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A REVIEW ON PHARMACEUTICAL COCRYSTALS

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ABSTRACT

Pharmaceutical cocrystals are solid substances and a promising technology which are used to improve the solubility of poor aqueous compounds. They are a very interesting and useful product for improving different properties of drug substances such as dissolution rate, melting point, solubility, chemical stability, etc on the other hand we can say that they are drug pharmacological action modification agents. In the present paper, we review the pharmaceutical co-crystals. Cocrystals are multi-component molecular design allows us to change in the physicochemical properties of solids according to the need, through manipulation of various intermolecular interactions. In this short review, we focus on some recent reports on pharmaceutical co-crystals and their emerging subclasses as Charge transfer co-crystals, Energetic co-crystals, and Ternary co-crystals and discuss their methods of characterization and applications of importance in the industrial pharmacy.

Keyword- Cocrystals, solubility, molecular design

INTRODUCTION

The advent of crystal engineering gives a new momentum of research in molecular solids. Attaining the desired properties in molecular solids by controlled manipulation of intermolecular interactions causes the key success in this area of research by taking strength and directionality of weak intermolecular interactions into account. “Pharmaceutical cocrystals” are multi component compound which formed between a molecular or ionic API (Active Pharmaceutical Ingredient).
Basically Co crystals are solid under ambient conditions and separated into two categories

- ✓ Those made of inorganic: organic components, and
- ✓ Those made only of organic components.

inorganic: organic co crystals include organic molecules co crystallized with alkali and alkaline earth salts, mineral acids, and halogens whereas organic: organic co crystals contained aromatic compounds, with a significant fraction containing di- or tri nitro aromatic compounds1

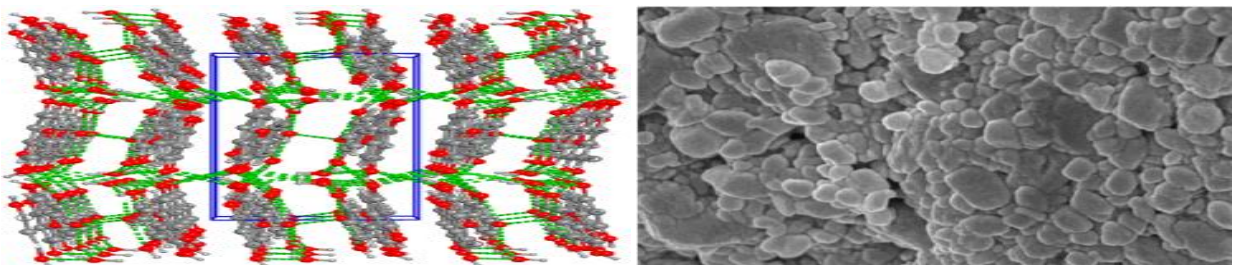

Figure 1-Structure of co crystals

Pharmacodynamically, co crystal former is a ballast molecule and not an active molecule. The stoichiometric Ratio of API and co crystal former are mostly simple as 1:1, 1:2, 1:3 or vice versa. It is not necessary that co crystals are only in binary compounds, ternary and quaternary co crystals are known. Co crystals can be Divided into: co crystal anhydrates, co crystal hydrates (solvates), co crystals of salts (unsolvated, unhydrated or solvated, hydrated) the borderline between salts and co crystals is blurred and can be distinguished by the location of the proton between an acid and a base, In salts, carboxyl proton is moved to the hydrogen of the base while in co crystals the proton remains on the carboxyl of the acid. In cases when pKa = pKa(base) - pKa(acid) = 0 – 3, the transfer of proton is ambiguous and we talk about the salt-co crystal.

Majority of the drugs are ineffective in their bioactivity due to poor solubility and permeability, and it limits their clinical applications. Co crystallization is widely used in the field of pharmaceuticals for improving the physicochemical properties of the drug molecules such as solubility, bioavailability, permeability, stability, melting point and shelf life. Because of the simple and profitable methods involved in designing a co crystal, and performance, co crystals are used as most viable method for improving the physicochemical properties of drugs but there is no particular method for design co crystals of all the drugs, the strategy which works for one, May not work for the other; each drug has to be dealt separately.

MATERIAL AND METHOD

Co crystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry, which are solids at room temperature referred as coformer and are held together with a molecular or ionic API by weak interactions, supramolecular synthons mainly hydrogen bonding. In order to formulation of co crystal, functional groups capable of forming supramolecular hetero or homosynthons should be present in the API and coformer.

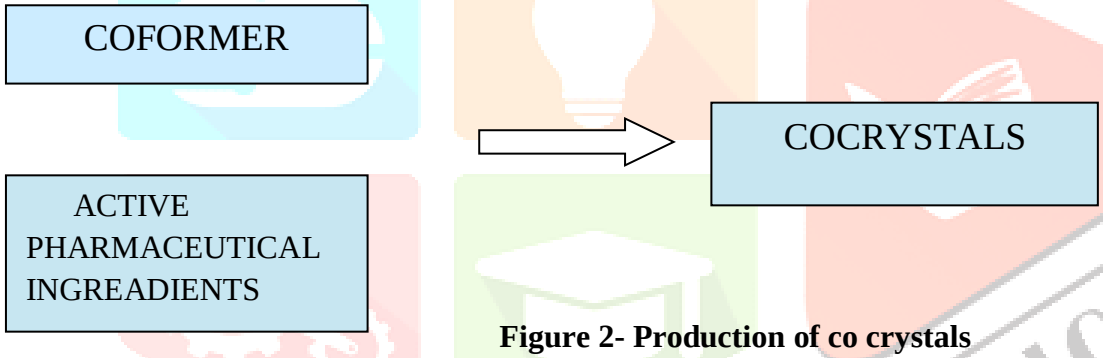

Figure 2- Production of co crystals

Steps involved in developing cocrystals are as follows

1) Choosing the target molecule (API)

2) Finding the complementary functional groups which is capable of forming a hydrogen bond.(coformer selection)

3) Methods of Preparation.

The preparation of co crystals involves a number of techniques for all phases some are as-Solution methods, evaporation co crystallization, cooling co crystallization, grinding method, neat/dry grinding method, liquid assisted drying method, anti-solvent method, slurry conversion method, super critical fluid technology etc.

Solution method-In this technique the material is mixed with the common solvent and evaporated completely where In evaporation stage the solution molecules are expected to undergo various hydrogen bonding reactions. But in case of co-crystallization which consists of API and conformers solubility of both plays an important role if the solubility of the two is not similar, then the one with low solubility than the other will precipitate out. This does not mean that solubility alone is the criteria for success. Considering the polymorphism of the compound of interest is also very necessary. If the polymorphism existed then changes are that the compound after co-crystallization may convert into a form which can bridge with the co-former.

Grinding- In this techniques materials are mixed, pressed and crushed in a mortar and pestle or in mill in general aspects this technique provides particle size reduction but in case of co-crystallization these method is viable for solid-state grinding along with liquid state grinding.

Slurring-It includes the addition of crystallization solvent in the API along with its acceptable former. The selection of this process is mainly depends upon the physical stability of the crystallization solution to co crystals and its solid former, major disadvantage of this method is that it requires large amount of solvent.

Solvent drop grinding- In this technique two materials can be grinded by adding a minor quantity of solvent, the solvent added is in very minute quantity which when added acts as a catalyst but does not form a part of the end product.

Hot melt extrusion- It involves highly efficient mixing and improved surface contacts, Co crystals are prepared without use of solvent. The selection of this method primarily depends on thermodynamic stability of compound. extrusion technique gives an advantage to carry out process at lower temperature.

Sono crystallization Method- **This** method used for preparation of organic cocrystals of very finite size.

Most important is joint co crystal growth from solution, joint solid state grinding with the addition of a small amount of a“molecular lubricant” like methanol, cyclohexan, chlorophorm etc, it also referred as liquid assisted grinding.
Furthermore, co crystal can be synthesized by evaporation, sublimation, melting, sonication etc. Identical starting components may not yield the same product under different co crystallization techniques differences in the solvent will change the intermolecular interactions and possibly lead to different co crystal formation. The intermolecular interactions and resulting crystal structures can generate physical and chemical properties that differ from the properties of the previous components it includes melting point, solubility, chemical stability, and mechanical properties.

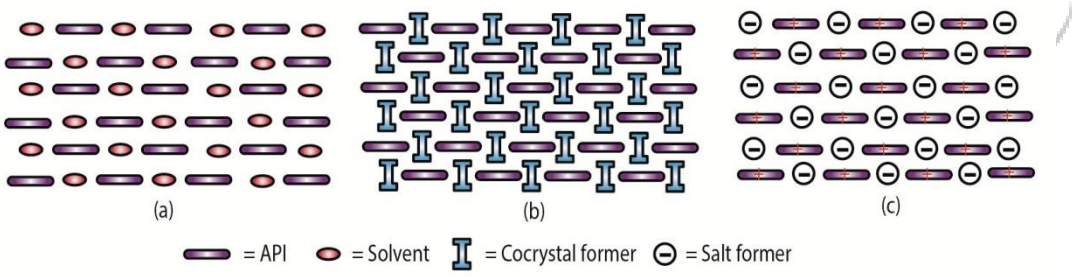

Diagram 3- Differences between API, Co crystals and Salt form

APPLICATION

Whether the co crystal is in some sense a physical mixture so a key question concerning the practical application of a cocrystal of a commercial API?
Co crystal should be regarded as a new chemical entity with all the concomitant safety and toxicological testing and also the USFDA defines co crystals as “solids that are crystalline materials composed of two or more molecules in the same crystal lattice” the FDA further stated that co crystals as dissociable “API-excipient” complexes, blurring the boundary between co crystals and physical mixtures. Among in many recent patents relating to potential commercial co crystal products, the possibility of combining two active ingredients in a single co crystal is an interesting one and has been claimed in the co crystallization.

Table no 1- Some recent patent related to cocrystalization-

S.No.	Combination of drug	Encounter area	Uses	References
1.	quercetin (a plant-derived flavonoid and antidiabetic agents such as metformin or tolazamide	physical properties and biological activity	anti-cancer	[23]
2.	Human insulin And lipophilic modifier	poor oral bioavailability and is commonly injected	improved physiological insulin profile	[23]
3.	novel choline cocrystal	physical properties	treating and/or preventing diabetic complications, treating and/or preventing homocystinuria	[23]
4.	co-crystal of carbamazepine and saccharin	Poor solubility	Treatment of neurological conditions	[22]
5.	co-crystal of carbamazepine and nicotinamide	Poor solubility	Treatment of neurological conditions	[22]
6.	co-crystal of tramadol hydrochloride–celecoxib	physicochemical and dissolution profiles	treatment of pain	[23]
7.	co-crystal of olanzapine and nicotinamide	physicochemical and dissolution profiles	treatment of psychosis and functional bowel disorders	[24]
8.	co-crystal of itraconazole and succinic acid	poor bioavailability	antifungal disorders	[25]
9.	co-crystal of modafinil and malonic acid	pharmacokinetics	Treat sleepiness	[25]
10.	co-crystal of 5-fluorouracil and urea	physical properties and biological activity	In anti-cancer therapy	[26]
11.	co-crystal of acetaminophen and 4,4′-bipyridine	improved tabletting properties improved solubility and stability profiles	antipyretic	[27]

CONCLUSION

Pharmaceutical co crystals are very important alternative to improve the bioavailability of poorly water-soluble drugs, weakly ionizable groups. Although, "pharmaceutical co crystal" term is still under discussion, but it is clear that this substances are very useful, and it is important to explore new co crystals of an API to improve or obtain some properties, such as habit, bulk density, solubility, compressibility, friability, melting point, hygroscopy and dissolution rate etc and also co crystals application is modification of drug pharmacological action. Investigation and production are very interesting for researchers and very useful for medics and pharmacologists.

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