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Cocrystals: An Emerging Approach to Modify Physicochemical Properties of Drugs

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ABSTRACT

Pharmaceutical cocrystals represents a class of Pharmaceutical materials with definite stoichiometries often stabilized by hydrogen bonding, which have recently emerged as interesting alternative solid forms with potential for improving the physical and biopharmaceutical properties of a drug substance. Pharmaceutical cocrystal is crystalline nonionic supramolecular complexes of two one being neutral molecules or an active pharmaceutical ingredient (API) and the other a cocrystal former. Cocrystal formation is studied in the development stage in order to solve an issue with solid form or formulation or to expand intellectual property. The review focuses on pharmaceutical cocrystals, cocrystal design, and methods of co crystallization, characterization, regulatory classification, cocrystals as intellectual property and some examples of candidate for preparation of cocrystals.

Keywords: Cocrystal, Co crystallization and Addition compound.

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INTRODUCTION

The term "crystal engineering" was introduced by R. Pepinsky in 1955[1]. Further G.M.J. Schmidt in the 1960's implemented in the context of topo chemical reactions on cinnamic acid [2]. It is estimated that more than 70% of all solid drugs are produced by crystallization. The design and optimization of pharmaceutical crystals that possess different molecular components is valuable to control Pharmaceutical properties of solids without changing the covalent bonds and Pharmacological action of drug substances. In the last few years, crystal engineering of APIs through co crystallization has gained an increased interest as means of optimizing the physical properties of solid dosage forms. Cocrystals are multiple component crystals or crystalline complexes stabilized by hydrogen-bonded assemblies between neutral molecules of the active pharmaceutical ingredient (API)[3]. Some questions arise while discovering new cocrystals of drug substances.

What are Cocrystals?

Cocrystals are most dynamically developing pharmaceutical structural homogeneous crystalline materials that contain two or more neutral building blocks that are present in definite stoichiometric amounts and are obtained through the establishment of strong hydrogen bonds, π-π, ionic bond or van der Waals interactions rather than by ion pairing[4]. Cocrystals have been defined in various ways by various people and they named it as Addition Compounds, Organic Molecular Compounds, Complexes, Heteromolecular Crystals[6]. Gautam Desiraju, a pioneer in the field, defined crystal engineering as "the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties"[5]. Another definition 'A cocrystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components exist as a stoichiometric ratio of a target molecule or ion and a neutral molecular cocrystal former(s) [7].

Advantages of Cocrystal

Cocrystal provide improvement in,

Solubility

Cocrystals of efavirenz were prepared with oxalic acid dihydrate & citric acid monohydrate as coformers using solvent drop grinding method & crystallization by fast evaporation from solvent under a reduced pressure. Equilibrium solubility profile of EFA-OXA and EFA-CITR shows an solubility enhancement of 1.8 and 2.7 folds of efavirenz as compared to commercial sample[10].

Bioavailability

Cocrystal of API and glutaric acid in a 1:1 molecular ratio was prepared and the single crystal structure is reported. Cocrystals shows enhanced aqueous dissolution rate by 18 times as compared to the crystalline form of the drug. Pharmacological studies were carried out on dog. Results confirmed that the cocrystal shows increased plasma AUC values by three times at two different dose levels[11].

Stability

Cocrystals of an anticonvulsant drug gabapentin with various carboxylic acid conformers were prepared using the reaction crystallization method (RCM). Result shows cocrystal of gabapentinare thermodynamically more stable and equal or less soluble than gabapentin hydrate and carboxylic acid coformers in pure water[8].

Melting point

Cocrystals of ibuprofen and 4,4-bipyridine was prepared and melting point was determined. The melting points of cocrystall were higher than their pure Ibuprofen. This shows improvement in melting point [12].From this we can resolve problem of hygroscopic drugs.

Salt versus Cocrystal Formation

Salt and cocrystal are somewhat confusing. While understanding the difference between a salt and a cocrystal. It is very important that pre-formulation activities and chemical/pharmaceutical development aspects should be considered. The important distinguishing points between Salt formation is acid–base reaction between the drug substance and a acidic or basic substance. The advantage of Cocrystals that it is an alternative to salts when these do not have ionizable sites in the drug substances (API)[13,14]

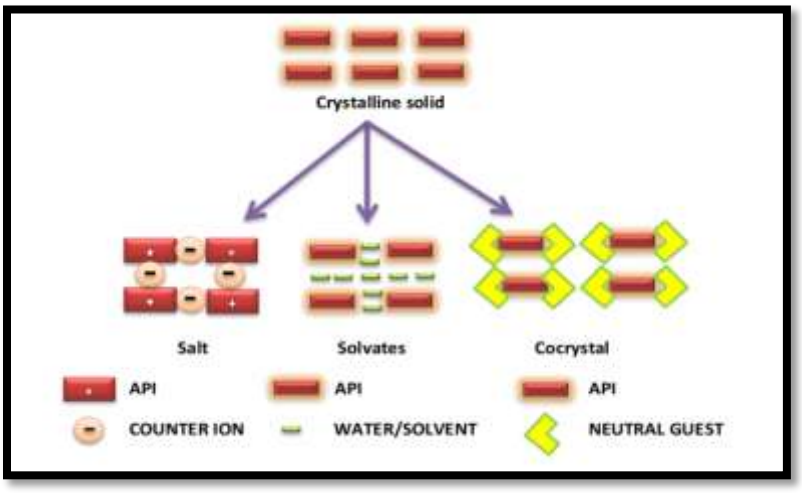


Figure 1: Difference between Salts, Solvates and Cocrystals

Cocrystal versus Solvates

The important distinguishing point between solvates and cocrystal is the physical state. Mainly in case of solvates one component is liquid. In case of cocrystal all components remain in solid state[13,14]

Cocrystal Design

Cocrystal design is based on crystal engineering principles. By understanding supramolecular chemistry of the functional group present in a drug and coformer. Hydrogen bonding can be easily formed between the drug and coformer if it contains functional groups like carboxylic acids, amides and alcohols. Ester and co-workers proposed guidelines to promote design of hydrogen-bonded solids along with graph set descriptors and classification of packing.

The rules of hydrogen bonding are:

1. All good proton acceptors and donors are only used in hydrogen bonding.
2. Six-membered ring with intramolecular hydrogen bonds form are preferred for intermolecular hydrogen bonds.
3. The best proton acceptor and donor remained after intramolecular hydrogen bond formation it will form intermolecular hydrogen bonds to one another [12].

Statistical analysis of hydrogen bonding motifs in the Cambridge Structural Database help to the identification of molecular properties and their role in cocrystal formation. The observed data from CSD will help to provide qualitative guidelines for the designing cocrystals.

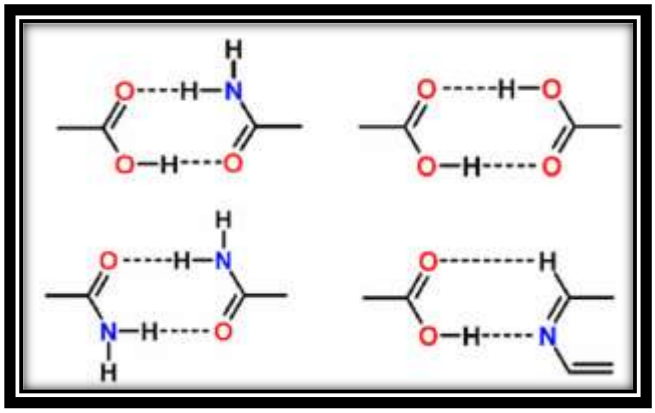


Figure 2:-Examples of commonly occurring Hydrogen bonding in cocrystals[3].

Methods of Co crystallization

Different techniques are used for the preparation of cocrystals they are as follows:

1. Solvent evaporation technique
2. Solid state grinding or mechanical milling technique
3. Solvent reduced technique

a. Slurrying technique

b. Solvent drop technology

4. Super critical fluid technology
5. Ultrasound assisted solution cocrystallization

Solvent evaporation technique:

This technique is commonly used for the preparation of cocrystals. In this technique both drug substance and coformer are dissolved in a common solvent and allowed to slow evaporation of a solvent. The technique works on the principle of formation of hydrogen bond in favorable drug substance and a complementary coformer[15]. For example:-Cocrystal forming ability of anti-HIV drug Zidovudine and lamivudine is studied in this work. In this work Zidovudine-lamivudine cocrystals prepared by using solvent evaporation technique by taking equimolar ratio of both. Ethanol is used as a solvent. Zidovudine-lamivudine is taken in equimolar ratios to which 10ml of ethanol is used. The solvent is allowed to evaporate for 2 days. Single crystals were obtained[24].

Solid state grinding

Solid state grinding is a technique in which mixing, pressing and crushing materials manually with a mortar and pestle or mechanically in a ball mill. This technique is also called as mechanical milling or neat grinding technique[16] For example:-Piroxicam cocrystals were prepared with help of a 20 carboxylic acid. In this equimolar ratios are taken and physical mixtures were prepared by using mixer mill. Three cycles of 3-5 min. was performed and determined by raman spectra[26].

Solvent reduced technique

a. Slurrying technique

Slurrying technique is used cocrystal formation in between drug and coformer. Drug substance (API) and coformer are dissolved in methanol in equimolar ratios at appropriate temperature. Then the solvent in slurry is allowed to evaporate at room temperature for 48 hrs. so it will promote cocrystallization[15]. For example:-Caffeine and syringic acid was slurried with water overnight under ambient conditions. The resulting solid was filtered and filtrate is allowed to dry for 10 days. Needle shaped crystals were formed[6].

b. Solvent drop technology

In solvent drop grinding technology the drug substance (API) and coformer are taken in equimolar ratios and these equimolar ratios are grind in a mortar and pestle to this addition of few amount of solvent. This solvent will act as a catalyst to favour co crystallization. This

method is advantageous than solid state grinding in terms of yield, ability to control polymorph production, better product crystallinity, and a larger scope of cocrystal former[15,16]. For example:- In this patent Intravenous formulation with water soluble cocrystals of Acetyl salicylic acid and the anine. In this Acetyl salicylic acid-the anine cocrystals prepared by taking both in equimolar ratios. Acetyl salicylic acid-the anine are taken in mortar and pestle in this few drops of methanol is added and grind until dried mass is formed. Further it is characterized[25].

Super critical fluid technology

Super critical fluid technique is more advantageous than other conventional method used in cocrystal formation. In this method API and a cocrystal former are mixed together by magnetic stirring and being pressurized by supercritical CO_2 in a high-pressure vessel. This pressurized supercritical CO_2 will act as anti-solvent which will lead to precipitate formation (cocrystals)[17]. For example:- Indomethacin–saccharin cocrystals were formed using supercritical fluid. In this Indomethacin–saccharin are taken in equimolar ratio (1:1) and added in a solvent to which supercritical CO_2 is pressurized in a high-pressure vessel to achieve super saturation and formation of cocrystals[28].

Ultrasound assisted solution co crystallization:

In ultrasound assisted solution co crystallization the API and cocrystal former are mixed together in appropriate solvent at a proper temperature. This solution was subjected to ultrasound pulses in a sonoreactor after giving 6-12 pulses there is formation of turbid solution. To prevent fragmentation cold water was supplied during sonication. Turbid solution was left for overnight for drying of solvent. For example:-Ultrasound assisted cocrystals of Caffeine/maleic acid were prepared. Slurry of Caffeine-maleic acid was prepared by taking equimolar ratios in methanol. This slurry was subjected to ultrasound pulses. Solid was filtered[18].

Characterization of Cocrystals

Characterization of cocrystal is not easy task but it can be characterized by correlating various methods. Various methods used for characterization are as follows.

1. **Fourier Transform Infrared (FT-IR) Studies:**
2. **Crystallographic Method:**
3. **Thermal analysis:**
4. **Nuclear magnetic resonance:**
5. **Scanning electron microscopy:**

Fourier Transform Infrared (FT-IR) Studies:

In Fourier Transform Infrared (FT-IR) spectrum is taken in range of 400-4000 cm^{-1}. It is a very

powerful and useful technique for screening of a cocrystal. It is very important tool to determine hydrogen bond formed between acid and base when carboxylic acid is used as a coformer also to determine neutral O-H·N hydrogen bond. The difference between carboxylic acid moiety and carboxylate ion can be determined by IR spectra. The neutral carboxylate ion shows a strong C=Ostretching band around 1700cm^{-1} and a weak C-O stretch near 1200 cm^{-1}. A carboxylate anion (-COO^{-}) shows resonance due to that C-O shows stretch in the fingerprint region around 1000-1400cm^{-1}. In case of neutral O-H···N hydrogen bond shows a two broad stretch around 2450 cm^{-1} and 1950 cm^{-1} [19].

Crystallographic Method:

Crystallography includes single crystal X-ray diffraction and powder X-ray diffraction. Single X-ray diffraction is used characterize cocrystal by measuring distances of hydrogen bond. But to separate a single crystal it is a very hard task in this case a powder diffraction is preferred. X-ray diffraction helps to measure distances between C-O and C=O bond. In carboxylic acid the distance between C=O is nearby 1.2 Å and C-O is nearby 1.3 Å. In case of deprotonation of C-O the resonance which is arising is stabilized by similar distances of bond. By comparing X-ray data of drug, coformer and cocrystal we can confirm formation of cocrystals[15,19].

Thermal analysis:

Thermal analysis of cocrystals includes Differential Scanning Calorimetry (DSC), Differential Thermal Analysis (DTA) and Thermo gravimetry (TGA). These methods are commonly used in pharmaceutical industry for characterization of purity, polymorphism, solvation, degradation of drug and also for compatibility. In this method thermal profile of drug, coformer and cocrystals is determined and melting point is compared change in melting point represent formation of cocrystal[l4,15].

Nuclear magnetic resonance:

Solid state nuclear magnetic resonance is used to characterize cocrystals. In this method chemical environment of nuclei of different polymorphs are studied due to magnetic non-equivalence. The resonance peak is different for different polymorphs having magnetically non-equivalent nuclei[15, 20].

Scanning electron microscopy:

Scanning electron microscopy is used to characterize surface morphology of the particles. Surface morphology of drug, coformer and cocrystal is useful for comparison and to determine change of morphology. The sample is analyzed by mounting sample on double sided adhesive tape that has been previously secured on copper stubs. Voltage of 10kV is used during

analysis[4,15,21]

Regulatory Classification of Pharmaceutical cocrystals

At present there is no regulatory paradigm exists governing cocrystal forms. Cocrystals are the intermediate between hydrates (ANDA-eligible) and salts (ANDA-noneligible)[23]. Cocrystals are classified as per the Agency's current regulatory framework as dissociable API—excipient molecular complexes with the neutral guest compound being the excipient.Cocrystals in the brief defined as the molecular association of Active Pharmaceutical ingredient(API) and its excipients occurs within the crystal lattice. In this way, an Active Pharmaceutical ingredient (API) that has been reacted with a co crystallizing excipient to generate an API and its excipients complex. If the approval of new cocrystal is via new drug applications (NDAs) and abbreviated new drug applications (ANDAs) will create impact on overall use of cocrystal technique by pharmaceutical industry[22].

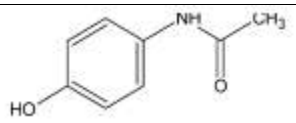
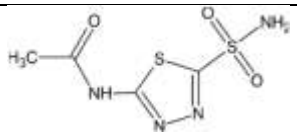
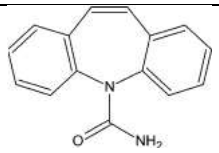
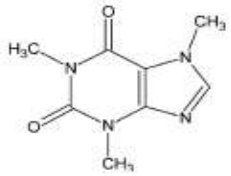
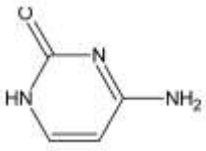
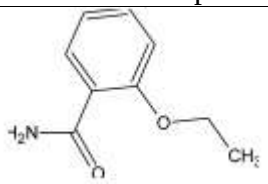
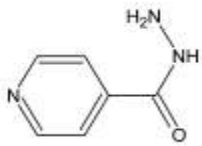
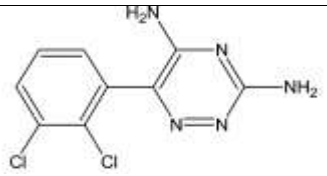
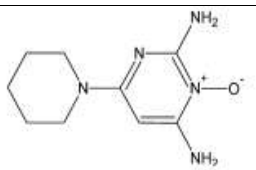
PHARMACEUTICAL COCRYSTALS AS INTELLECTUAL PROPERTY

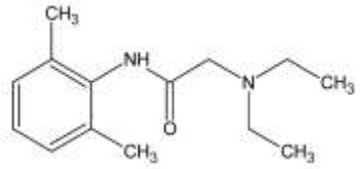
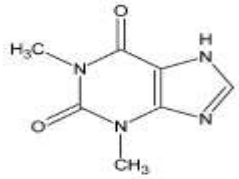
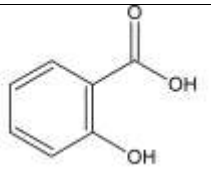
Solid forms plays important role in pharmaceuticals. As compared to other solid forms, cocrystals have scientific and regulatory advantages, due to which opportunity for intellectual property rights[13]. Therefore Pharmaceutical cocrystal gain interest of pharmaceutical researcher's and Pharmaceutical industry. Cocrystals will help pharmaceutical industry for development of pipelines[14].

Cocrystal Systems Having Pharmaceutical Interest

Here are some examples of drugs which have potential to form a cocrystal to enhance their physicochemical properties.

Table 1: Examples of drugs having interest in cocrystal formation [29]

 Acetaminophen	 Acetazolamide	 Carbamazepine
 Caffeine	 Cytosine	 Ethenzamide
 Isoniazid	 Lamotrigine	 Minoxidil

		
Lidocaine	Theophylline	Salicylic acid

CONCLUSION

Pharmaceutical cocrystals are a class of solid forms with lot of advantages like fine tune properties of drug. Cocrystal has ability to fine tune Physicochemical and biopharmaceutical properties. Cocrystal due to their large advantages attracted the interest of Pharmaceutical researcher's and Pharmaceutical industry. Patentability also has gained lot of interest of Pharmaceutical industry. As concern with the Studies of polymorphism of cocrystals should be strengthen in order to promote the development of new pharmaceuticals. The value of cocrystalsis clear to a Pharmaceutical industry with respect to regulatory aspects, and also capable for developing pipeline onto the market.

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