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Cocrystallization: An Approach to Improve Bioavailability by Altering Physicochemical Properties of Poorly Soluble API's

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ABSTRACT

Biopharmaceutics Classification System (BCS) class II and IV suffer from poor aqueous solubility and hence low oral bioavailability during formulation development. Cocrystallization is one of the latest approaches based on crystal engineering and has been used to enhance specific physicochemical parameters like melting point, solubility, dissolution rate, chemical stability, and tablet ability of the active pharmaceutical ingredients. Cocrystal is crystalline single-state material composed of two or more than two different molecular association systems of active pharmaceutical ingredients (API) with a stoichiometric ratio of a pharmaceutically acceptable coformer incorporated within the crystal lattice. Various methods have been used for the preparation of cocrystals such as grinding, solvent evaporation, hot-melt extrusion, spray drying, etc. Currently, cocrystal gained exciting opportunities in the drug discovery and development of new medicine by improving the poor physicochemical properties of APIs. There are a huge number of documents, literature available on cocrystals. However, there is a shortage of reviews on the selection of Coformer. In this work, attempts have been made to fill this gap. This review also focuses on an overview of pharmaceutical cocrystal and their method of preparation, selection of coformers with the improved pharmaceutical application of cocrystal.

INTRODUCTION

Biopharmaceutics Classification System (BCS) classifies APIs into four major categories based on their stability and permeability habits. BCS class II and class IV drugs are having poor solubility characteristics [1]. About 40 % of the newly synthesized APIs suffer from the drawback of poor aqueous solubility [2]. Drug with low water solubility usually shows dissolution-limited absorption which ultimately results in low bioavailability. The most recent decade estimates that approximately 40 % of currently marketed drugs and up to 75 % of new chemical entities under development are suffering from poor water solubility, thus improving the solubility of poorly water-soluble active pharmaceutical ingredients (APIs) is a major challenge for research and development scientists [3]. Thus, in modern pharmaceutical development, solubility enhancement technologies for poorly water-soluble APIs are becoming crucial to improve bioavailability [4]..Nowadays, attention has been paid to cocrystals as alternative solid forms to overcome problems in drug delivery. The example of improved physicochemical parameters of APIs by cocrystallization includes improving solubility, dissolution, bioavailability, stability, and mechanical properties [5].

PHARMACEUTICAL COCRYSTAL

Pharmaceutical cocrystal may be defined as a molecular complex of an API with one or more cocrystal formers in a well-defined stoichiometry through hydrogen bond or other non-covalent interactions, such as hydrogen bonds, π-π stacking, and van der Waals interactions [6]. Cocrystallization is a reliable approach to alter physical and chemical properties of active pharmaceutical ingredients (APIs) such as solubility, dissolution rate, hygroscopicity, melting point, stability, and compressibility without modifying their biological activity and empirical structure [7]. Nowadays, cocrystallization has received increasing attention in the pharmaceutical field and has been broadly reported in scientific papers [8]. Cocrystals are crystalline single-phase solid materials composed of two or more different molecular and/or ionic combinations in a fixed stoichiometric ratio, both of which are solid at room temperature, held together within crystal lattice through non-covalent interaction [9, 10]. One of the components must be an active pharmaceutical ingredient (API) and another Conformer should be a safe compound from the Generally Recognized As Safe (GRAS) list by US-FDA [11].

SOLID STATE ACTIVE PHARMACEUTICAL INGREDIENTS

Solid Active Pharmaceutical Ingredients (APIs) can exist in two morphological forms: crystalline or amorphous. Crystalline APIs are more preferable to amorphous API due to better stability towards pharmaceutical development [12]. Many times, due to bioavailability or stability issues APIs cannot be formulated in their pure existing form. Thus, they are converted to solid forms such as salts, cocrystals; solvates, hydrates, and polymorphs. Each of them has different characteristics of the physicochemical property, which ultimately impact bioavailability [13]. Crystal engineering has become one of the foremost effective strategies to modify the physicochemical properties of active pharmaceutical ingredients (APIs). Some examples of utilization of crystal engineering to overcome solubility issues are pharmaceutical polymorphs, cocrystals, and salt formation [14].

Crystalline solids are thermodynamically stable and characterized by the presence of three-dimensional long-range order of the molecule. However, amorphous solid is thermodynamically unstable and characterized by the presence of random atomic structure and short-range order of the molecule, thus solidification in a random manner, structurally similar to the liquid state. Polymorphism is the ability of pharmaceutical substances to crystallize into different crystalline forms, thus they are also known as polymorphs. Hydrates and solvates are multicomponent crystalline solid containing both host molecule and guest molecule within the crystal lattice. The term solvate is used, If solvent(s) molecule (solvated organic compound) present within the crystal lattice, while the hydrate is used for the crystal that contains water molecule(s) within the crystal lattice of Active Pharmaceutical Ingredients (APIs) and excipient [15, 16, 17].

Salt contains a three-component system; an acid, a base, and one or more solvents. The formation of salt is possible by the intermolecular hydrogen bonding due to transfer from the proton between ionizable functional groups (acid, base). Hence salts formation is possible only active pharmaceutical ingredients (APIs) having ionizable moiety in it, for transfer of a proton in the ionic state. The pKa value of the components plays a vital role in the transfer of a proton [18, 19].

CO-CRYSTALS VERSUS SOLVATES

Cocrystals are multicomponent crystalline solids formed nearly close to solvates or hydrates, except components exist as solids within the crystal lattice at room temperature [20]. Unique

differentiation between solvates and cocrystals is made by the physical state of the isolated pure components: if one component within the crystals lattice is liquid at room temperature, the crystal is designed as solvates while both components are solids within the crystals lattice at room temperature, the crystals are designed as cocrystals [21].

COCRYSTAL VS SALT

Generally, proton transfer from acid to base distinguishes salt and cocrystals formation [22]. Transfer of the proton depends upon the pKa value of the participating component, if no proton transfer occurred favored the formation of cocrystals if proton transfer completed favored the salt formation [12]. Salt formations of active pharmaceutical ingredients (APIs) require the presence of at least one ionizable center on chemical structure [23]. Salt formations take place, active pharmaceutical substances (APIs) and mixtures acting as ion counters are greater than 4 (pKa> 4) [24]. There will be no proton transfer, when the difference between the pKa value of API and Coformer (ΔpKa) in range of negative values, therefore the possibility of cocrystal formation in such case. While the formation of salt is observed due to completion of proton transfer at ΔpKa value is greater than 3. When ΔpKa value remains adjacent to that of a base, then the process results as salt and when it exists adjacent to the acid, then the process results as a cocrystal [25, 19].

PREDICTION AND COFORMER SELECTION

APIs when co-crystallized with pharmaceutically accepted co-formers new crystalline forms of the APIs with modified physicochemical properties are obtained. During co-crystallization, ionic salts are obtained when proton transfer occurs if not neutral co-crystals with hydrogen bonds obtained [26]. Crystal engineering strategies are applied in the preparation of novel cocrystals by the identification of a potential functional group, which can be utilized in the formation of supramolecular synthon [6]. These are homogeneous phases, which are solids at room temperature and are held together by weak non-covalent interaction, mainly hydrogen bonding [7]. Various approaches for the selection of Coformer were supramolecular synthon approach, Hansen solubility parameter, pKa based model, Cambridge structural database, hydrogen bond calculation, and Binary and ternary phase diagrams.

Supramolecular Synthons Approach

E.J. Corey was framed the term "synthon" in 1967, while Desiraju mainly used the term "supramolecular synthons" when describing a series of cocrystals as “structural units within

the supramolecule which may be formed or assembled by known or possible intra / intermolecular interactions" [27, 28]. "Kinetically defined structural units that ideally express the core features or kernel of a crystal structure, and which encapsulate the essence of the crystal in terms of molecular recognition" known as supramolecular synthons [29]. Supramolecular synthons further classified into two groups:

i. Supramolecular homosynthons: It is composed of the same functional group intermolecular interactions. (e.g. amide-amide or carboxylic acid-carboxylic)

ii. Supramolecular heterosynthons: It is composed of the different functional group intermolecular interactions. (e.g. carboxylic acid-pyridine or carboxylic acid-amide) [30].

Hansen solubility parameter (HSP)

By using HSP, the prediction of miscibility of drug and suitable coformer can be made during cocrystal formation. It has been used in pharmaceutical science to predict the miscibility of drugs with carriers or with excipients in solid dispersion [31]. From chemical structures using the Van Krevelen method Hansen solubility parameters were calculated to determine solubility parameters for polymeric excipients the weight average molecular weight were used. Further HSP was divided into three different partial parameters of solubility: dispersion (δd), polar (δp), and hydrogen bonding (δh) [32]. The estimation of miscibility between drug and suitable Coformer were determined based on Hansen solubility parameters. Drug and Coformers are considering to be miscible when the difference solubility parameters are within a certain limit, i.e. $\Delta\delta - \leq 5$ MP0.5 or $\Delta\delta t < 7$MP0.5. Miscibility of two molecules at the molecular level is possible only when the difference in Hansen solubility parameter being less than 7 MP0.5 [33].

Cambridge structural database

Cambridge Structural Database (CSD) is a database containing small molecules crystal structure displayed as a measurement of the strength of a certain class of intermolecular arrangements involving strong hydrogen-bonded bimolecular ring patterns [29]. During the synthesis of cocrystals, analysis of existing crystal structure is the prime step; Cambridge Structural Database (CSD) guides statistical analysis of molecular packing design along with empirical information of corresponding common functional groups and how they occupy in molecular association [34]. Besides, novel Coformer is classified through Cambridge structural database with the systematic screening way, by selecting those that can form hydrogen bonds

in various styles of hydrogen bond with API, which maximizes suitable Coformer finding possibilities [35].

Hydrogen bond

Another approach for the selection of Coformer for the solid cocrystal systems is based on the pairing of H-bond donor and acceptor [36]. Hydrogen bonds play a crucial role during cocrystallization due to their solidity and directionality [37]. Complementary hydrogen bonds among API and Coformers are normally required inside the formation of a cocrystal [33]. The suitable Coformer is predicated on the ability to form reversible or non-covalent interaction with API. Both Coformer and APIs should contain hydrogen bond donor moiety or hydrogen bond acceptor moiety such as ether, ketone, alcohol, ester, carboxylic acid, amide, amine, etc [38].

pKa based model

Formation of cocrystals and salts arefrequently predicted by proton transfer between acid and base or by calculation of the ΔpKa= [pKa (base)–pKa (acid)]. It is generally accepted that transfer of the proton will occur from acid to base if the difference within the pKa values is greater than 3. A smaller ΔpKa value (less than 0) favours the cocrystals formation whereas higher values (more than 3) favor the salt formation. This model is not an exact prediction of the formation of cocrystal and salt between the ΔpKa values 0 and 3 but the probability of formation of salt will increase when the ΔpKa increases [39- 41].

Binary and ternary phase diagrams

Ternary phase diagram (TPD) based cocrystal screening has been used to screen suitable Coformer for desired cocrystal systems [42]. Phase diagrams utilized different solid phases that can be formed between API-Coformer combinations. Phase diagrams can be created either from two components (API-coformer) or from three-component (API-Coformer-solvent) systems [43]. Generally, binary phase diagrams are constructed with the resulting outcome from the thermal analysis method [44]. The melting point or character of both API and Coformer determines the solid solution/eutectic and cocrystal forming attribute for exploration systems. In general, the eutectic forming binary system adopts a V-shaped curve while cocrystals forming systems adopt a W-shaped curve [45-47]. Ternary phase diagrams (API-Coformer-solvent) help in deciding the cocrystal arrangements area for a given structure [48, 49].

METHOD OF PREPARATION

APIs when co-crystallized with pharmaceutically accepted co-formers to yield neutral cocrystals with hydrogen bonds or ionic salts when a proton transfer occurs, thus new crystalline forms of the APIs with desirable physical and chemical properties are obtained [26]. Preparation of cocrystals via traditional solution-based high throughput techniques suffers from disadvantages similar to the preparation of cocrystals via solution and has low success rates. Screening of cocrystals via slurry and mechanochemical-based high throughput screening improve success rates of screening have been reported in most research papers [50]. Solid-state and solution-based techniques are two main processes that have been used for the synthesis of co-crystals. Synthesis of co-crystals via solid-state techniques used no or very little solvents during the production, while solution-based techniques utilized a large number of excess solvents with subsequent isolation steps. The traditional technique for screening of co-crystals is solvent evaporation [9]. The most commonly used techniques for cocrystal synthesis include slow evaporation and liquid-assisted grinding [2]. There are several efficient methods of cocrystal preparation, such as solvent-assisted grinding, anti-solvent crystallization, slurry cocrystallization, and solvent evaporation approaches [51].

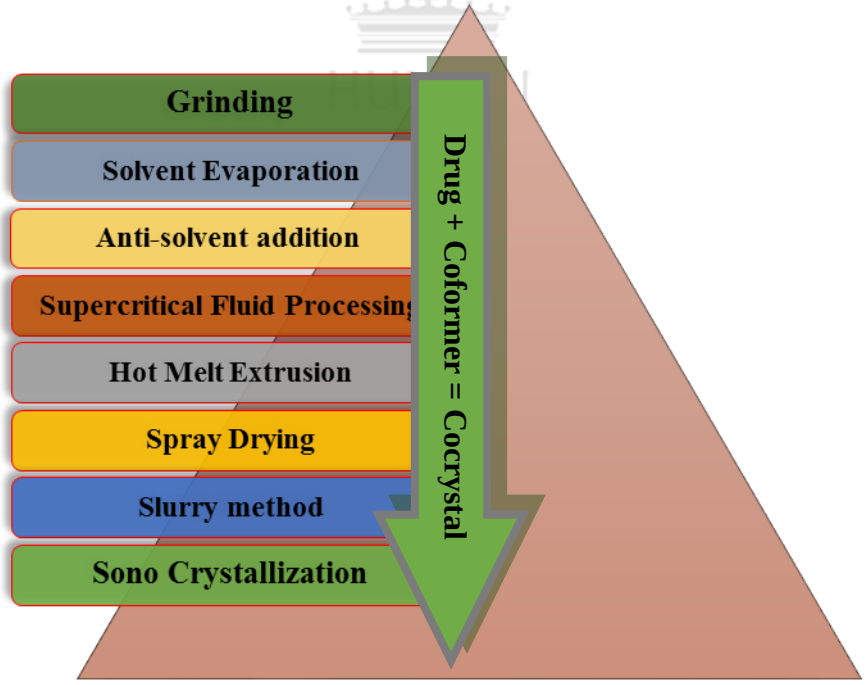

Figure No. 1: Different methods of preparation of cocrystal.

Table No. 1: Example of some reported methods of preparation

Drug	Coformer	Method of preparation	References
Nebivolol hydrochloride	4-hydroxybenzoic acid and nicotinamide	Liquid assisted grinding and solvent evaporation method.	52
S-Ibuprofen and RS-Ibuprofen	Nicotinamide	Ball milling, recrystallization from melt blending, and evaporation from a solution.	53
Theophylline	Acesulfame, saccharin	Solvent drop grinding method	54
Hesperetin	Picolinic acid, nicotinamide, and caffeine	Solvent drop grinding technique	55
Isoniazid	Vanillic acid, ferulic acid, caffeic acid, resorcinol	Slurry crystallization	56
Mefenamic acid	Nicotinamide	Gas Antisolvent	57
Mefenamic acid	Paracetamol	Gas Antisolvent	58
Ibuprofen	Isonicotinamide, Mannitol, Xylitol, Soluplus and PVP K15.	Spray drying, Hot melt extrusion	59
Ibuprofen	Nicotinamide, soluplus	Hot-melt extrusion	60
Myricetin	Isonicotinamide, Caffeine, Nicotinamide, Proline	Solvent evaporation method	61
Nateglinide	Benzamide	solvent evaporation	62
Ibrutinib	Saccharin	Solvent evaporation	63
Chlorbipram	Fumaric aicd, Gentisic acid and salicylic acid	Slow solvent evaporation method	64

STUDIES ON PHYSICOCHEMICAL AND MECHANICAL PROPERTIES OF COCRYSTAL

Pharmaceutical cocrystallization is a reliable method to modify and improve the physical and chemical properties of drugs such as solubility, stability, dissolution rate, hygroscopicity, and compressibility without changing their pharmacological activity [65]. Therefore, in the latest pharmaceutical development, to improve the bioavailability of poorly water-soluble (PWS) drugs candidates' solubility and dissolution rate enhancement technologies are becoming excessively crucial [50].

Melting point

Melting points are a unique identification of drug substances used for classification and characterization. They reflect purity, quality, stability, and information about formulation strategies. The melting points of crystalline drugs reflect the temperature at which the solid is in equilibrium with its liquid [66]. The melting point is essential property utilizes in the estimation of vapor pressure, boiling point, and aqueous solubility [67]. Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) are the most used techniques for the determination of melting point [68].

Solubility

The solubility and dissolution rate of drugs are decisive factors after oral administration for the rate and extent of absorption. This factor offers key challenges for the discovery and formulation development of effective drugs in the pharmaceutical sector. In the present context, more than 60 % of drugs coming from synthesis and 40% drugs in the pharmaceutical discovery and developments are poorly soluble and face bioavailability problems [69]. Cocrystals are meta-stable solid and easily dissociate into their respective components in solution due to their weak intermolecular interaction between APIs and coformer [70]. Altering physical and chemical properties of poorly water-soluble drug candidates to improve bioavailability through cocrystallization has attracted expanding interest over recent years. Cocrystals improve solubility by a mechanism supposed to be changed lattice and solvation energies due to the presence of the coformer. Animal studies observed that improved solubility of cocrystals has influenced higher GI absorption of cocrystals [71].

Tabletability

Ideally, a mixture of several excipients and one or more active pharmaceutical ingredients (APIs) is directly compressed to the specified shape, dimension, weight, and hardness [72]. Tablets are obtained in the tableting process (Die filling, Compression, Decompression, and Ejection.), where the powders are transformed into a dense compact [73]. Among the various properties of API, the most important one is the Crystallinity, which is directly involved in the compatibility, tablet hardness, lamination, disintegration time, dissolution rate [74].

Stability

Different stability studies like chemical stability, thermal stability, solution stability, and photostability should be performed during the development of pharmaceutical cocrystals. The stability studies of pharmaceutical products are the vital parameter for the pharmaceutical development of the new drug as well as new formulations. Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain their quality attributes throughout the shelf life [75]. During the developments of pharmaceutical cocrystals, different stability studies should be performed like chemical stability, thermal stability, solution stability, and photostability [19].

Bioavailability

The solubility determines the therapeutic effectiveness of active pharmaceutical ingredients (API). API, with low aqueous solubility, indicates its low bioavailability [36]. Therefore, in modern pharmaceutical development solubility and dissolution rate enhancement technologies for poorly water-soluble drug drugs become crucial to improve the bioavailability [69].

Table No. 2: Some Reported performances implication of cocrystal systems

Cocrystal systems	Implication	Performances	References
Norfloxacin-Isonicotinamide	Solubility	Apparent solubility of norfloxacin with the cocrystal after 72 h, an approximately three-fold enhancement in the solubility of the cocrystal.	76
Indomethacin-Saccharin	Dissolution rate	Cocrystal showed a higher dissolution rate compared with pure indomethacin.	77
Acyclovir-Fumaric acid	Solubility	Improved water solubility compared with pure acyclovir.	78
Carbamazepine-Trans-cinnamic acid	Dissolution rate	Cocrystals exhibited faster dissolution rates than pure carbamazepine.	79
Caffeine-oxalic acid	Stability	Superior stability at all relative humilities up to 98% relative humidity (RH) for 7 weeks relative to caffeine.	80
Adefovir dipivoxil-suberic acid-succinic acid	Stability	Both cocrystals displayed considerably improved thermal stability compared with pure adefovir dipivoxil.	81
Simvastatin-nicotinamide	Stability	Found stable for one month, at 40 degrees C and relative humidity (RH) 75 %.	82
Paracetamol-Theophylline	Tabletability	Showed an increase in compressibility than pure Paracetamol.	83
Carbamazepine-Nicotinamide, Carbamazepine-Saccharin	Tabletability	Both cocrystals systems showed an increase in tensile strength for a given pressure.	84, 85
Metformin-sodiumsalicylate	Tabletability	Dramatically improved tabletability of Metformin HCL, when co-crystallized with sodium salicylate.	86
Resveratrol-4-	Tabletability	Both cocrystal systems exhibit much-	87

aminobenzamide, Resveratrol-isoniazid		improved tabletability than pure Resveratrol.	
Daidzein-isonicotinamide, Daidzein-cytosine, Daidzein-theobromine	Melting point	The DSC thermogram of Daidzein showed a single endotherm at 336 ˚C, and the cocrystals showed a single endothermic transition at 179.63 ˚C (Daidzein-isonicotinamide), 291.65 ˚C (Daidzein-theobromine), and 276.88 ˚C (Daidzein-cytosine).	88
Ferulic acid-Isonicotinamide, Ferulic acid-Urea	Melting point	The DSC thermogram of Ferulic acid showed a single endotherm at 172.8 °C and the cocrystals Ferulic acid-Urea, Ferulic acid-Isonicotinamide showed an endothermic transition at 158.1 °C and 143.9 °C respectively.	89

CONCLUSION AND FUTURE PERSPECTIVES:

Cocrystallization of poorly water-soluble drugs is one of the novel approaches to improve their aqueous solubility. A lot of crystal engendering efforts are directed on the synthesis of a cocrystal of poorly water-soluble drugs with suitable Coformers. The physicochemical properties of cocrystal like melting point, aqueous solubility, and hence their bioavailability depends upon the types of Coformer used. However, at present, Coformers are either chosen based on empirical acknowledge or based on complex procedures requiring detailed investigation and calculation. Therefore, the development of a new and fast Coformer screening tool is necessary to screen Coformer suitable for cocrystallization. Furthermore, efforts are also needed to develop a general understanding of intermolecular interactions that influence the cocrystallization outcome by employing supramolecular chemistry and crystal engineering principles. While a rational design of a cocrystal can lead to a successful outcome at the end of cocrystallization, it is equally important to develop a solvent-free cocrystal production method. Additionally, further research effort also needs large-scale

production and also needs to focus on stability. At present, very little documented information is available on the aspects related to cocrystal stability.

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