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The Selection and Screening of Conformers

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Many drugs fall in the Biopharmaceutics Classification System category of class II and class IV drugs i.e. low solubility/high permeability and low solubility/low permeability respectively. Due to their hydrophobicity, there is difficulty in forming a stable formulation. Crystal engineering is implemented with a water-soluble molecule (called conformer) and an active pharmaceutical ingredient to improve the aqueous solubility. This review primarily is written to provide a general understanding of the experimental techniques used during the screening of cocrystals. It also discusses the challenges and future perspectives of cocrystal engineering and their importance to be thermodynamically stable to be acknowledged as a potentially marketable product.

Keywords: Cocrystallization; cocrystals; conformers; crystal engineering; selection; pharmaceutical cocrystals; screening; solubility enhancement;

1. Introduction

"Pharmaceutical co-crystals have been defined as co-crystals, which contain an API as one component and another component as a co-former in a stoichiometric ratio" This definition is given by H Lee [1]. The main advantage of formulating the crystals is that by the presence of a co-former that acts as a property modifying component, the physicochemical properties of the APIs can be enhanced without affecting the pharmacological activity [2]. The United States Food Drug Association (USFDA) has made a record of compounds that can be possible conformers used in crystallization [3]. Selection of the co-former is the most important course of action in crystallization. The screening can be done by two methods: computationally or experimentally. Many of the conformer screening computational methods used in literature in history are thermodynamics-based methods. Lattice energy calculations have been used in cocrystallization experiments to screen co-formers to form cocrystals that are inherently thermodynamically stable [4]. Several other parameters, including interaction energies [5,6], electrostatic potentials [7], solubility behavior [8,9], and hydrogen bond propensities [10] can be used.

Factors determining cocrystallization include carbon chain length of dicarboxylic acid conformers [10,11], hydrogen bonding property [12–16],synthonic engineering [13,17,18], flexibility of synthon forming functional groups [19,20], molecular recognition points, CSD [21]. Experimental methods employed are: pKa rule [22,23], Fabian's method [10], COSMO-RS [24], Hansen Solubility Parameter [25],Virtual co-crystal screening [26], cocktail co-crystal method [27], thermal analysis [28–31], and synthon matching [18,32]. This review focuses on the experimental methods in the selection and screening of cocrystals.

2. Experimental Methods

2.1 Carbon Chain Length-of-Dicarboxylic Acid-Conformers

Carbon chain length of the dicarboxylic acid database figures out the pairs of molecules that can form pharmaceutical cocrystals on the grounds of prior calculated molecular properties. According to Fabian's method described later in the paper, the strongest and most effective descriptor correlation was associated with the polarity and shape of the conformers [10].

Carboxylic acids are frequently used as conformers in cocrystal engineering because they can be used to develop heterosynthons with small molecules containing pyridine and amide functional groups. They also form homosynthons with API having an acid functional group. The propensity of this formation with carboxylic acids not only is dependent on the particular functional group but is also dependent on its length of the carbon chain.

In one experiment, two types of pharmaceutical cocrystals with different constitutions of the components viz. poly (3-octyl thiophene) and poly (3-hexylthiophene) were used. In the two constitutions described, TR (i.e. isothermal temperature range) in the equal duration of time of crystallization, a consistent pattern is found. The pattern is that the TR decreases with the increasing length of the alkyl chain in the two blends [11]. The conformers of longer carbon chains aren't likely candidates for cocrystallization with actives where the conformer's geometrical placement into API-lattice is little [11,33].

2.2. Property of Hydrogen Bonding

Hydrogen bonding has a prominent contribution to the interaction between the drug and conformer. In cocrystallization, non-covalent bonding like Van der Waal forces and hydrogen bonding forces are present [12,13]. The magnitude of success in cocrystallization can also be estimated by the number of hydrogen bond acceptors and donors in the conformer and API. The more number of hydrogen bond interactions increases the likelihood of the conformer molecules forming crystals with the active pharmaceutical ingredient [14]. Two researchers Etter [15] and Donohue[16] formulated a set of rules called Hydrogen Bond Rules to estimate the success of cocrystallization [12,15,16].

The rules are as follows:

1. Almost all appropriate donors (such as –COOH,-NH4+) and appropriate acceptors (such
-OH,-NH3) are utilized in hydrogen bonding.
2. Six-membered ring intramolecular hydrogen bonds (such as C-H…O) are formed first. Then preference to intermolecular hydrogen bonds (such as N-H…O and O-H…O) is given.
3. The best proton donors and acceptors available after intramolecular hydrogen bond formation later are available in intermolecular hydrogen bonds.
4. All acidic hydrogen atoms are part of hydrogen bonding in the crystal lattice.

2.3. Synthonic Engineering

The API molecules have a specific functional group also known as molecular recognition point which has interactions with the conformer and thus creates supramolecular units or supramolecular synthons [17].

Moreover, functional groups will greatly affect the chief role in cocrystallization. Choice of an appropriate functional group for the API is crucial. Essentially, synthons existing in the supramolecular units are considered elementary structural units linked by non-covalent bonding [18].

There are two kinds of supramolecular synthon approaches:

(1) Supramolecular homosynthons: They comprise the exact functional group existing in drug and conformer such as carboxylic acid-acid homosynthons (Figure1.1(A)) and amide-amide homosynthons (Figure 1.1 (B)) [18]. These interactions are represented in Figure 1.1.

(2)Supramolecular heterosynthons: They comprise dissimilar functional groups like carboxylic acid-amide heterosynthons, the acid-pyridine heterosynthons [18]. These are represented in Figure 1.2.Heterosynthons can also be formed by hydrogen bonding as seen in Figure 1.3.

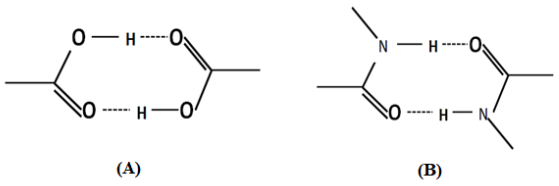

Figure1.1. Schematics illustration of supramolecular homosynthons : (A) acid-acid dimer [34,35]and (B) amide-amide dimer [35]

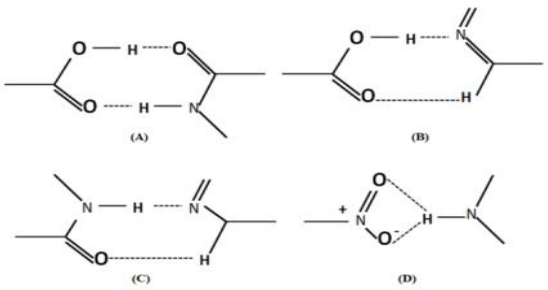

Figure1.2. Schematic illustration of supramolecular heterosynthon (A) acid-acid dimer [36]; (B) acid pyridine dimer [34,35]; (C) amide-pyridine dimer [34,35]; (D) nitro-amine interaction [37]

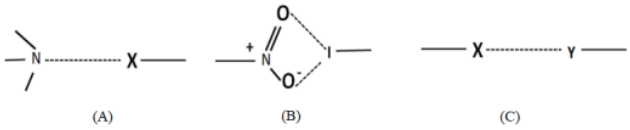

Figure1.3. Schematic illustration of supramolecular heterosynthons brought about hydrogen bonding (A) amine- halogen interaction; (B) nitro-iodo interaction ; and (C) halogen bonding with X as Cl, Br, I and Y as electron donor such as N or O [37].

2.4. Synthon-Forming Groups and Its Flexibility

The conformational flexibility of molecules and the position of their functional groups exercise a significant role in determining the extent of cocrystallization [19,20]. Although some molecules contain the same functional groups, it doesn't necessarily confirm their cocrystallization with the API. Therefore Nangia and coworkers [19,20] identified that the conformational flexibility of supramolecular synthons plays a significant part in design and development.

2.5. CSD

Cambridge Structure Database, CSD, houses structural data for thousands of organic and organometallic compounds [21]. CSD is demonstrated to be a valuable tool for facilitating the quantitative analysis of structural motifs and also for the discovery of new supramolecular synthons [21]. It gathers data about common functional groups and

searches in its library for appropriate conformers for the drug API. The CSD approach reduces research time and experimental cost by using its system to find suitable cocrystals forming pairs [18,38,39].

The link to the database is the following:

https://www.ccdc.cam.ac.uk/solutions/csd-system/components/csd/

2.6. pKa Rule

The formation of salts and pharmaceutical cocrystals can be understood by way of proton exchange between acid and base. pKa value establishes the ability of an acid molecule to give up a proton [23].The equation ΔpKa = pKa(base)-pKa(acid) predicts the formation. Proton transfer can occur from acid to base when the difference in their respective pKa values is larger than 2 i.e. the formation of salts. A smaller difference in pKa such as pKa< 0 indicates the formation of cocrystals as there is no proton transfer [22,23]. More importantly, when Nangia et al were developing cocrystals of clotrimazole (CLT) with some conformers of carboxylic acid, there was an identification describing salt formation with maleic acid (MA). The stoichiometric ratio (CLT: MA) was 1:0.5 but the value of calculated ΔpKa for the experiment was 0.93. Hence in conclusion ΔpKa cannot always be relied upon and utilized to predict if the resulting formation is salt or pharmaceutical cocrystals [40].

2.7. Fabian's Method

Reliable co-crystal forming pairs are found from the CSD. Certain parameters are considered for every molecule known as molecule descriptors for example single atom, surface area, etc. The system database figures out the pairs of molecules which were capable of developing pharmaceutical cocrystals on account of calculated molecular properties. The strongest and most effective descriptor correlation was associated with the polarity and shape of the conformers [10].

2.8. COSMO-RS

For the selection of appropriate conformers by screening, COSMO-therm software was used to predict the conformers' miscibility in the supercooled liquid (melt) phase. The COSMO-RS theory stated that the suitable ranking of conformers for the particular API should be concentrated on the conformers that have a higher probability of crystallization. Therefore this provides indications to the amelioration of the drug's miscibility. The probability is calculated by the excess solubility, Hex (factor for H-bonding interactions) between the conformer and API mixture. This is compared to the pure components. All these values reflect the tendency for the two compounds to co crystallize [24].

2.9. Hansen Solubility-Parameter

A concept to figure out miscibility of the active pharmaceutical ingredient and the conformer is calculating Hansen solubility parameter. The formation success-rate is enhanced by using similar miscibility components [9]. The theory establishes that if the total HSP's difference was < $7.0MPa^{0.5}$, the two components would be miscible else it is considered to be immiscible [41]. The partial solubility parameters: δ_d,$\delta_p$and δ_h can be calculated using the

combined group contribution methods of Van Krevelen–Hoftyzer and Fedors (Table 1.1) [9]:

Partial solubility parameter	Equation
δ_d (dispersion)	$(\sum_i F_{(d_i)})/(\sum_i V_i)$
δ_p (polar)	$((\sum_i F_{(p_i)}\text{^}2)\text{^}0.5)/(\sum_i V_i)$
δ_h (hydrogen bonding)	$[\![((\sum_i F_{(h_i)})/(\sum_i V_i))]\!]\ \text{^}0.5$

Table 1.1 Partial solubility parameters

Where i is the structural group within the molecule

F_{d_i} is the group contribution of dispersion forces

F_{p_i} is the group contribution of the polar forces

F_{h_i} is the group contribution of the hydrogen bonding energy

V_i is the group contribution of the molar volume

There are various approaches to determine the miscibility. Van Krevelen and Hoftyzer used one approach to find miscibility of two compounds wherein the $\Delta\underline{\delta}$ factor is used.

$$\Delta\underline{\delta} = [(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2]^{0.5}\text{A}$$

Good miscibility can be achieved at $\Delta\underline{\delta} \leq 5$ MPa0.5 [25,42].

2.10 Virtual Cocrystal Screening

Virtual Cocrystal Screening is the concept where the conformers are screened by predicting plausible intermolecular interaction sites i.e. mostly H-bonding existing on the molecules' surface [26]. Conferring to this theory the H-bond strength depends on the H-bond acceptor and H-bond donor. All the respective sites interact with one another. MEPS approach is a calculated gas-phase approach used for screening for conformers for the API. It assumes the ΔE, energy difference, and makes a presumption. The cocrystallization probability is around 50.0 percent higher when the ΔE of two cocrystals and two pure solids is greater than 11kJ/mol [26].

2.11. Cocktail Cocrystals Method

A method for screening conformers is called "the cocktail cocrystals method." In this method, four conformers are subjected to grinding simultaneously with the particular drug in the ball mill. This method reduces the workload; it is more feasible and not as time-consuming as other methods which are single time-consuming in nature. Interactions between the chemical moieties between the drug and conformers formed strong bonds. These strong bonds or synthons were formed; both heterosynthons and homosynthons [27].

2.12. Thermal Analysis

DSC (Differential Scanning Calorimetry) is commonly used for the screening of this formation [28]. The physical mixture is heated in a specific stoichiometric ratio. A suggestion is offered where the total number of exotherms and endotherms can determine cocrystal formation [29,30]. This is tabulated in Table 1.2. From many systems analyzed, it was found that the existence of an exothermic peak was linked with the formation of cocrystals [31]. The advantages and disadvantages of thermal analysis/DSC are given in Table 1.3.

3 endotherms two exotherms	Cocrystal formation having stoichiometric diversity
2 endotherms one exotherm	Singular cocrystal formation having definite molar-ratio
1 endotherm	No crystal formation at all.

Table 1.2 Ratios of endotherm and exotherm

As DSC gives ambiguous results, other techniques are employed along with DSC, such as Hot stage microscopy, to improve the overall screening efficiency.[43,44] Another method developed is the measurement of saturation temperature of the pharmaceutical cocrystals and their components [45]. It is a more effective method for screening than DSC and HSM, however, solvent use is required and it's a very time-consuming method [46].

Advantages of thermal analysis/DSC:	Disadvantages of thermal analysis/DSC:
● Rapid screening method ● Small amount of sample needed for analysis ● No solvent required ● "Green technique"	● Inappropriate for volatile or unstable compounds ● During the DSC process, physical transformations occur, which make the nature of compounds difficult to understand. ● Ambiguous results, therefore other techniques used in combination with this.

Table 1.3 Partial solubility parameters

2.13. Synthon matching

Synthon matching is a computer-based method that studies the intermolecular interactions in the crystal lattice. This type of screening determines the possibility of H-bonding between API and conformer [18]. Applications such as ESCET, Crystal explorer, and many more are used to understand the intermolecular interactions in crystals quantitatively and quantitatively [32].

3.0 Challenges and Future Prospective of Cocrystal Engineering

Choosing an appropriate conformer for the synthesis of a thermodynamically stable cocrystal is of high importance. Many times, in the search of synthesizing cocrystals eutectics, amorphous solids, or other solid solutions formulations are formed. Therefore the choice of a suitable conformer that produces crystals with the drug is of greatest importance. Developing a system or concept in the selection and screening of a good conformer has still not been recognized. At the present moment, there is very little information on its stability which includes the cocrystal-polymorph conversion or the degradation of cocrystals. Another future prospective is to introduce this formulation in preclinical trials and then later clinical trials so that further development can take place and convert the formulation into a marketed product.

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