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# Pharmaceutical Co-crystal : An Emerging Technique to enhance Physicochemical properties of drugs

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**Abstract :** Major constraints in development of new product are poor aqueous solubility, stability and low oral bioavailability, low permeability. As majority of drugs marketed worldwide are administered by oral route and about 40% -50% of the new molecular entities were never invade into the market because of such biopharmaceutical issues. So issues related to poor physicochemical property of an active pharmaceutical ingredient (API) can be resolved using co-crystallization approach. Crystallization emerge as potential technique for enhancement of solubility of poorly aqueous soluble drugs also helps to improve physicochemical with preserving the pharmacological properties of the API . Cocrystals are solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates/hydrates nor simple salts. It is multicomponent system in which one component is API and another is called cofomer. Cofomer selection is the main challenging step during cocrystal synthesis , so various screening methods for the selection of cofomers was explained . This article also summarizes differences between cocrystals with salts, solvates and hydrates along with the implications and limitations of cocrystals .It also provides a brief review on different methods of cocrystal formation and characterization techniques of cocrystals. Lastly this article highlights 85 synthetic and 14 herbal cocrystals along with its method of preparation and cofomers used.

**Keywords :** Pharmaceutical cocrystals, cocrystallization, solubility, stability, bioavailability, dissolution ,supramolecular synthons.

## Introduction

Over the years about 60-70% of compound have been categorized into BCS Class II (low solubility/high permeability) and IV (low solubility/low permeability) category.<sup>1,2</sup> Researchers have investigated various approaches to enhance the solubility of drugs, such as size reduction, solid dispersion,

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complexation, salt formation, nanoparticles, self-emulsifying drug delivery system (SEDDS), addition of co-solvents, nano-suspension and emulsion and cocrystal formation. Each technique has its own merits and demerits.<sup>3</sup> Amongst all these techniques, cocrystals has been found to be unique in a way that it does not affect the pharmacological properties of the drug, but it may improve the drug's bioavailability and physicochemical characteristics such as melting point, tableability, solubility, stability, bioavailability and permeability.<sup>4</sup>

## Cocrystals

Cocrystals was discovered in late 1800s and early 1900s, the first reported cocrystals, quinhydrone was studied by Friedrich Wohler in 1844. Due to various stability issues, API cannot be properly formulated and hence they are converted into solid forms such as polymorphs, salts, solvates, hydrates, amorphous, and co-crystals. Each of them imparts a different physicochemical property and affects other performance. Currently the most challenging situation is to enhance solubility of certain drugs. It's easy to solve solubility problem of amorphous form, but difficult for crystalline drug so the concept of cocrystals came into existence.<sup>5</sup> The term -cocrystal and design rules of hydrogen bonding of an organic cocrystal were first reported by Etter.<sup>6,7</sup>

In 2013, USFDA proposed a brief definition of cocrystal in the draft guidance as -solids that are crystalline materials composed of two or more molecules in the same crystal lattice.<sup>9</sup> A more refined definition of a cocrystal can be -multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable molecule or ion. Pharmaceutical co-crystals are non-ionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API.<sup>5</sup> Desiraju was the first who reported the supramolecular synthon concept of hydrogen bond formation in the crystal structures.<sup>8</sup> This review highlights the improvement in dissolution profile of drug, bioavailability and solubility by co-crystallization technique.

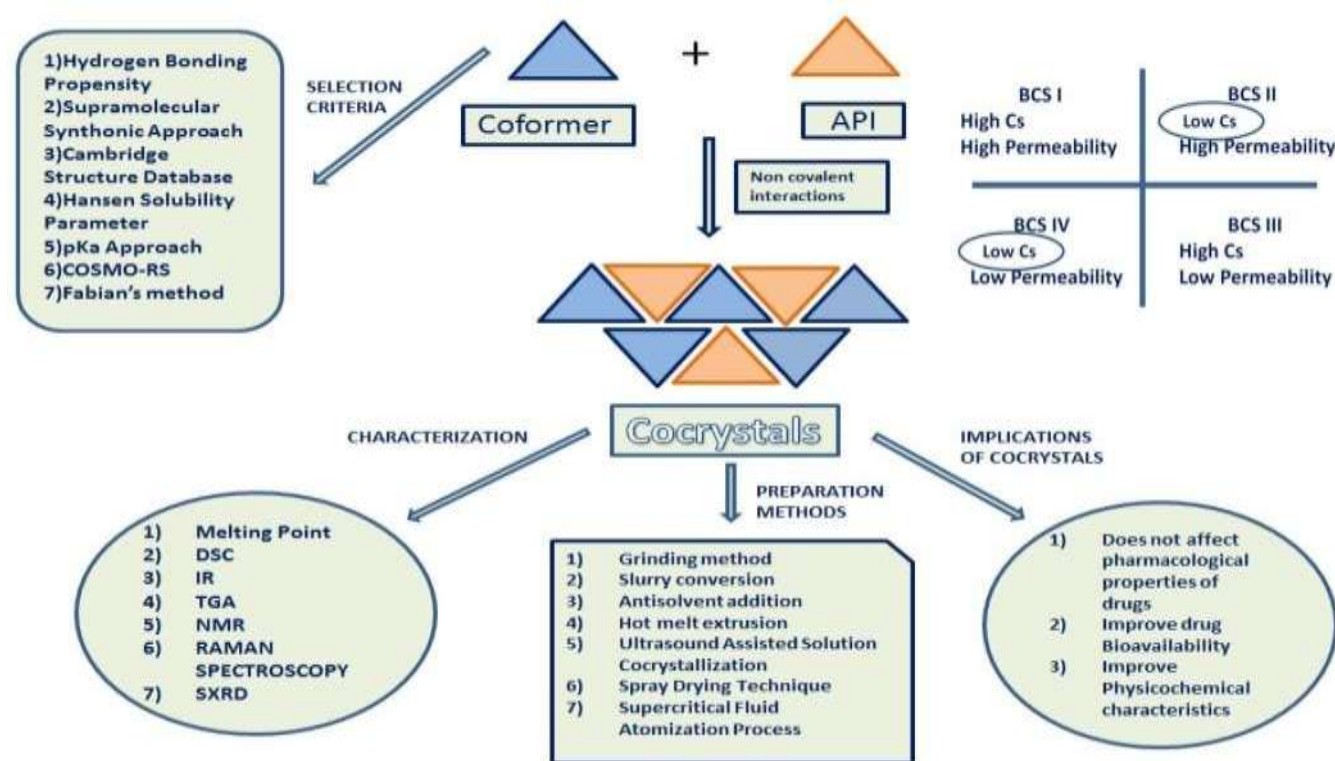
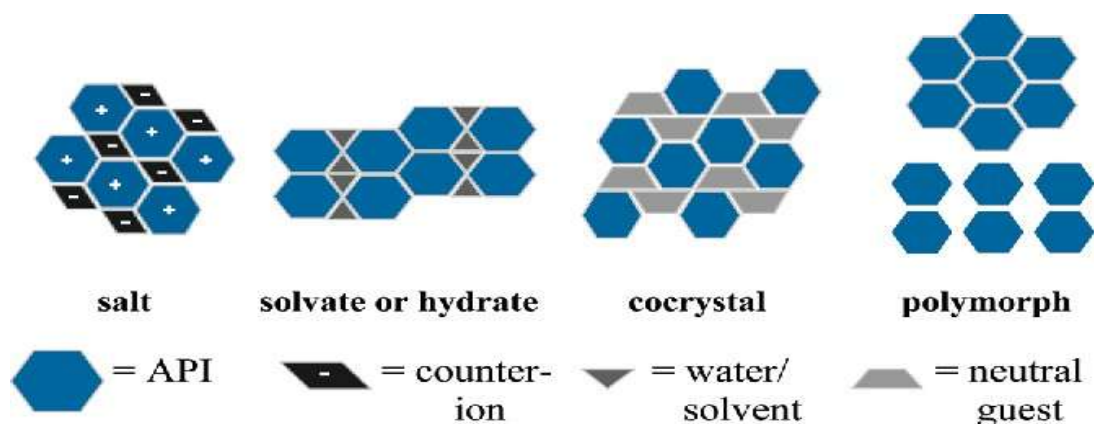
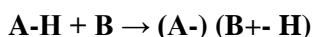


Figure 1 : Depicts the brief review on cocrystals synthesis and their characterization.

### Difference Between Cocrystals, Salt, Solvates and Hydrates

USFDA defined the cocrystal, salt and polymorphs in the draft guidance. The polymorphs are defined as the compounds which are present in different crystalline forms such as solvates or hydrates (also known as pseudopolymorphs) and amorphous forms. Polymorphs have different physicochemical properties due to their crystal lattice structures. Salts are the compounds which are formed by complete transfer of proton from one compound to another.<sup>9</sup> Salt formation is an acid–base reaction between the API and an acidic or basic substance. The widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs. Whereas Salts and cocrystals can be differentiated based by a proton transfer from an acid to base. A complete transfer of proton takes place between acid-base pairs, whereas, no proton transfer occurs during cocrystal formation.<sup>10,11</sup>

The difference between cocrystals, salts solvates and hydrates was explained in fig. 2. Salt formation is a three component system having an acid (A), a base (B) and one or more solvents. A salt is formed by transfer of a proton (H<sup>+</sup>) from an acid (A) to base (B).



**Figure 2:API solid form classification based on structure and composition.**

Proton transfer is thought to mainly depend on the pK values of the components. The general rules for the packing of hydrogen bonded molecules in crystals were developed by Etter.<sup>12,6</sup>

In cocrystal approach two components are bound to each other by noncovalent interactions such as hydrogen bonding,  $\pi$ - $\pi$  stacking, van der Waal forces. A prediction can be made by  $\Delta\text{pK}_a$  value whether cocrystals are formed or not. It is generally accepted that a salt will be formed if the  $\Delta\text{pK}_a$  value is greater than 3 and  $\Delta\text{pK}_a$  value less than 0 will lead to the formation of cocrystals. This parameter is not accurate to predict the formation of cocrystals in solids between the  $\Delta\text{pK}_a$  values 0 and 3 but the possibility of salt formation will increase when the  $\Delta\text{pK}_a$  increases.<sup>13, 14</sup> Cocrystals and solvates can be differentiated based on their physical state of the components. The compounds which are liquid at room temperature are called as solvates whereas those compounds which are solid at room temperature are called as cocrystals. If the solvates contain water as a solvent in their crystal lattice then they are known as hydrates.<sup>15</sup>

Different polymorphic cocrystals and solvates of caffeine and anthranilic acid were prepared by using different solvents via liquid assisted grinding.<sup>17</sup>

## Implications of Cocrystals

Physicochemical properties of drugs can be tailored by various approaches such as salt formation, micronization, solid dispersion, amorphous drugs and encapsulation.<sup>15</sup> In 2004, pharmaceutical cocrystals were described as a distinct class of novel, crystalline materials which could alter the physicochemical properties of APIs. <sup>16</sup> Cocrystals are solids that are 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. <sup>21</sup> The cocrystals have the advantages that they will exist in stable crystalline form and without altering the pharmacological properties, the APIs will benefit of their physicochemical properties enhancements because of the presence of coformer in crystal structure which is a property modifying component. <sup>19,20</sup> The factors which play important role in affecting the physicochemical properties are the properties of APIs and cofomers, the nature of molecular interaction between them and the employed synthetic procedures.<sup>15,18</sup>

Another distinctive advantage of cocrystals over the more common salts is that cocrystals can be made for non-ionisable APIs as well as for those complex drugs which have sensitive functional groups that may not survive the harsh reaction conditions of strong acids or bases.<sup>22,23</sup>

Pharmaceutical cocrystals can remediate the physicochemical properties of drugs such as melting point, tableability, solubility, stability, bioavailability, permeability and these properties are highlighted here with suitable examples.

### 1 Melting point

Melting point is the physical properties of solid and used for determination of purity. Pure substances or solid melt at sharp melting point with narrow range. Thermodynamic stability of any API can be govern by its melting point so utility of high melting point conformer for its better stability and also useful in case of thermolabile drugs, so selection of conformer is very important in case of synthesis of cocrystals. Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) are most common techniques used to determine melting point. <sup>24</sup> Jadhav et al synthesized cocrystal of fenofibrate using different cofomers like para amino benzoic acid, benzoic acid and salicylic acid and the results obtained states that the melting point of of fenofibrate was decreased than pure one and individual conformers.<sup>25</sup>

### 2 Tableability

Tableability means ability of substance to get covert in tablet form. Resveratrol cocrystal was synthesized by Zheng zheng et al using 4-aminobenzamide and isoniazid as cofomers and its

enhanced solubility and tableability was studied. Zheng observed that tableability of RES is poor and because of this even at high pressure that is 0.6 MPa and lamination of tablets, while tablets prepared with cocrystals of Resveratrol-4-aminobenzamide, tensile strength more than 3 MPa is attained at 250 MPa compaction pressure.

Author concluded that cocrystal formation improved tableability of drug.<sup>26</sup>

### 3 Solubility

As mentioned in introduction that about 60 to 70 % drugs are belongs to BCS Class II (low solubility/high permeability) and IV (low solubility/ low permeability). With development of cocrystal one can increase the solubility of poorly soluble drug , many researchers have improved solubility of drug with this technique .<sup>27</sup> Cocrystals of efavirenz was synthesized by using oxalic acid dihydrate and citric acid monohydrateas cofomers to improve its solubility and dissolution rate. As both conformers have high water solubility that is 14.3g/100 ml and 64.7g/100 ml respectively and contain hydrogen bond donor and acceptor groups, which can be used for designing cocrystals of efavirenz leading to improvement in solubility.<sup>28</sup>

#### 4 Stability

Development of cocrystal involve different stability studies like chemical stability, thermal stability, solution stability and photostability. Simvastatin-nicotinamide co-crystals was synthesized by Iyan et al and the cocrystals was evaluated for stability study at 40<sup>0</sup>C and Relative humidity RH (75%) and the it was found to be stable.<sup>29</sup>

#### 5 Bioavailability

Bioavailability is defined as the rate and extent of pure drug that reaches into systemic circulation. Low oral bioavailability of APIs is one of the major challenges in development of formulations, with help of cocrystallization one can enhance or improve the bioavailability of API . Many researchers have enhanced the bioavailability of different drugs with conversion in cocrystal form. Cocrystal of Fexofenadine was synthesized by Mounika et al using Tartaric acid as cofomer by solvent evaporation technique and it was concluded that co-crystals Fexofenadine shows maximum release as compare to the formulation.<sup>27</sup>

#### 6 Permeability

Recent investigation states that cocrystals not only can improve dissolution properties of drugs but also may modify the permeability of drugs. These results may expand the applications of cocrystals from class II drugs to class III and more importantly to class IV of BCS.<sup>30,32</sup> Drug absorption and distribution of drugs mainly depends upon the permeability of drugs across the biological membrane. Permeability of drugs mainly depends upon the n-octanol/water partition coefficient by using log P and (C log P) for unchanged form of drug.<sup>23</sup> The cocrystal of BCS class III drug (5- fluorouracil) was synthesized using 3-hydroxybenzoic acid, 4- aminobenzoic acid and cinnamic acid and it was reported that cocrystal has better permeability to that of pure drug.<sup>30</sup> Permeability of drugs, however, has been improved through the use of cofomers/excipients such as lactic acid, tartaric acid, fumaric acid and glutaric acid (higher lipophilicity of the acids). These cofomers are applicable not only to molecules of a specific physical and chemical nature, but to a wide range of crystalline materials and is often required to determine the appropriate approach towards improving solubility and permeability during drug development.<sup>31</sup> Permeability study of hydrochlorothiazide and cocrystals with different cofomers was studied by using Franz diffusion cells. The amount of drug flux in all cocrystals was higher as compared to pure drug except for succinamide cocrystals. And it was concluded that Cocrystals permeability was improved due to formation of heterosynthion between drug and cofomer.<sup>32</sup>

#### Limitations

Although preparation of co-crystals is simple but exact relationship between co-crystal structure and physical properties still unexplored.<sup>33</sup> The optimum temperature range should be known for solid-state grinding method because excessive heating may cause accidental phase transition, conglomerate crystallization or polymorphism. Solid state grinding method results in too small particle size and hence it is difficult to identify structure using X-ray crystallography.<sup>34</sup> Phase separation of co-crystals into individual component up on storage at certain relative humidity condition also a concern for its applicability.<sup>35</sup> Another limitation includes phase change during formulation development of API. Cocrystals may also be susceptible to counter ion displacement with excipients during manufacturing.<sup>35</sup>

## Crystal design approaches for selection of coformer

A pharmaceutical co-crystal is a single crystalline solid that includes two neutral molecules, one being an API and the other a co-crystal former. Co-crystal former or coformer may be an excipient or another API. <sup>36</sup> The USFDA had maintained a list of substances which is numbering in thousands and can be used as potential coformer for pharmaceutical cocrystals

[37] The non API component used as coformer should be non-toxic with no adverse side effects. Ideally, the cocrystal former should be included on the US FDA -Everything added to food in the United States (EAFUS) list, which comprises over 3000 substances that are suitable as food additives, or approved as Generally Regarded as Safe (GRAS). <sup>38</sup>

Cocrystals contain two or more components which are held together by supramolecular synthons. In order to obtain cocrystal, functional groups capable of forming supramolecular hetero or homosynthons should be present in the API and coformer, so the selection of cofomers that are compatible with a particular API is the main challenging step during cocrystal synthesis. <sup>39</sup>

For screening of cofomers, researchers have used various knowledge based approaches which include the followings: hydrogen-bonding propensity, synthonic engineering, supramolecular compatibility by Cambridge Structure Database (CSD), pKa based models, Fabian's method, Lattice energy calculation, the conductor-like screening model for real solvents (COSMO-RS), Hansen solubility parameter, virtual cocrystal screening (based upon molecular electrostatic potential surfaces-MEPS), thermal analysis, measuring saturation temperature, Kofler contact method and matching. <sup>40,41</sup>

### 1) Hydrogen Bonding Propensity

In cocrystals, drug and cofomers interact with each other by noncovalent interaction such as hydrogen bonding, Vander waals forces or  $\pi$ - $\pi$  stacking interactions. <sup>42</sup> Hydrogen bonding plays an important role and responsible for the formation of cocrystals. <sup>43</sup>

The general rules for the hydrogen bond formation are followings : <sup>6</sup>

1. All good proton donors and acceptors are used in hydrogen bonding.
2. Six membered ring intermolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.
3. The best proton donors and acceptors remaining after intramolecular hydrogen bond formation form intermolecular hydrogen bonds to one another.

Hydrogen bond formation can be analyzed by predicting the involvement of proton donors and acceptors in a crystal structure with the help of Cambridge structure database. <sup>43</sup> The propensity of hydrogen bond formation between donor and acceptor can be analyzed by giving a value between 0 and 1. The value 1 indicates the formation of hydrogen bond whereas value 0 indicates no hydrogen bond formation. The values for hydrogen bonding propensity were calculated for different functional groups present in indomethacin and nicotinamide ranging from 0.71 to 0.03. High value of interaction between -NH<sub>2</sub> of isonicotinamide and carboxylic acid group of indomethacin was observed during prediction of H-bond propensity. The observed hydrogen bonding pattern in the cocrystals represented one of the most probable of all the possible combinations of donors and acceptors in the constituent molecules. <sup>44</sup>

So by using this approach a quantitative measure of interactions between two components of the system can be determined and this can reduce the time and efforts during screening of active molecules and suggests effective method for the selection of drug-coformer system. <sup>44,43</sup>

## 2) Supramolecular Synthonic Approach:

In 1995, first time Desiraju described the term –supramolecular synthon as the spatial arrangements of crystalline structures in the supramolecules which will be formed by known intermolecular interactions. The intermolecular interactions in the crystalline structures would be the key parameter for designing the cocrystals.<sup>46</sup>

Crystal engineering relies on the basic principles of supramolecular chemistry, chemistry beyond the molecule, in developing novel entities by manipulating the non-covalent intermolecular interactions. Hydrogen bonding, metal coordination, van der Waals forces, hydrophobic forces, electrostatic effects and pi-pi interactions are some of the interactions which are commonly encountered in this regard.<sup>47</sup>

Crystal engineering is also based on understanding the basic behind formation of synthons using non covalent interaction. The term synthon was coined by Corey in the context of organic chemistry and defined as –structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions. A supramolecular synthon is a pattern that is composed of molecular and supramolecular elements. When crystal patterns repeat regularly, the pattern of interactions can be called a supramolecular synthon.<sup>[48]</sup>

Supramolecular synthons are further categorized into:

- (a) supramolecular homosynthon: composed of identical self-complementary functionalities
- (b) supramolecular heterosynthons: composed of different but complementary functionalities.

This concept may be better explained with the help following fig.3

### Types of supramolecular synthon

#### a) Supramolecular homosynthon    b)Supramolecular heterosynthon

Example of the supramolecular synthon which is commonly used are given below includes

- (1) Homosynthon formed between carboxylic acid dimer
- (2) Heterosynthon formed between carboxylic acid group and pyridine group
- (3) Homosynthon formed between amide dimer
- (4) Heterosynthon formed between carboxylic acid group and amide group
- (5) Heterosynthon formed between alcohol and ether group.<sup>[45,49]</sup>

The ability to form the supramolecular homosynthons of functional groups was amides>acids>alcohols. The supramolecular homosynthons should be broken and lead to formation of heterosynthons when other groups were present in the complexes.<sup>[50]</sup> Supramolecular heterosynthons are generally more favoured than homosynthons, e.g., the acid- amide and the acid-pyridine heterosynthons are commonly used as compared to carboxylic acid and amide homodimers.<sup>[49]</sup>



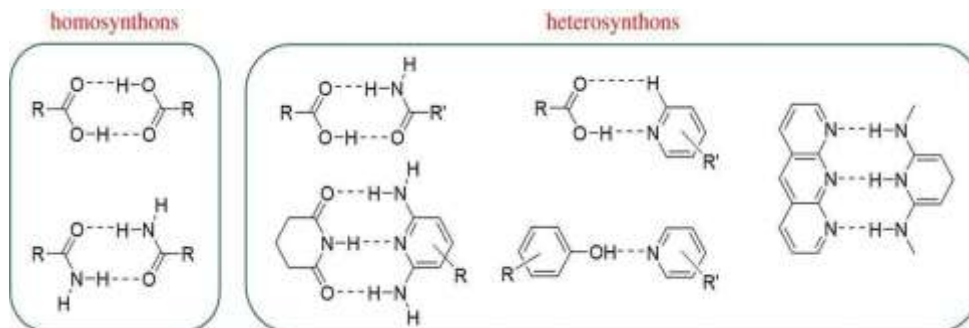


Figure 3: Types of supramolecular synthons

### 3) Cambridge Structure Database:

Cambridge Structure Database (CSD) is a valuable tool to determine the intermolecular interactions in crystals. The origin of the Cambridge Crystallographic Data Center (CCDC) was summarized by Groom and his coworkers in 1965 and development of Cambridge Structure Database (CSD) with its importance in the structural chemistry, material sciences and life sciences, including drug discovery and development was summarized.<sup>51,52</sup> CSD is a validated tool to facilitate the statistical analysis of packing motifs and thereby provide information about common functional groups. CSD is used to provide the information about molecular association of drug and coformers based on functional groups that engage into supramolecular synthons. A library of suitable coformers can be prepared by CSD for an API. This is a computer-based approach used to find appropriate cocrystal forming pairs, and reduces the research time and experimental cost.<sup>45,49,20</sup>

### 4) Hansen Solubility Parameter:

Hansen solubility parameter is another important approach used to measure the miscibility of drug and coformers used for cocrystal systems. The miscibility of the components in the solid state could predict the cocrystal formation. The synthesis of cocrystals success rate was improved by using the components which have similar miscibility.<sup>35</sup> The concept of a solubility parameter was introduced by Hildebrand and Scott, who proposed that materials with similar values would be miscible.<sup>35,53</sup>

The Hansen solubility parameter (HSP) model, which was developed later, is based on the concept of dividing the total cohesive energy into individual components (dispersion, polar and hydrogen bonding).<sup>35,54</sup> In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions.<sup>35,55</sup> Further, it has been suggested that HSPs could predict the compatibility of pharmaceutical materials, and their use is recommended as a tool in the pre-formulation and formulation development of tablets.

HSPs have been widely used to predict liquid–liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surfaces.<sup>35,56</sup> The solubility parameters (i.e. cohesion energy parameters) can be used to predict the physicochemical properties such as solubility, melting point, etc. of a material.<sup>35,57</sup> The cohesive energy is the sum of the forces (van der Waals interactions, covalent bonds, hydrogen bonds and ionic bonds) that hold the material intact.<sup>35</sup> The cohesive energy per unit volume is termed the cohesive energy density (CED). The CED can be used to calculate the solubility parameter ( $\delta$ ) based on regular solution theory restricted to non-polar systems, as follows<sup>35,53</sup>

$$\delta = (\text{CED})^{0.5} = (\Delta E V / V_m)^{0.5} \quad (1)$$



Where,

EV is the energy for vaporization

V<sub>m</sub> is the molar volume.

δ is measured in units of (J/cm<sup>3</sup>)<sup>0.5</sup>, or (cal/cm<sup>3</sup>)<sup>0.5</sup>

Attempts have been made to extend the Hildebrand and Scott approach to include polar systems and strongly interacting species. One of the most widely accepted approaches, using HSPs, proposes that the total force of the various interactions can be divided into partial solubility parameters, i.e. dispersion (δ<sub>d</sub>), polar (δ<sub>p</sub>) and hydrogen bonding (δ<sub>h</sub>). These partial solubility

parameters represent the possibility of intermolecular interactions between similar or different molecules. The total solubility parameter (δ<sub>t</sub>), also called the three-dimensional solubility

parameter, can be defined as follows :<sup>35</sup>

$$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5} \quad [45] \quad (2)$$

Various methods have been used to estimate the HSPs of a material such as various theoretical and experimental methods based on solubility, calorimetry, sublimation, vaporization, inverse gas chromatography and group contribution methods.<sup>35,56</sup>

As other method requires practical knowledge, the group contribution method is a commonly used theoretical method that only requires knowledge of the compound's chemical structure to calculate the HSPs\*1,48+. The partial solubility parameters can be calculated using the combined group contribution methods of Van Krevelen–Hoftyzer and Fedors as follows:<sup>35,58,59</sup>

$$\delta_d = \frac{\sum_i F_{d_i}}{\sum_i V_i} \quad (3)$$

$$\delta_p = \frac{\left( \sum_i F_{p_i}^2 \right)^{0.5}}{\sum_i V_i} \quad (4)$$

$$\delta_h = \left( \frac{\sum_i E_{h_i}}{\sum_i V_i} \right)^{0.5} \quad (5)$$

Where

i is the structural group within the molecule,

F<sub>d</sub>i is the group contribution to the dispersion forces,

F<sub>p</sub>i is the group contribution to the polar forces,

F<sub>h</sub>i is the group contribution to the hydrogen bonding energy,

V<sub>i</sub> is the group contribution to the molar volume

It was demonstrated that the two components should be miscible if total HSPs difference was

$<7\text{MPa}^{0.5}$ , otherwise immiscible<sup>68</sup>. Another method estimates the miscibility of two components if the difference is  $\leq 5\text{MPa}^{0.5}$  between two substances which are supposed to be cocrystal formation.<sup>58,60</sup> The predicted miscibility of drug/coformer systems by Hansen SPs was correlated with miscibility predicted by DSC and possible structure of cocrystals was determined confirmed by findings of FTIR & PXRD.<sup>60</sup>

### 5) pKa Approach :

Cocrystals or salts formation can be predicted by proton transfer between acid and base. The formation of salts or cocrystals can be predicted by determining the  $\Delta\text{pKa} = [\text{pKa}(\text{base}) - \text{pKa}(\text{acid})]$ . It is generally accepted that proton transfer will occur from acid to base if the difference in the pKa values is greater than 2 or 3. A smaller  $\Delta\text{pKa}$  value (less than 0) indicates the formation of cocrystals whereas higher value (more than 2 or 3) indicates the formation of salts.<sup>13,14</sup> But the intermediate value of  $\Delta\text{pKa}$  between 0 and 3 was unable to give a clear cut distinction between cocrystals and salts. A co-crystal to salt continuum exists between  $0 \leq$

$\Delta\text{pKa} \leq 3$  values.<sup>13,14,61</sup>

The nature of hydrogen bonding (neutral or ionic) during the formation of cocrystals between polycarboxylic acid and bipyridine compounds was analyzed with different compounds in the

$\Delta\text{pKa}$  range -2.5 to +2.5 and predicted that the carboxylic acid- .....pyridine (OH.....N) interaction will be neutral if  $\Delta\text{pKa}$  less than 0 and interaction will be ionic ( $\text{N}^+\text{-H} \dots\dots\text{O}^-$ ) when  $\Delta\text{pKa}$  more than 3.75. The nature of the hydrogen bond would be intermediate i.e. ( $\text{O}-\text{H} \dots\dots\text{N}$  and/or  $\text{N}^+\text{-H} \dots\dots\text{O}^-$ ) when the  $\Delta\text{pKa}$  between 0 and 3.75 values.<sup>13</sup>

The formation of ionized and non-ionized complexes was predicted by calculating the pKa values ( $\Delta\text{pKa}$ ) and a linear relationship was found between  $\Delta\text{pKa}$  and probability of proton transfer between acid-base pairs. Cruz-Cabeza (2012) calculated the difference in aqueous pKa values ( $\Delta\text{pKa}$ ) for 6465 crystalline complexes containing acid-base pairs and separated the complexes in three zones on the bases of  $\Delta\text{pKa}$  values. In Zone 1 ( $\Delta\text{pKa} < -1$ ), about 99.1% crystalline complexes were observed non-ionized i.e. no transfer of proton whereas in zone 3 ( $\Delta\text{pKa} > 4$ ), 99.2% crystalline complexes were found to be ionized i.e. complete transfer of proton. But in zone 2 ( $-1 \leq \Delta\text{pKa} \leq 4$ ), both ionized and non-ionized crystalline structures were observed. The relative occurrence of ionized complexes increases linearly with increasing the  $\Delta\text{pKa}$  values. It was observed that during the salt formation, probability of proton transfer between acid-base pairs increased 17% with increase in one  $\Delta\text{pKa}$  values from  $\sim 10\%$  at  $\Delta\text{pKa} = -1$  to  $\sim 95\%$  at  $\Delta\text{pKa} = 4$ . It would be found that the  $\Delta\text{pKa}$  rule is widely used for designing the formation of salts and cocrystals.<sup>62</sup>

### 6) COSMO-RS:

COSMO-RS (COnductor like Screening MOdel for Real Solvents) is a universal theory to predict the thermodynamic equilibrium properties of liquids, which was originally developed by A. Klamt at Bayer AG.<sup>3</sup>

For screening of suitable coformers for an API, COSMO-therm software based on COSMO-RS fluid-phase thermodynamic approach was used to describe the miscibility of coformers in super cooled liquid (melt) phase.<sup>63</sup>

COSMO-RS thermodynamics is based on the statistical physics of interacting molecular surface segments. The polar and hydrogen bond interaction energies are quantified based on the surface screening charge densities, which result from a quantum chemical continuum solvation calculation.<sup>64,65</sup>

Due to its ability to treat mixtures at variable temperatures and to compute accurate solvation energies based on first- principles, it has become very popular in chemical engineering and in wide areas of physical and medicinal chemistry.

COSMO-RS being a fluid phase thermodynamics model, we can compute a virtually liquid mixture of the cocrystallization components and obtain the excess enthalpy of stoichiometric m:n mixtures, typically 1:1 mixtures, created out of the pure components A and B:

$$H_{\text{ex}} = H_{\text{AB}} - mH_{\text{pure,A}} - nH_{\text{pure,B}}$$

$H_{\text{pure}}$  and  $H_{\text{AB}}$  represent the enthalpies in the pure reference state and in the m:n mixture respectively.  $H_{\text{ex}}$  contains all enthalpic contributions and is not limited to hydrogen bonding interactions, though those may be separated from the overall enthalpy by COSMOtherm. In our on-going studies we found that the excess enthalpy  $H_{\text{ex}}$  is a superior descriptor to the pure hydrogen bonding interaction. Compounds with  $H_{\text{ex}} < 0$  are strongly interacting in solution (equivalent to a negative deviation from Raoult's law) and prefer the mixture enthalpically over their pure liquids. we demonstrate that  $H_{\text{ex}}$  corresponds nicely with an increased probability of forming cocrystals. Since it is plausible to assume, that such liquid phase enthalpic preference will also pertain in a mixed crystal, i.e. in a cocrystal of the components, it is plausible to use the liquid phase excess enthalpy as a guide for cocrystal screening. Within several other applications in many areas of chemistry, chemical engineering and pharmaceutical chemistry, COSMOtherm has been proven to be a valuable tool for solvent screening, i.e. for screening for a suitable solvent for a given solute X. <sup>64,65,66</sup>

## 7. Fabian's method:

Different sets of reliable cocrystal forming structures were extracted from the CSD and the molecular descriptors (single atom, bond and group counts, hydrogen bond donor and acceptor counts, size and shape, surface area and molecular electrostatic) were calculated for each molecule. On the basis of calculated molecular properties, the database described pairs of molecules that were able to form cocrystals. The strongest descriptor correlation was related to the shape and polarity of cocrystal formers.<sup>6</sup>

## Different methods of cocrystals formation

Different methods have been reported by authors for the preparation of cocrystals . Few traditional methods based on the solution and grinding were reported for the synthesis of cocrystals.<sup>68</sup> Co-crystals is generally prepared by solvent and solid based methods. The solvent-based methods involve slurry conversion , solvent evaporation, cooling crystallization and precipitation. The solid based methods involve net grinding, solvent-assisted grinding and sonication (applied to either to wet or dry solid mixtures) 80 to 85° C.<sup>69</sup> Some newly emerging methods used for the formation of cocrystals are ultrasound assisted solution method,<sup>5,70</sup> supercritical fluid atomization technique,<sup>71,72</sup> spray drying technique,<sup>73,74</sup> hot melt extrusion technique<sup>75,76</sup>.The list of synthetic and herbal cocrystal prepared by various method along with the cofomers have been listed in Table no 1,2.

**1] Grinding methods :** Over past few years grinding methods have been widely used method and found to be superior than other methods (solution or melt).<sup>77,78</sup>

Grinding techniques are of two types: neat or dry grinding and wet grinding. In dry grinding, drug and cofomer are mixed together in a stoichiometric ratio and ground them by using either mortar and pestle or ball mill.<sup>[79]</sup> Wet Grinding was performed in a similar manner that of neat grinding by addition of some drops of solvent in the mixture.<sup>[80,81]</sup>

Muhamad et al prepared Ibuprofen-amino acids cocrystals by dry grinding as well as liquid assisted grinding method.<sup>[82]</sup> Sungyup et al synthesized Adefovir dipivoxil Co-crystals by using glutaric acid and suberic acid as conformer by liquid-assisted grinding,<sup>83</sup> Cocrystals of Fenofibrate was synthesized by Gaikwad et al. using grinding method.<sup>84</sup> Alhalaweh et al prepared Nitrofurantoin cocrystal by liquid assisted grinding method using urea, 4-hydroxybenzoic acid, Nicotinamide and valline as a cofomers.<sup>135</sup>

**2] Slurry Conversion:** methods for evaluation. Slurry Conversion is the process in which slurry is prepared by addition of different solvents in the mixture of API and suitable cofomers. The solvent is decanted and the solid material is dried and characterized by different Kharisma et al. synthesized the cocrystal of Simvastatin and Aspartame as conformer by using slurry conversion technique This method is selected for the preparation of cocrystals when the drug and conformer should be stable Using this technique Noriyuki et al synthesized corystals of stanolone and mestanolone.<sup>89</sup> Prafulla et al synthesized caffeine/maleic acid co-crystal by ultrasound-assisted slurry co-crystallization techniques. Erizal et al prepared cocrystals of trimethoprim and sulfamethoxazole by slurry technique.

**3] Antisolvent Addition:** In this method conformer and active pharmaceutical ingredient (API) was precipitated or recrystallization using buffers (pH) and organic solvents as an antisolvent. The Adefovir dipivoxil cocrystal was synthesized by sea et al using Antisolvent precipitation technique.<sup>119</sup> Co-crystals of aceclofenac using chitosan, in which chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.<sup>92</sup>

**4] Hot Melt Extrusion:** Extrusion is useful technique for synthesis of cocrystals, it involves highly efficient mixing and improved surface contacts. In this technique the co-crystals was prepared without use of solvent. The method was primarily selected based on thermodynamic stability of compound. This method was studied with the use of four models for cocrystal formation. Solvent drop extrusion technique is usually carried out at lower temperature and is used to optimized and make the process more flexible. Hot melt extrusion method was used in synthesis of Carbamazepine-nicotinamide cocrystals by kevin et al. Continuous cocrystallization, API and conformer poured in the twin extruder. As a result of continuous addition of mixture the barrel temperature also increases.<sup>93</sup>

**5] Ultrasound Assisted Solution Cocrystallization:** For the preparation of nanocrystals Sonochemical method has been widely used.<sup>5</sup> In this technique, API and cocrystal former are dissolved together in a solvent and the solution is kept in a sonoreactor to form the solution turbid. Cold water is supplied during the sonication to maintain the constant temperature of sonicator and prevent fragmentation. The solution is kept overnight for drying. Pure cocrystals were obtained by this method and the purity of cocrystals can be assessed by using X-ray diffraction study.<sup>70</sup> Prafulla et al studied synthesis of corystals of Caffeine/Maleic Acid by Ultrasound-assisted Slurry Co-crystallization. Author constructed two phase diagram that is one in the absence of and one in the presence of ultrasound, prepared slurry by varying quantity of amounts of caffeine, maleic acid, and water and other one was subjected to 12 ultrasound pulses of 5 s each separated by a gap of 1 s, using a 20-kHz high-power ultrasound set at 50% amplitude at 25°C.<sup>90</sup>

**6] Spray Drying Technique:** In this technique cocrystals are prepared by spraying the solution or suspension of drug and conformer with hot air stream to evaporate the solvent. This is the most preferred technology because this is a fast, continuous, and one-step process. Thus, spray drying process will offer a unique environment for the preparation and scale-up of cocrystals.<sup>73,74</sup> Alhalaweh et al. synthesized theophylline cocrystals using urea, saccharin and nicotinamide as a conformer by using spray drying technique.<sup>95</sup>

Cocrystals of 2,4,6,8,10,12 hexanitrohexaazaisowurtzitane (CL- 20) and 2,4-dinitro-2,4- diazapentane (DNDAP) in a 2 : 1 molar ratio was synthesized Ning et al. using rapid and continuous spray drying method .<sup>96</sup>

### 7] Supercritical Fluid Atomization Process:

A recently emerging technology in pharmaceutical industry, utilize supercritical fluids. Supercritical fluids use offers additional advantages compared to the other co-crystal production methods. Co-crystallization by supercritical solvent is a method where an API and a co-crystal former are mixed together by magnetic stirring after being pressurized by supercritical CO<sub>2</sub> in a high-pressure vessel. The Supercritical Anti-Solvent (SAS) technique explores the anti- solvent effect of supercritical CO<sub>2</sub> to precipitate particles from solutions; the supercritical fluid enhanced atomization SEA technique explores essentially the CO<sub>2</sub> atomization enhancement in a spray drying process. Theophylline saccharin Co-crystal new form with a 1:2 stoichiometry was obtained by the supercritical fluid enhanced atomization process method that has not been previously reported by traditional screening methods. Pure co-crystals of itraconazole: malic acid was produced using either supercritical CO<sub>2</sub> or a traditional liquid solvent, such as n-heptane and were Confirmed by both XRD and DSC. Phase transformation during processing affect the mechanism of conversion of crystalline drugs to co-crystal .<sup>97</sup> Courtney et al studied synthesis of Cocrystals of itraconazole and succinic acid by gas antisolvent (GAS) cocrystallization using pressurized CO<sub>2</sub>. Author dissolved itraconazole and succinic acid in a liquid solvent (tetrahydrofuran) at ambient conditions and pressurized solution with CO<sub>2</sub>, which decreased the solvating power of tetrahydrofuran and caused crystallization of itraconazole–succinic acid cocrystals. Characterized cocrystals by Powder X-ray diffraction, Fourier transform infrared spectroscopy, differential scanning calorimetry, and scanning electron microscopy .<sup>98</sup>

### Advantages of supercritical fluid technology

SFT has overcome the limitations of conventional coating techniques like thermal and solvent based methods because most of the pharmaceuticals are thermolabile advantages such as,

1. Rapid one step processing.
2. Moderate operating temperature, has made supercritical fluids a fascinating technology specially for heat sensitive materials.
3. It has enabled the particle size to be reduced to such a great extent, that it can be used for aerosol drug delivery system.
4. It minimizes the use of hazardous and toxic organic solvent.
5. SFT has proved to be an effective alternative for the preparation of solid dispersions and microspheres. Such solid dispersions and microspheres exhibit good flow properties, small particle size, and the residual organic solvent level is quite low as compared to the conventional techniques.

### Limitations of supercritical fluid technology (SFT)

The elevated pressure required, high maintenance cost and requirement of the accessories/auxiliary equipments limits the use of SFT for most of the pharmaceuticals. Therefore, it seems that this technique can not completely substitute the conventional techniques as it is not applicable for processing of all pharmaceuticals.<sup>99</sup>

## Characterization of co-crystals:

Cocrystal characterisation is an important constituent part within cocrystal research. The basic physicochemical properties of cocrystal can usually be characterised by Infrared spectroscopy, Raman spectroscopy, Single crystal x-ray crystallography and powder x-ray diffraction, Melting point apparatus, Differential scanning calorimetry, Thermo gravimetric analysis, solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), and terahertz spectroscopy.

**1) Melting point:** Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase.<sup>100</sup> Melting point of pure API, co-formers and cocrystals are obtained by capillary method using liquid paraffin<sup>17</sup> or DSC is the preferred for obtaining melting point data and thermal data such as enthalpy of melting. DSC has recently been used as a tool for rapid cocrystal screening.<sup>101</sup>

**2) Differential Scanning Calorimetry (DSC):** In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.<sup>102</sup>

**3) Infrared spectroscopy:** Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material.<sup>11</sup> The study of molecular motions by use of vibrational spectroscopy is also sometimes employed in the characterization of polymorphs.<sup>102</sup>

**4) Terahertz time-domain-spectroscopy (THz-TDS):** is an alternative tool to PXRD for the characterization of cocrystals. Chiral and racemic molecular and supramolecular structures can be distinguished by terahertz spectroscopy.<sup>12</sup> Terahertz spectroscopy was used to distinguish the identical molecular structure cocrystals of theophylline with different coformers (such as malic acid and tartaric acid) which were present in chiral and racemic forms.<sup>103</sup>

**5) Thermo gravimetric analysis:** Physical and chemical properties of solids are determined by using thermal analysis as a function of increasing temperature (with constant heating rate) or as a function of time (with constant temperature and/or constant mass loss). TGA is a suitable method for determination of hydrates/solvates forms of cocrystals or presence of volatile components as well as decomposition or sublimation temperature. Thermal stability, compatibility and purity of cocrystals can be predicted by TGA analysis. The weight loss of sample mass during the TGA analysis is the indication of loss of volatile component or decomposition of cocrystal.<sup>38, 104</sup>

**6) Nuclear Magnetic Resonance:** Spectroscopy methods are also used to characterize cocrystals like vibrational spectroscopy and nuclear magnetic resonance. NMR is a powerful characterization tool that can provide detailed information on the structure of organic pharmaceutical cocrystals and complexes.<sup>105, 106</sup>

**7) Raman spectroscopy:** Is tool used for observation of crystallization process. It is used to differentiate between polymorphs, salts, cocrystals, solid solutions and hydrated salts.<sup>107</sup> Fourier- transform Raman is also used to for the identification and quantitative analysis of cocrystal.<sup>108,109,110</sup>

**8) Single X-ray diffraction (SXR):** Is a technique for determination of the solid-state structure of cocrystals at an atomic level. The problem is that a single pharmaceutical co crystal which is qualified for SXR testing cannot always be produced.<sup>85</sup> Therefore, powder Scanning electron microscope is the instrument used to determine the particle size and morphological analysis of cocrystals. A high energy electron beams scan the atoms that provide the information about the sample surface's topography.<sup>45,111, 72</sup>

Dissolution study is used to determine the amount of drug release with time in dissolution medium and predict the in vivo performance of the formulation. The drug samples can be collected in the suitable quantity at predetermined time interval and can be examined with the help of suitable means like HPLC or UV.<sup>112,113</sup>

Solubility study can be assessed by Higuchi and Connors method for solubility determination. The solubility of pure drug, physical mixture and cocrystals can be determined in water or suitable medium given in the referred pharmacopoeia. Drug sample and medium should be added in a conical flask, and should be shaken for 24 h at room temperature on rotary flask shaker. The entire samples should be protected from light by wrapping the flask by aluminium foil if the drug is sensitive to light. After 24 h samples are filtered through Whatman filter paper and aliquots are suitably diluted and assayed by HPLC or UV at suitable wavelength.<sup>114,115</sup>

Stability study provides the information about shelf life of drug products under different storage conditions. Drugs products should be kept in glass vials under variable environmental factors (such as humidity, temperature, light) for different intervals of time. After that, the samples are analysed for thermal study, drug release study, XRD study and FTIR study and compared with the results obtained before stability study.<sup>116</sup>

**Table 1: List of Synthetic Cocrystals along with their Coformers and their Method of preparation**

Drug	Coformer	Method of Preparation	References
Telmisartan	Saccharin  Glutaric acid	Solvent-assisted grinding ,Slurry approach and Solution crystallization  By refluxing a mixture of the two components	117
Acetazolamide	Hydroxybenzoic acid and Nicotinamide	Neat grinding (NG) and Reaction crystallization (RC)	118
Adefovir dipivoxil	Stearic acid	Antisolvent precipitation	119
Ibuprofen	Nicotinamide	Slow evaporation	120
Ethenzamide	Gallic acid, 2-nitrobenzoic acid, 3-nitrobenzoic acid, 2,4-dinitrobenzoic acid, 3-toluic acid	Solvent evaporation method	121
Resveratrol	4-aminobenzamide and Isoniazid	Liquid assisted grinding (LAG) and Rapid solvent removal (RSR) methods	26
Febuxostat	Urea, Acetamide, Nicotinamide, p-aminobenzoic acid, Saccharin	Liquid-assisted grinding	122
Mefenamic acid	Nicotinamide	Gas anti-solvent (GAS) process	123
Felodipine	Glutaric acid	Solvent ultrasonic method	124
Nevirapine	Para-Amino Benzoic Acid	Neat grinding	125
Aripiprazole	Orcinol ,Catechol, Resorcinol , and Phloroglucinol	Neat grinding (NG), Liquid-assisted grinding (LAG), and Solvent evaporation (SE)	126
Brexpiprazole	Succinic acid and Catechol	Nano Ball Milling using stainless steel balls	127
5-Fluorocytosine	Adipic, Succinic, Terephthalic, Benzoic, and Malic acids	Method not specified	128
5-Fluorouracil	Gentisic acid , 4-dihydroxybenzoic 4-aminopyridine	Mechanochemical method	129
Diacerein	Urea and Tartaric acid	Solvent drop grinding method	130
Fenofibrate	Nicotinamide.	Kneading, Solution crystallization, Antisolvent addition and Solvent drop grinding methods	131
Fenofibrate	p-amino Benzoic Acid, Benzoic Acid	Solvent Evaporation Technique	132



ketoconazole	Nicotinamide 4-Amino benzoic acid	Solvent evaporation method	133
Dimethylglyoxime	Acridine , Phenanthroline monohydrate and Acetamide	Mechanochemical synthesis	134
Nitrofurantoin	Urea , 4-Hydroxybenzoic aci, Nicotinamide , Ciitric acid , L- Proline and Vanillic acid vanillin	Liquid assisted grinding (LAG) methods	135
Dexlansoprazole	Isonicotinamide	Solvent crystallization	136
Darunavir	Succinic acid	Cooling crystallization method	137
Piroxicam	Sodium acetate	Dry grinding method	138
Gliclazide	Succinic acid and Malic acid	Liquid assisted grinding	139
Diketopiperazine	Urea	Cooling crystallization method	140
Tadalafil	Malonic acid	Slurry approach , Spray drying	141
Dipfluzine	Benzoic acid	Solvent-assisted co-grinding Solvent ultrasonic methods	142
Levofloxacin	Stearic acid and Saccharin sodium	Solvent evaporation method	143
Furosemide	Caffeine, Urea, <i>p</i> - Aminobenzoic acid, Acetamide, Nicotinamide, Isonicotinamide, Adenine, Cyt osine	Liquid-assisted grinding	144
Nateglinide	Benzamide	Kneading and Solvent evaporation.	145
Imidazopyridazine	Adipic acid, Glutaric acid, and Fumaric acid	Liquid-assisted grinding (LAG)	146
Phenazopyridine	Phthalimide	Sonochemical approach	147
Glibenclamide	Oxalic acid	Solvent Drop Grinding Method	148
Ezetimibe	L-Proline, Imidazole and a Solvate formamide	Wet milling/Grinding or Solution crystallization methods	149
Nateglinide	Benzamide	Dry Grinding , Kneading and Solvent evaporation	150
11-Azaartemisinin	Trans-cinnamic , Maleic and Fumaric acids	Liquid-assisted grinding	151
Etravirine	L-Tartaric acid	Slow evaporation and Physical mixturing	152
Sulfadimidine	4-Aminosalicylic acid	Grinding (Dry and Liquid-Assisted Milling) Spray Drying, Crystallization from Solution, Physical Mixture	74
Naproxen	Picolinamide , Naproxen , Isonicotinamide	Liquid-Assisted Mechanochemistry	153
Dexlansoprazole	Isonicotinamide	Solvent crystall ization	154
Carbamazepine	2,3-dihydroxy benzoic acid, 1- Naphthoic acid Anthracene-9- carboxylic acid	Liquid assisted grinding	155
Theophylline	Urea , Saccharin and Nicotinamide	Spray drying.	95
Ethenzamide	Glutaric, Malonic, and Maleic acids	Neat grinding and Slow evaporation from solution	156
Triflusal	Benzamide, Isonicotinamide, Picolinamide, propionamide, Urea, and Valpromide,	Solvent-evaporative crystallization experiments at ambient conditions, Grinding experiments	157
Lamotrigine	Phthalimide, Pyromellitic caffeine, Isophthalaldehyde	Solid-state grinding Solvent-drop grinding	158

Fluconazole	Salicylic acid	Solvent evaporation method	159
Ciprofloxacin	Nicotinamide	Solvent assisted co grinding method	160
Ketoprofen	Malonic acid	Solvent evaporation method	161
Praziquantel	Citric acid , Malic acid , Salicylic acid and Tartaric acid	Liquid assisted grinding	162
Tenoxicam	Glycolic acid, 4-Hydroxybenzoic acid Ketoglutaric acid Succinic acid , Maleic acid Malonic acid , Oxalic acid	Solvent-drop grinding	163
Vinpocetine	Boric acid	Slow evaporation technique	164
Famotidine	Tartaric acid Maleic acid	Solution method	165
Indomethacin	Saccharin	Cooling batch crystallisation without seeding	166
Meloxicam	Aspirin	Solution, Slurry, and Solvent drop grinding methods	167
Griseofulvin	Acesulfame	Solution crystallization technique.	168
Aceclofenac	Sodium Saccharin	Solvent-drop grinding method	169
Felodipne	Xylitol	Wet co-grinding	170
Acyclovir	Tartaric acid, Succinic acid, Malonic acid, Glutaric acid, Adipic acid, Citric acid, 4- Amino benzamide, 4-Hydroxy benzamide, 4-Amino benzoic acid, Malic acid, Oxalic acid, Fumaric acid	Solvent evaporation, Wet grinding, an Anti-solvent addition	171
Hydrochlorothiazide	Phenazine, Picolinamide, 4- dimethylaminopyridine	Solution crystallization method	172
Fexofenadine	Tartaric acid	Solvent evaporation	27
oxetine Hydrochloride (Prozac)	Benzoic acid, Fumaric acid Succinic acid.	Solvent Evaporation method	173
Tadalafilin	Salicylic Acid	Solvent evaporation method Neat grinding method Co grinding method	174
Clarithromycin	Urea	Solvent evaporation	175
Paracetamol	Caffeine	Dry grinding, Liquid assisted grinding (LAG) Solvent evaporation (SE) Anti-solvent addition	176
Efavirenz	Lactic acid and Adipic acid	Solvent evaporation	177
Danazol	Vanillin	Solution crystallization	178
Simvastatin	Aspartame	Slurry approach	179
Prulifloxacin	Salicylic acid	Solution crystallization method	180
Lornoxicam	Saccharin, Salicylic acid, Tartaric acid and Pyrogallol	Liquid assisted grinding Reaction co- crystallization Cooling crystallization	181
Simvastatin	Aspartame	Slurry approach	182
Mesalamine	Glutamine	Liquid assisted grinding	183

Dipfluzine	Benzoic acid	Solvent-assisted grinding Solvent ultrasonic method	184
Simvastatin	Malic acid	Liquid assisted grinding	185
Mefloquine hydrochloride	Benzoic acid, Citric acid, Oxalic acid, Salicylic acid, Pure Mefloquine tablets, Saccharin, Succinic acid	Solution cocrystallization method	186
Eprosartan mesylate	Succinic p-Aminobenzoic Salicylic acid	Liquid-assisted grinding	187
Apixaban	Oxalic acid	Grinding followed by anti-solvent addition	188
Telaprevir	4-aminosalicylic acid	Ball milling and Solvent evaporation	189
AMG 517	Sorbic acid	Melt crystallization, Grinding, and Recrystallization from solvents	190
Tranilast	Urea and Nicotinamide	Solvent ultrasonic methods	191
Griseofulvin	Acesulfame	Solution crystallization Technique	192
Norfloxacin	Isonicotinamide	Slow evaporation technique	193
Pyrazinamide	Malonic acid, Succinic acid, Glutaric acid	Slow evaporation technique	194
Piracetam	L-Tartric acid (1:1) Citric acid Mandelic acid	Solution and Solvent drop grinding method, Solvent drop Grinding and Solvothermal method	195
Sulfonamide	Pyridine-N-oxide	Traditional solution crystallization method Liquid-assisted grinding	196
Nicotinamide	Citric acid	Liquid-assisted grinding	197

**Table 2: List of Herbal Cocrystals along with their Coformers and their Method of preparation**

Drug	Coformer	Method of Preparation	References
Baicalein	Nicotinamide	Slow evaporation, Rotary evaporation Cogrinding	198
Betulinic acid	Ascorbic acid	Solubilization of drug and coformer by using isopropyl alcohol followed by slow evaporation technique	199
Emodin	Nicotinamide	Slow or Rapid solvent evaporation method	200
Naringenin	Isonicotinamide , Picolinic acid Betaine	Slurry method , Liquid diffusion method	201
Hesperetin	Picolinic acid, Nicotinamide and Caffeine	Solvent drop grinding technique	202
Chrysin	Cytosine and Thiamine hydrochloride	Mechanochemical technique using solvent drop grinding method	203
Luteolin	Isoniazid and Caffeine	Liquid assisted grinding method	204
Myricetin	Piracetam	Slow evaporation, Solvent-drop grinding	205
Curcumin	N-acetylcysteine	Cocrystallization with Supercritical Solvent technique	206
Scoparone	3,5- difluorobenzoic acid Urea, Pyrimethamine Succinimide	Solvent crystallization method	207
Caffeine	Hydroxybenzoic Acids	Solution-Mediated Phase Transformation	208
Quercetin	Caffeine caffeine:methanol Isonicotinamide Theobromine dihydrate	Slurry method	209
1.Caffeine ( form i) 2.Caffeine ( form ii ) 3.Carbamazepine	Pterostilbene	1.Grinding method and Solvent based methods 2.Vapour diffusion experiment 3.Grinding method and Solventbased methods.	210
Genistein	Isonicotinamide	Slow evaporation technique	211

## Conclusion:

Over last decades researchers are interested in improving physicochemical properties like solubility, bioavailability, dissolution. To improve these properties various approaches like Salts, hydrates and solvates, cocrystals came into existence. It was concluded that Pharmaceutical co-crystals represent a advantageous class of crystal form in the context of pharmaceuticals. It is very important alternative way to improve the bioavailability of poorly water-soluble drugs, especially for these neutral compounds or those having weakly ionizable groups and has possibility to achieve high dissolution rate as compared to its amorphous form. Cofomer selection is one of the most important and challenging step in cocrystal development. The basic requirement for a cofomer is to be pharmaceutically acceptable among the formulations and also classified as generally regarded as safe (GRAS). In above literature various theoretical and experimental approaches are mentioned to overcome the challenging steps of cocrystal screening. Despite of various advantages there are some limitations but by applying practical knowledge we can resolve the issues related to co-crystal. Studies regarding polymorphism, Phase transition and counter ion displacement with excipients should be carried out to accelerate the commercialization of the proposed system. Future research will be focused on the scale-up issues and screening methodology of co-crystal to elevate the profile of cocrystals in intellectual and pharmaceutical background.

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