrystal .drug and co former are dissolved in a common solvent and kept for sonication at a constant temperature. [1] This method was primarily developed for the preparation of nanocrystal [3]. comparative study of the method of preparation of caffeine and theophylline as API and L-tartaric acid co former by solvent drop grinding method and sonochemical method has been commerced [6].

6) **Supercritical fluid technology**: Substance is characterized by a critical point that is obtained at specific conditions of pressure and temperature. Compound subjected to pressure and the temperature high then its critical point, fluid said to be supercritical.[7]

Drug + conformer

↓

Dissolve to gather in high-pressure supercritical fluid

↓

Atomize the solution with atomizer at normal temperature and pressure cases conversion of co_2 from a liquid state to gas.

↓

Formation of co-crystal [2]

7) **Spray drying technique:** Compounds are dissolved in a common evaporating solvent and spray to hot steam of air for evaporation of solvent yield to good co-crystals. After the preparation of co-crystals, rigorous scrutiny has been carried out for conformations and purity of prepare co-crystal.[1]

Drug + Coformer

↓

Prepare solution/ suspension with evaporation

↓

Spray the solution in the hot air stream to evaporate the solvent

↓

Formation of co-crystal [2]

CHARACTERIZATION OF COCRYSTALS: [1] [3] [6]

1) Solubility:

1. The Cocrystallization technique is mainly used to improve the solubility of insoluble or low solubility drugs.
2. So solubility determination is an important characterization.
3. Cocrystals show increased solubility.

2) Maximum wavelength:

1. The UV scan of the crystal solution is performed.
2. The UV scan gives peaks showing Lambda max of API and Coformer if the coformer is a drug.

3) Stability:

Ensure the chemical stability, solution stability, thermal stability, and relative humidity of crystals.

4) Crystallographic methods:

1. Can be performed by single-crystal X-ray diffraction (SXRD) and powder X-ray diffraction (PXRD).
2. Single-crystal X-ray diffraction:
   -Provide unambiguous atomic positions and complete structural information.
   -Limitation: Requires a single crystal for study.
3. Powder X-ray diffraction:
   -More frequently used than Single-crystal X-ray diffraction to verify the formation of cocrystals.
   - Sample should be triturated to get fine powder and should obey Bragg's law ($n\lambda=2d \sin\theta$) for analysis.
   -Can use on daily basis for determining solid-state nature and purity of every batch of synthetic drugs from diffractometer by using microcrystalline cellulose.

5) Differential Scanning Calorimetry (DSC):

1. Used to study the change in heat flow between sample and reference along with this it can be used for determination of melting point, Glass transition, the heat of fusion, levels of crystallinity.
2. The thermogram is obtained from DSC screening.
3. The thermogram of co-crystals shows a different exothermic peak from that of the pure thermogram of drug and Coformer
4. followed by an endothermic peak.
5. The melting point and heat of fusion detected for co-crystals will be different from that of the pure components.

6. If a physical mixture that cannot form co-crystals is heated, then only a single endothermic peak associated with eutectic melting can be seen in a thermogram.

6) Thermal analysis (Thermogravimetry, Differential thermal gravimetry):
Used for characterization of polymorphism, purity, salvation, degradation, and drug compatibility.

7) Spectroscopy (Vibrational, Infrared, Nuclear magnetic resonance spectroscopy)

1. Vibrational Spectroscopy:
   -This study the Vibrational, rotational, and low-frequency modes in the system.
   -Using Infrared absorption spectroscopy and Raman spectroscopy.
   -It identifies the characteristic peak of cocrystals.
2. Infrared Spectroscopy:
   - IR spectrum of cocrystals and pure drug coformer is different
   - This difference is due to the formation of hydrogen bonding.
3. Nuclear magnetic resonance spectroscopy:
   -It provides structural information of cocrystals.

8) Scanning electron microscopy:

1. To characterize the surface morphology of the particles.
2. It is used to determine cocrystals micrograph and particle size.

9) Melting point:

1. It is the point at which the solid phase and liquid phase are in equilibrium with each other.
2. It has been done for API, conformer, cocrystals by a capillary method using liquid paraffin or by differential scanning calorimetry (DSC).

PROPERTIES OF COCRYSTALS: [8]
The pharmaceutical cocrystals exhibit the following properties.

Table 1: Properties of co-crystals.

SR.NO.	PROPERTIES	DESCRIPTION	EXAMPLE
1	Chemical stability	Chemical stability increases	Cocrystallization of carbamazepine with coformers such as saccharin (SAC) or nicotinamide (NCT) exhibits greater stability against hydration and degradation
2	Melting point	It differs for cocrystals than individual components due to changes in molecular interactions, composition, and structure.	Carbamazepine melting point is 192°c. Carbamazepine- Nicotinamide cocrystal melting point is 160°c.
3	Hygroscopicity and hydrate formation	It can alter API Hygroscopicity and Prevents hydrate and solvate in API.	-Carbamazepine with saccharin (SAC) or nicotinamide (NCT). -Caffeine and theophylline with Dicarboxylic acids.
4	Dissolution rates and solubility	Cocrystals alter the dissolution rate of the crystalline drug.	Itraconazole has low aqueous solubility. 2:1 cocrystals of Itraconazole with 4 dicarboxylic acids (l-tartaric acid, maleic Acid, succinic acid, and fumaric acid) shows a 4-20 fold faster dissolution compared to the crystalline drug.
5	Mechanical property	Shows different mechanical properties due to differences in molecular interactions and crystal structure.	1:1 cocrystal of caffeine with methyl gallate shows improved tablet ability

INTELLECTUAL PROPERTY OF CRYSTALS: [1] [7]

- For an invention to be patentable it should be Novel, Utility, And non-obviousness.
- But the patent filing of cocrystals is related to their particular chemical compositions, supramolecular systems in the crystal structure, and beneficial properties.

Table 2: Difference between United state food and drug administration (USFDA) and Europian medicine agency (EMA) intellectual policy for cocrystals.

SR.NO.	UNITED STATE FOOD AND DRUG ADMINISTRATION (USFDA)	EUROPIAN MEDICINE AGENCY (EMA)
1	Defined as -Solids that are crystalline materials composed of two or more molecules in the same crystal lattice.	Defined as -The single crystal or homogenous crystal which is made from two or more components in a definite stoichiometric ratio -The arrangement in the crystal lattice is not based on ionic bonds.
2	In the year 2013	In the year 2015
3	It distributes direction on the regulatory classification of co-crystal	Arranged co-crystal is a comparative method to salts and API
4	Co-crystals are considered as same as API from	co-crystal is viewed as equivalent to the API except if it shows diverse Pharmacokinetic properties, a methodology that the industry considered progressively satisfactory
5	Regulatory regard: Similar to polymorph of the same API	Regulatory regard: Similar to salts of the same API
6	Coformer: Neutral guest compound (excipient)	Coformer: Non-active components/ Reagents (excipient)

RECENT ADVANCEMENTS: [3] [9]

Quick conformer screening technique: For the cocrystallization, conformer plays an important role and its proper selection is most important. At present empirical method is used for conformer selection but a quick conformer screening technique is important for the screening of conformer for cocrystallization.

1) **Application for neutraceuticals:** As neutraceuticals having poor bioavailability cocrystallization is beneficial.
2) **Multidrug nano cocrystals:** This is used for Malignant growth and torment related issue. It increases bioavailability and gives a quick onset of action due to quick-dissolving.
3) **Discoveries of new synthons:** Synthons are structural unit of the building of cocrystals
4) **Polymorphism of cocrystals:** Sometimes cocrystals have more polymorphism than conformers. In recent many polymorphic cocrystals are developed mainly trimorphic.
5) **High-order cocrystals:** This structure expands the solid-state landscape of drugs. The examples are still limited because of less attempt to made high-order cocrystals. One of the strategies used for preparing high order cocrystals is cogrind multiple compounds employing LAG.
6) **Salt cocrystals (CAB cocrystals):** Salt cocrystals have the advantage of high potency and the limitation of hygroscopicity. An example of hygroscopicity is valproate Hemi sodium salt.

APPLICATIONS OF COCRYSTALIZATION IN PHARMACY:[10]

Table 3: Examples of drug and co-former used in pharmacy

SR.NO.	DRUG	CATEGORY	COFORMER
1	Fluoxetine hydrochloride	Antidepressant	Benzoic acid (BA), Succinic acid (SA), Fumaric acid (FA)
2	Carbamazepine	Antiepileptic	Saccharin
3	Itraconazole	Antifungal	Succinic acid
4	Oxcarbazepine	Antiepileptic	Saccharin, Succinic acid
5	Aceclofenac	Non-Steroidal Anti-inflammatory Drug (NSAID)	Chitosan
6	Isoniazid	Antitubercular	Protocatechuic acid
7	Paracetamol	Analgesic, Antipyretic	Caffeine

CONCLUSION:

This article summarized information about co-crystal and their methods and properties etc. According to the literature survey, it can be concluded that crystal importance in the pharmaceutical industry or the formation of the dosage form. Co crystal is helpful to the drug to improve their solubility, stability, or bioavailability. One of the important aspects related to co-crystal intellectual property rights the molecule it satisfies all criteria then it means granted to the product intermediate. Finally, we conclude that the new advancement in co-crystal, which is responsible for a great opportunity for the pharmaceutical industry in the future aspect.

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