A Brief Review On Pharmaceutical Co-crystals
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Abstract:
Recent studies has found that, discovering and developing novel medications is insufficient to attain therapeutic excellence and gain market economies. As a result, changed formulations of currently available medications are getting more significant. Also, poor water solubility and inadequate bioavailability of an active medicinal ingredient are two factors that limit the growth of a new product. The pharmacological action of the pharmaceutically active ingredient is unaffected by co-crystallization, with pharmaceutically acceptable molecules, although it can improve physical qualities such as solubility, stability and rate of dissolution. Most importantly, it is possible to use co-crystal to generate novel pharmaceuticals with improved solubility, improving treatment efficiency and safety. The most significant factor in the production of co-crystal is thermodynamic stability. Co-crystal formation can be performed by Grinding Methods, Spray Drying Method, Solvent Evaporation Technique, Ultrasound Assisted Solution Co-crystallization, Supercritical Fluid Atomization Technique, Hot Melt Extrusion and other techniques are used. A brief description of co-crystal formation techniques, properties of co-crystal (solubility, tabletability, melting point, stability, bioavailability, permeability) as well as its pharmacological uses has been incorporated in the following review paper which further help to know more about the concept of co-crystals in depth.

Keywords: Co-crystallization, Bioavailability, Solubility, Stability, Dissolution rate.

Introduction:
Among the different pharmaceutical dosage forms, oral solid dosage forms (such as- tablets and capsules) are frequently chosen due to their numerous benefits in terms of cost, stability, easy handling and patient compliance [1-3]. Many medications therapeutic efficacy has decreased because they have low aqueous solubility, reduced dissolution rate, chemical stability and moisture uptake tendency [4-5]. Due to limited water solubility, which results in limited drug bioavailability, no active pharmaceutical ingredients (APIs) have been created in formulations [6].
Co-crystals, a well-known but understudied family of crystalline solids, have piqued the interest of crystal engineers and pharmaceutical scientists in the recent decades and the pre-formulation stage currently includes the drug development process. Co-crystallization has proven a valuable strategy in the design of pharmaceutical materials with desired properties since the advent of crystal engineering [7,8].

The co-crystals technique is unique in that it has no effect on the drug's pharmacological qualities, but it may improve its efficacy, also bioavailability and number of physicochemical characteristics including solubility [9], stability [10], dissolution, melting point and Permeability [11-12]. Co-crystal can be constructed using a combination of theoretical and/or experimental approaches [13].

Co-crystal:

The definition of pharmaceutical co-crystal is given as: 'Co-crystals are crystalline single phase solids made up of two or more distinct molecular and/or ionic compounds generally in a stoichiometric ratio that are neither solvates nor simple salts' [14]. A pharmaceutically approved co-crystal is made up from the active pharmaceutical ingredient (API) combination with a benign material termed as coformer [15]. Co-crystal formers is refers to introduce active pharmaceutical ingredients (APIs) into crystalline lattices, resulting in the production of novel solid moieties known as co-crystals. Co-crystallization occurs when two or more distinct molecules recognize each other through energetically beneficial intermolecular interactions. The physicochemical characteristics of a co-crystal are determined by the intermolecular interactions strength and the arrangement of its constituents in the crystal lattice [16,17]. "By combining geometric analytic knowledge with the so-called "hydrogen-bond principles," a rational synthesis of co-crystals can be created [18,19]. A number of noncovalent interactions between the drug and the coformers, including Hydrogen Bonding, II staking and Van der Waal forces results in the formation of co-crystal. The creation of co-crystals is a promising method for changing an API's physicochemical properties without changing its chemical structure [20,21]. The proper selection of the specific coformer by understanding intermolecular interactions, crystal engineering techniques can be applied to the construction and modulation of novel solid forms with fine-tuned properties [22].

The organic acids (such as fumaric acid, malic acid, glutaric acid, succinic acid, oxalic acid), and nutraceuticals (such as quercetin, pcoumaric acid, and saccharine) that are commonly used as excipients can also be used as conformers [23]. Co-crystals differ from traditional crystalline APIs in terms of polymorphic shapes, physical qualities and intermolecular packing patterns [24]. Both compounds (drug and coformer) should be solid during the co-crystallization process and neither should serve as a solvent form [25,26]. The primary purpose of a pharmaceutical co-crystal is to increase an API solubility and modifying molecules of drug in co-crystal form which has no bearing on their pharmacological reaction; also, physical qualities of drug molecules as compaction behavior, hygroscopicity and solubility in water will be increased [27,28].
Properties of Co-crystal:

1) Solubility:

The ability of a substance to dissolve the greatest quantity possible in a specific amount of solvent at a certain temperature. The formulations of drugs that are difficult to dissolve are investigated for solubility. There are different ways for the improvement in solubility of drugs as formation of salt, method of dispersion of solid, reduction in particle size and so on [29,30], but several researchers use co-crystallization technique for the improvement in solubility [31,32]. Solubility of Ketoconazole (an antifungal drug) shows 53 times increased solubility in salt formation and 100 times increased solubility in co-crystal form as compared to ketoconazole. Co-crystals shows higher solubility than salt formation [33]. Also, the co-crystallization is beneficial in enhancing dissolution because higher solubility of a substance leads to higher dissolving rate [34]. For the determination of solubility in pure solvent, a theoretical method based on the ratio of solution concentrations of co-crystal components at the eutectic point (Keu method) was used. Also, this technique is a valuable tool for selection of co-crystal and formulation without material and time requirement of traditional methods [35,36].

2) Stability:

Stability is a vital factor to consider when designing a dosage forms. There is a molecular structures change as a result of co-crystallization, which modifies the mechanical characteristics of solids. So, the stability study of polymorphic co-crystals is important. Also, other stability studies are taken into account when developing medicinal co-crystal are chemical stability, solution stability, thermal stability, photostability and various humidity stress conditions [37]. Any chemical change occurs in the drug product is given by the study of chemical stability [38]. Chemical stability is important for drug discovery and the formation of pharmacological dosage forms [39]. In pharmaceutical co-crystal the solution stability is considered for the study of dissolution and bioavailability related difficulties. Solution stability is the stability in which the solute must be surrounded or solvated, by the solvent and it should not precipitate into crystalline form under any condition [40,41]. Packing of crystals has a greater influence on the co-crystal's stability in terms of temperature and humidity. Since many APIs are light sensitive, a photo stability research will be conducted to investigate the changes occurs due to light [42,43].

3) Melting Point:

Melting Point is the property of a solid which is used to determine the purity and stability of thermodynamic system of a product [44,45]. It is one of the most significant characteristics which is considered at the time of co-crystal formulation. The choice of coformer has an impact on API's thermal stability. In other words, choosing a coformer with a high melting point improve API's thermal stability. Also, low melting point co-crystals can help with thermolabile drugs [46,47]. The method of Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA) is applied for the determination of melting point and thermal analysis [48]. Co-crystals with a high melting point are required, however they
have an issue with aqueous solubility, whereas low melting point co-crystal causes processing, drying and stability issues [49,50].

4) **Permeability:**

The drug absorption and distribution are affected by the permeability of an API over a biological membrane. Drug permeability is primarily determined by the n-octanol/water partition coefficient, which may be calculated using log P and (C log P) for the unmodified form of the drug [51,52]. The permeability of 5-fluorouracil, a BCS class-III medication, was investigated by creating co-crystals with several coformers and it was discovered to be higher than the pure drug. The development of a heterosynthon between the drug and the coformer enhanced the permeability of co-crystals [53,54].

5) **Tabletability:**

Co-crystallization alter the crystallographic (supramolecular) features of parent component for creation of new crystal phase with several components which improve the tabletability [55]. Co-crystal formation results into the specific crystal packing which is an important parameter during re formulation study which affect compaction parameters [56]. The definition of tabletability is given as "the ability of the powder material to be changed into a tablet of defined tensile strength when compaction pressure is applied" [57,58]. By varying packing of crystal by co-crystallization results into the change in mechanical properties of tablet formulation. The transformation of co-crystal of resveratrol with 4-aminobenzamide and isoniazid may result into the improved tabletability [59,60].

6) **Bioavailability:**

The most effective method of drug delivery is through the mouth. However, less oral bioavailability is a significant issue during the development and designing of new formulations of APIs [61,62]. The pace and degree of absorption of the active component or the percentage of a drug's active moiety that is absorbed and reaches the systemic circulation is known as bioavailability [63,64]. Pharmaceutical co-crystal with increased solubility in water and oral bioavailability is designed and synthesized by using crystal engineering. Meloxicam co-crystal with aspirin shows better oral bioavailability than pure drug and also enhanced onset of action [65,66].

**Method Of Preparation Of Co-crystal:**

1) **Grinding Method:**

Grinding methods of formation of co-crystal are superior to others and are widely used.

There are two types of grinding:

a. **Dry (Neat) Grinding:**

The medication and coformer are combined in a specified ratio and ground either manually with a mortar and pestle or mechanically using a Ball mill in dry grinding [67,68]
b. **Wet Grinding:**

Wet grinding, the procedure is same as dry grinding, except that a few drops of solvent are mixed with the API as well as coformer mixture while grinding [69,70].

2) **Spray Drying Method:**

Spray drying is the ideal method because it is quick, continuous and only requires one step. This technique of spray drying offers a unique environment. Spray Dryers are used in this technique [71,72]. In the spray drying process a solution or suspension of API and coformer is sprayed with a hot air stream to evaporate the solvent [73,74]. The co-crystals of drugs which are not very soluble in water are successfully prepared by this spray drying method [75].

3) **Solvent Evaporation Technique:**

For the creation of co-crystal, solvent evaporation technique is most common and reliable method. To make co-crystal, the API and coformer are dissolved in common solvent with an appropriate stoichiometric ratio and to obtain co-crystals, the solvent was allowed to slowly evaporate at room temperature. The solubility of API and coformers is a crucial consideration when selecting a solvent [76]. The presence of solvent in the co-crystal formation plays an important role on purity of co-crystal [77]. This technique works on the principle, that the functional division of drugs and a complementry coformer undergo intermolecular interaction such as hydrogen bonding and produce thermodynamically favored products. This technique has limitation that it does not comply large scale [78,79].

4) **Ultrasound Assisted Solution Co-crystallization:**

This method is used to make co-crystals of extremely small size i.e., for nanocrystals. In ultrasound assisted solution co-crystallization the API and coformers are dissolved in appropriate solvent at suitable temperature and put into a sonicator. This solution was treated to ultrasound pulses in a sonoreactor, as a result a turbid solution was produced after 6-12 pulses [80]. During sonication, cold water is used to maintain consistent temperature of the sonicator and avoid fragmentation. The solution is permitted to dry overnight. This procedure yielded pure co-crystals and the X-ray diffraction technique is used for the determination of purity of co-crystals [81].

5) **Supercritical Fluid Atomization Technique:**

The co-crystallization with a high-pressure supercritical fluid, such as CO₂, is used to mix the medication and coformers and then atomizer is used to atomize the solution, resulting in co-crystals [82]. In the supercritical antisolvent (SAS) method the co-crystals are created from solution using the antisolvent action of supercritical fluid [83]. Several supercritical fluid-based microparticle generation techniques that take advantage of the properties of the supercritical fluid have been developed. Recently, the ability of supercritical fluid-based systems to create diverse solid forms of APIs, such as polymorphs, has been studied [84]. The Supercritical Fluid Anti-Solvent (SAS) approach investigates the anti-solvent action of
CO₂ at supercritical pressure in precipitating co-crystals from fluids, whereas the Supercritical Fluid Enhanced Atomization (SEA) technology, focuses on improving CO₂ atomization in a spray drying process. Theophylline saccharin co-crystal novel form with a 1:2 stoichiometry was created using a previously unreported supercritical fluid enhanced atomization procedure [85,86]. This process has advantages and limitations like:

**Advantages:**

i. It is fast and one step process.

ii. It is an fascinating technology, especially for heat sensitive materials.

iii. It is possible to obtain tiny particles.

iv. SFT is effective for the creation of dispersions of solids and microspheres.

**Limitation:**

The application of SFT is limited because the high pressure required, high maintenance costs and the necessity for accessories/auxiliary equipment. It is not applicable for all pharmaceuticals [86].

6) **Hot Melt Extrusion Method:**

The hot melt extrusion method is only applicable for thermodynamically stable compounds. It is a single step method. In this technique, The synthesis of co-crystal does not require the use of a solvent [87]. The co-crystals are made this way by combining heat and high-intensity mixing to make the drug and coformer miscible in the molten stage with better surface contact and high efficiency mixing [88,89]. Both the Drug & API must be miscible in molten form and this method should not applicable for the thermolabile medicines [90].

**Application:**

Co-crystal formation is an alternative technique applicable for solid state than other modifications by pharmaceutical industry to improve physiochemical characteristics of drug (bioavailability, solubility, stability, etc). Also, it is advantageous in discovery of drug (e.g., new molecule synthesis, nutraceutical co-crystals), and chiral resolution [91,92]. In the creation of nutraceuticals co-crystal engineering is used recently. Nutraceutical are the products which contains nutrients. Along with the API, they can also be employed as coformers for better-combined health benefits [93,94]. Co-crystals are also utilised to separate and purify the API during the manufacturing process [95].

**Conclusion:**

This review study identified co-crystal formation as a beneficial and favoured change in the field of pharmaceutical sciences. The use of pharmaceutical co-crystals to improve the physicochemical properties of active medicinal substances is a highly important alternative, due to the formation of a new two or more components crystal phase, co-crystallization resulted in changed crystallographic (supramolecular) characteristics in comparison to the parent components. This article provides a typical overview of the numerous procedures that are applicable for generation of co-crystals, as well as their characterisation. This
review also includes pharmacological applications of co-crystals. Overall, co-crystals formation are predicted to play a significant role in drug development in the future.

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