Advanced Techniques in Preparation of Cocrystals

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Abstract: Pharmaceutical Cocrystals is a popular but less studied class of Pharmaceutical compound 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. As technique provides tailoring of API to overcome problems associated with newly developed drug molecule it has attracted interest of Scientist. Even though cocrystallization is a powerful tool it is limited to lab scale development only. The aim of present article is to highlight advanced techniques which can be used in development of cocrystals.

Keywords: Novel methods, cocrystals, Cocrystal Advancements, Hydrogen bonding.

I. 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 topochemical 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 cocrystallization 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.

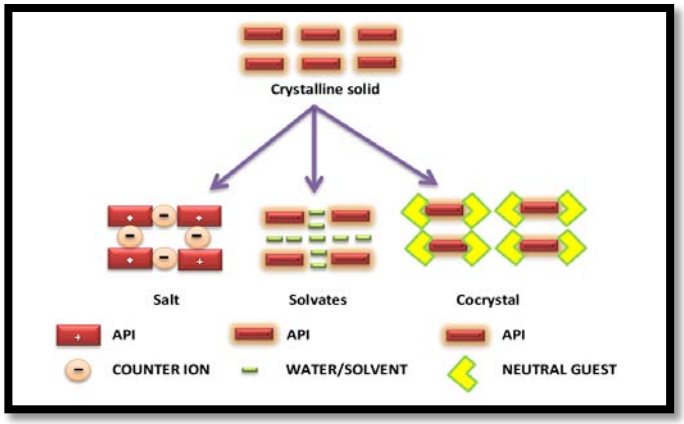
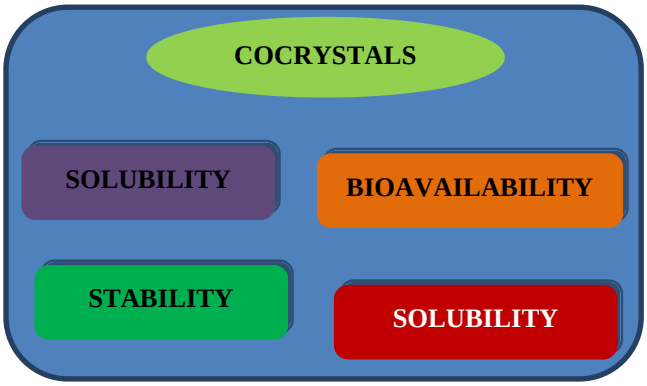


Figure 1: Difference between Salts, Solvates and Cocrystals

II. 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].GautamDesiraju, 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].

III. ADVANTAGES OF COCRYSTALS [8, 9, 10, 11, 12]



IV. 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. Etter 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.

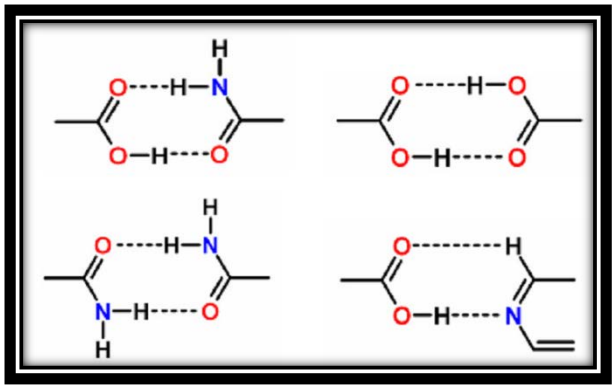


Figure 2:- Examples of commonly occurring Hydrogen bonding in cocrystals[3].

V. TECHNIQUES OF COCRYSTALLIZATION

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

Traditional Techniques

1. Solvent evaporation technique
2. Solid state grinding or mechanical milling technique
3. Solvent reduced technique
   a. Slurrying technique
   b. Solvent drop technology

Advanced Techniques

1. Microwave assisted synthesis
2. Super critical fluid technology
3. Ultrasound assisted solution cocrystallization
4. Spray Drying
5. High Shear Granulation

1. 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 [19].

2. 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 [21].

3. Solvent Reduced Technique

a. Slurrying technique

Slurryingtechnique 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 cocrystallization. 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 theanine. In this Acetyl salicylic acid-theanine cocrystals prepared by taking both in equimolar ratios. Acetyl salicylic acid-theanine 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 [20].

VI. ADVANCED TECHNIQUES

1. Microwave Assisted Synthesis

In microwave assisted synthesis drug substance (API) and coformer are taken in equimolar ratios and these equimolar ratios with or without solvent is subjected to microwave irradiation in a microwave reactor. The target time and temperature is determined by microwave heating profiles of drug and coformer which is maintained throughout the experiment. For example A 1 : 1 and 2 : 1 molar mixture of caffeine and maleic acid neat or with solvent was subjected to microwave irradiation in 30 ml capacity glass tube. The target temperature was set at 80 uCwith hold time of 60 s. Solvent mediated experiments were performed using 50mL (2%), 100mL (4%) and 250 mL (10%) of solvent for a batch of 2.5 g caffeine–maleic acid mixture. This finally leads to formation of cocrystals[24].

2. 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 CO2 in a high-pressure vessel. This pressurized supercritical CO2 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 CO2 is pressurized in a high-pressure vessel to achieve supersaturation and formation of cocrystals [22,23].

3. Ultrasound Assisted Solution Cocrystallization

In ultrasound assisted solution cocrystallization 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].

4. Spray Drying

In spray drying technique both drug substance and coformer are dissolved in a common solvent and sprayed at particular atomization pressure with a constant vacuum application. Spray dried product is recovered with help of cyclone collector and stored at ambient temperature. For example, Methanolic solution consisting of Carbamazepine and Nicotinamide in equimolar proportion was sprayed at atomization pressure of 1.20 ± 0.02 kg/cm and vacuum was main- tained at100 ± 3 mm of water column. Spray dried product was recovered from cyclone collector, stored in desiccator at ambient temperature and characterized for solid state properties[25].

5. High Shear Granulation

In high shear granulation technique both drug substance and coformer with a binder mixture granulated with granulation fluid in a granulator. The impeller speed and chopper speed is maintained constant during granulation. After final granulation the large agglomerates were passed through a sieve. For example, Equimolar ratio of drug Piracetam and coformer as L- Tartaric acid and Hydroxy propyl cellulose as a binder mixture were granulated with 4.0 ml of purified water as granulation liquid. The chopper speed was constant during granulation with 1000 rpm, two different impeller speed levels were applied: low (100 rpm) and high impeller speed (800 rpm).

Furthermore, cocrystal formation over two different granulation time levels was investigated, at a low (15 min) and at a high level (60 min) after the water was added drop-wise with a pipette. After the granulation process, large agglomerates were disassembled by a sieve with a mesh size of 800lm. Further it is characterized[26].

VII. CONCLUSION

Pharmaceutical 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. Even though more advantageous the branch is not much studied due to limitation of large scale production. The study will help to highlight on advance techniques in cocrystallization which will help in large scale production of cocrystals.

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