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Pharmaceutical Co-crystals -A review

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ABSTRACT

Co-crystal formation is one of the methods to improve the physico-chemical properties of the active pharmaceutical ingredient. Co-crystallization with pharmaceutically acceptable compounds do not affect the pharmacological activity of the API but can improve physical properties such as solubility, dissolution rate, moisture stability and compaction behavior. Co-crystals are most dynamically developing group of multicomponent solid pharmaceutical substances. Co-crystals can be divided into co-crystal anhydrates, co-crystal hydrates (solvates), co-crystals of salts (unsolvated, unhydrated, solvated or hydrated). Techniques for preparation of co-crystals are solvent evaporation, anti-solvent method, hot melt extrusion and solvent free grinding. Co-crystals are characterized by hot stage microscopy, differential scanning calorimetry, X-ray diffraction, IR and Raman spectroscopy.

INTRODUCTION

Co-crystals are solids that are neutral crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio, which are neither solvates nor simple salts [1]. If at least one of the coformers is an API and the other is pharmaceutically acceptable, then it is recognized as pharmaceutical co-crystal [1]. Co-crystals of different stoichiometric with the same coformer is possible, as illustrated bycarbamazepine and *p*- amino benzoic acid in 1:1, 2:1 and 4:1stoichiometric configurations [2]. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of molecular networks with the same molecular components or with the different molecular components in the crystalline state [3].

Crystal forms are more preferred than the other forms because of their stability, reproducibility. Amorphous and other solid solutions such as partially crystalline forms, subcooled liquid and the different types of crystal forms that have variable dissolution rates and intrinsic solubility, which severely affect bioavailability [4]. Various methods have been designed for solubility improvement of API such as salt formation, micronization, emulsification and polymer drug vehicles [5].

Co-crystals are most dynamically developing group of multicomponent solid pharmaceutical substances. Co-crystals can be divided into co-crystal anhydrates, co-crystal hydrates (solvates), co-crystals of salts (unsolvated, unhydrated, solvated or hydrated).The solubility enhancement of biopharmaceutical class II and IV drugs is challenge for the formulation scientists. Thus, the knowledge of crystal engineering along with the molecular properties of active pharmaceutical ingredients can poses a great option [6].

PHARMACEUTICAL CO-CRYSTALS

A co-crystal is a multicomponent crystal in which all components are usually solid at room temperature in a stoichiometric ratio and it involves non-covalent interactions such as hydrogen bonds, vander-waals bonds, ionic bonds in a crystal lattice. Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Physicochemical properties of pharmaceuticals can be improved by obtaining cocrystals using co-crystallization. Co-crystallization with pharmaceutically acceptable compounds did not affect the pharmacological activity of the API but can improve physical properties such as solubility, stability, compaction behavior [7,8].

Pharmaceutical co-crystals can be defined as crystalline materials comprised of an API and one or more unique co-crystal formers, which are solids at room temperature. The improvement of physical and chemical property by using crystal engineering can be useful for pharmaceutical co-crystals. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other crystal former.

CO-CRYSTALS AND SOLVATES

The main difference between the solvates and co-crystals is the physical state of the isolated pure components: if one of the component is a liquid at room temperature, the crystals are designated as solvates: if both components are solids at room

temperature, the crystals are designated as co-crystals [9].

SALT VERSUS CO-CRYSTAL AND IONISATION

The most important requirement for salt formation is the existence of an ionic center in an API. Hence in case of APIs which are non-ionizable, these are incapable of salt formation. In case of forming a salt form the number of pharmaceutically acceptable, non-toxic acids and bases are relatively small [10].

If taken into consideration the technique of cocrystallization the scenario is totally different. As in cocrystallization whether API is ionic are non-ionic, the counter molecule called coformer may be an excipient, food additive, preservatives, vitamins, minerals, amino acids and other biomolecules or another API.

To design a co-crystallization experiment two aspects should be kept in mind the first being the evaluation of the robustness of the potential intermolecular interactions and considering the hydrogen bonding rules. Robustness can be checked by analyzing the trends within the Cambridge structural database (CSD) or by retrospective data. Hydrogen bonding rule should be considered which says that the strong hydrogen bond donor tends to interact with the best hydrogen bond acceptor in a given crystal structure. This best donor best acceptor rule can be of great utility in the design of specific hydrogen bonding interactions.

The fundamental difference between a salt formation and a cocrystal is very important to both preformulation activities and chemical/pharmaceutical development aspects. Salts are often chosen instead of the free acid or base as these can improve crystallinity, solubility and stability of a pharmaceutical compound and cocrystal now serve as new alternate in pharmaceutical terms.

PHYSICOCHEMICAL PROPERTIES OF COCRYSTALS

Physical and chemical properties of cocrystals are of great importance to the development of the API. The overall motivation for investigating pharmaceutical cocrystals as an alternative approach during drug development is the adjustment of the physicochemical properties to improve the overall stability and efficacy of a dosage form. Physicochemical properties such as melting point, solubility, dissolution, stability have been studied.

MELTING POINT

The melting point is the temperature at which the solid phase is in equilibrium with the liquid phase. There are complex correlations between the melting point of pharmaceutical product and its process ability, stability and solubility.

STABILITY

Stability is a very important parameter when evaluating the properties of pharmaceutical drug products, which is generally improved with cocrystals. Usually, the stability testing of a newly developed cocrystal includes four aspects: relative humidity stress, thermal stress, chemical stability and solution stability.

SOLUBILITY

Solubility is another parameter for evaluating the properties of a pharmaceutical cocrystal. Traditional methods for improving the solubility of poorly water-soluble drugs include salt formation, solid dispersion, and particle size reduction (micronisation). Pharmaceutical cocrystals can improve solubility, dissolution, and bioavailability of poorly water soluble drugs.

INTRINSIC DISSOLUTION RATE

Intrinsic dissolution rate (IDR) measures the rate of dissolution of a pure drug substance from a constant surface area, which is independent of formulation effects and measures the intrinsic properties of the drug as a function of dissolution media, eg: pH, ionic strength and counter ions. The intrinsic dissolution rate is a good indicator for in vivo performance of APIs.

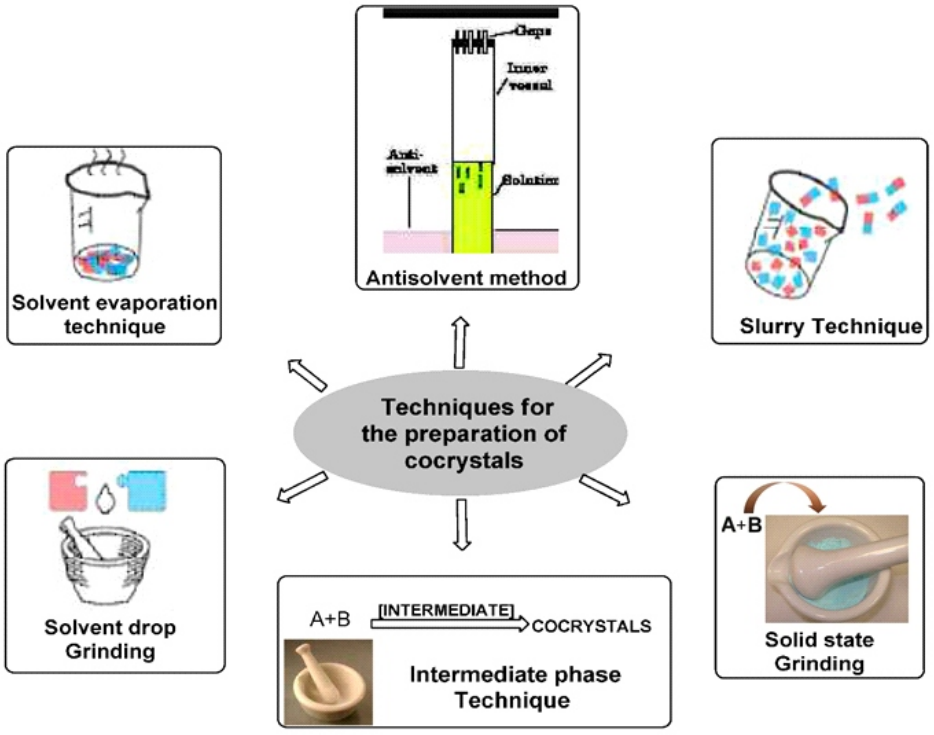

Figure 1: Techniques used for preparation of co-crystals

Different techniques commonly used for the preparation of co-crystals are solvent evaporation technique, antisolvent method, slurry technique, solid state grinding and solvent drop grinding. Figure 1 shows the different techniques used for the preparation of co-crystals.

Solvent Evaporation

Solvent evaporation is the simplest technique of co-crystallization.

In this technique, drug and coformer is dissolved in a common solvent with suitable stoichiometric ratio and evaporate. During evaporation, the solution of the molecules undergoes changes by forming hydrogen bonds between different functional groups and produce thermodynamically favoured product. The intrinsic dissolution rate was increased of fluoxetine hydrochloride by using multiple coformers like succinic acid, fumaric acid, and benzoic acid. Norfloxacin co-crystals were synthesized with isonicotinamide, malonic acid, and maleic acid as coformer. The disadvantage of the technique is it requires a large amount of solvent.[4,11]

Anti-solvent Addition

A solvent is added to the solution , in which the compound is less soluble causing precipitation of solids. Filter the suspension and solids can be characterized. Carbamazepine-saccharin and indomethacin-saccharin co-crystals were prepared by antisolvent crystallization [12]

Hot melt extrusion

It is also known as solvent drop extrusion method. It is a process of converting the raw material into a product of uniform shape and density by forcing it through a die under controlled condition.

It involves the synthesis of co-crystals without the use of solvent which includes highly efficient mixing and improved surface contact.The selection of this method is mainly depends upon the thermal stability of the compound.

This technique can be carried out at low temperature. Carbamazepine- nicotinamide co-crystals were prepared by this method [13]

Solvent free grinding: In this technique, the materials are mixed, pressed and crushed in a mortar and pestle or in a ball mill. In general, aspects, this technique provides particle size reduction but in case of co-crystallization, this has proved to be viable method for solvent-free grinding. Caira and co-workers studied it on six pharmaceutical co-crystals of sulpha drug sulphadimidine with various carboxylic acids, including anthranilic acid and salicylic acid.[14]

Slurry technique: Slurry of drug and coformer was prepared in different organic solvents and water. The resulting suspension was stirred at room temperature and solvent was decanted. The resulting solid material was dried and characterized. Acyclovir-succinic acid co-crystals were prepared by slurry technique.[15]

Solvent drop grinding: This is performed by adding small amount of solvent during the grinding process. Supramolecular selectivity has been enhanced by this technique and small amount of solvent is not part of the final product. This method enhances co-crystalization rate compared with the solid state grinding.Advantage of this technique is the ability to control the production of polymorphs and improved the crystallinity of the product.[12]

Characterization of co-crystals

Different methods have been used for the characterization of co-crystals. Those are hot stage microscopy (HSM), differential scanning calorimetry (DSC), X-ray diffraction, IR and Raman spectroscopy.

Hot stage microscopy is used for characterization of co-crystals as a function of time and temperature. This technique is a combination of thermal analysis with microscopy. Thermal changes like melting point, melting range, crystal growth, crystalline transformations, etc. can be visualized using HSM. When used with DSC it has expanded the visual collection capabilities. DSC measures the heat of fusion, heat of transition and heat capacity. Degree of crystallinity can be determined by DSC. X-ray diffraction is another technique used for the characterization of co-crystals. Danazol: vanillin co-crystals were characterized by powder X-ray diffraction technique (PXRD)[16]. Co-crystals of fenofibrate with nicotinamide were also characterized by PXRD. Shifting of the peaks is clear

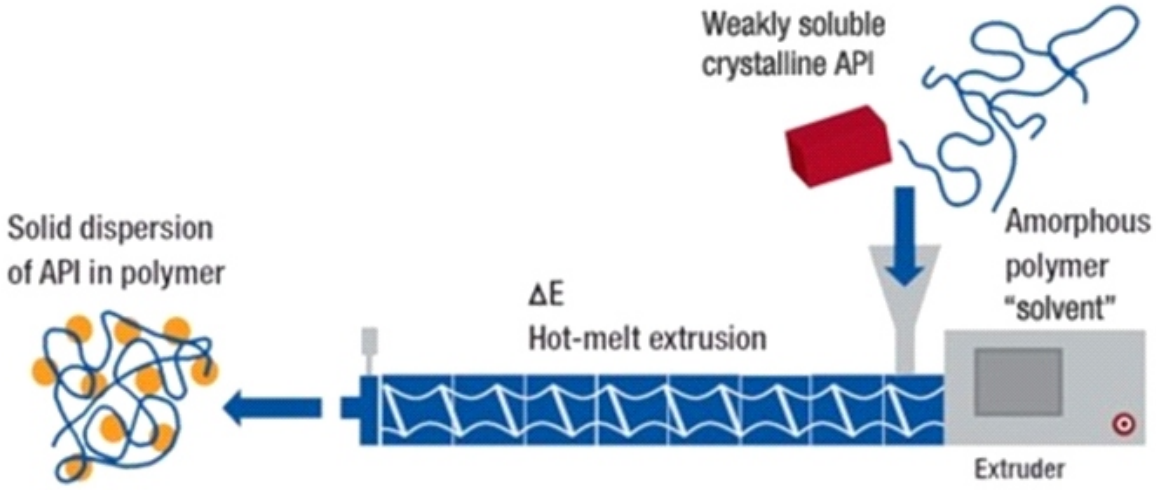

Figure 2: Preparation of cocrystals by hot melt extrusion technique

indication of formation of co-crystals. Fourier transform infrared spectroscopy (FTIR) and Raman spectroscopy was also commonly used tools for characterization of co-crystals. Fenofibrate nicotinamide co-crystals were also characterized by these techniques[17]. Co-crystals of fenofibrate with succinic acid, sucrose and saccharinewere characterized by FTIR, DSC, PXRD and SEM (scanning electron microscopy)[18]. Appearance of new peaks in the IR spectrum indicate the formation of co-crystals. In the DSC, crystal formation is determined by using melting point curve.

ADVANTAGES OF COCRYSTALS

Cocrystals having advantages like stable crystalline form (as compared to amorphous solids), no need to make or break covalent bonds, theoretical capability of all types of API molecules (weakly ionized /non ionizable) to form cocrystals, the existence of numerous potential counter molecules (food additives, preservatives, pharmaceutical excipients and other APIs), the only solid form that is desirable via crystal engineering and can be produced using solid state synthesis.

CONCLUSIONS

Bioavailability of poorly water-soluble drugs especially neutral compounds or compounds with weakly ionisable groups can be improved by preparing cocrystals. Crystal habit, compressibility, friability, dissolution rate and stability can also be improved by making cocrystals. In conclusion, cocrystals improve the bioavailability of poorly water-soluble drugs and improve the pharmaceutical properties of drugs.

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