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### **Pharmaceutical Co-Crystals: An Emerging Approach for Enhancement of Solubility and Bioavailability of a Drug**

**Shraddha Patil\*, Komal Mhatre, Abhay Shirode, Vilasrao Kadam**

*Department of Quality Assurance, Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai-400 614, Maharashtra, India*

#### ABSTRACT

Co-crystallization is an emerging approach for enhancing physicochemical properties like solubility, stability, bioavailability of poorly soluble drugs of BCS class II in pharmaceutical development without changing the chemical composition and considered better alternatives to optimize drug properties. Co-crystal is a crystalline entity consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former formed by intermolecular interactions like Hydrogen bonding,  $\pi$ - $\pi$  stacking and Van der Waals forces. In this article, an overview of pharmaceutical cocrystals will be presented along with the intermolecular interactions (Chemistry of Co-crystals), methods of their preparations, characterization of co-crystals altered physicochemical properties. Furthermore, this article also gives a brief explanation about newer trends in co-crystals with application of co-crystals in medicines and industries.

\*Corresponding Author Email: [shaktipalpatil@yahoo.com](mailto:shaktipalpatil@yahoo.com)

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## INTRODUCTION

The pharmaceutical industry encompasses wide variety of products out of which most are manufactured as solid dosage forms. Successful pharmaceutical development of a drug molecule depends not only on its potency and selectivity but also on its stability<sup>1</sup>. Thus, the properties active pharmaceutical ingredients (APIs) depends on the identity of its constituents as well as on their arrangements. Many potential drugs failed due their unfavourable properties such as poor water solubility, unfavourable bioavailability, physical and chemical instability, inappropriate dissolution<sup>2</sup>. It is easy to solve solubility problem of amorphous form, but difficult for crystalline drug<sup>2</sup>. The precise control of molecular orientation and packing arrangement in the crystal of drug molecules can improve their solubility with no alteration in stability and biological activity<sup>1,4</sup>. The solid APIs exist in different forms such as crystalline solids, amorphous forms, polymorphs, solvates, hydrates, salts<sup>5,6,7</sup>.

Many a times an API cannot be formulated in its pure form due to various issues of instability, solubility, compatibility, dissolution, etc. Thus, they are converted to solid forms such as polymorphs, salts, solvates, hydrates, amorphous and co-crystals. Improving the solubility of BCS class II drugs is currently one of the main challenges for the pharmaceutical industry for drug development. The traditional approaches for enhancing poor aqueous solubility (e.g., salt formation, micronization, solid dispersion formulations) often fail to produce a viable solid form, as the increase in dissolution rate achieved is frequently insufficient to provide adequate enhancement of bioavailability. Over the last decade, there has been growing interests in the design of pharmaceutical co-crystals, which emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility<sup>6</sup>.

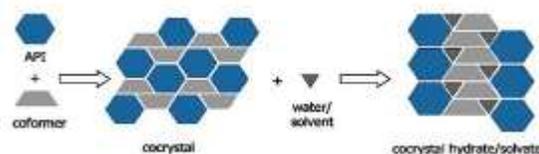
### **What are co-crystals?**

The crystalline materials possess different physical properties from their molecular arrangements within their solid forms. When these arrangements or the interactions within the solids are altered, it results in the formation of new crystals having altered physical or chemical properties<sup>2</sup>. These are commonly called as mixed crystals or crystal that contains two or more molecules. Co-crystals are made up of various reactants which are solids at room temperature. These are formed by non-covalent interactions between solid molecules such as hydrogen bonding, Van der Waal forces and  $\pi$ - $\pi$  interactions<sup>1,5,9</sup>. Solvates or hydrates contains solid and liquid components into them where as cocrystals have only solid components presents into them at room temperature. Hence, a co-crystal can be defined as “a multicomponent crystal that is formed between two compounds that are solids

under ambient conditions”<sup>2</sup>. The co-crystal approach has valuable advantages for pharmaceutical companies in terms of opportunities for intellectual property protection and the possibility of extending the life cycles of established APIs<sup>2</sup>.

### How are co-crystals different from solvates and hydrates?

Co-crystals are often confused with pseudopolymorphs like solvates and hydrates. Co-crystals differ from solvates and hydrates in physical state of components present into them<sup>1,2,5</sup>. Solvates and hydrates are crystalline forms of solid drugs belongs to multi-component systems. The multi-components systems are either comprised two or more solids or one or more solids and liquid<sup>5</sup>. Solvate is a crystal form with either stoichiometric or non-stoichiometric amount of solvent and hydrate is a solvate with water as the solvent. A co-crystal is also a multicomponent system, but that is formed between two compounds and both are in solid state under ambient conditions<sup>2,5,10</sup>.



**Figure 1: Solvate Hydrate and Co-crystal**

### Co-crystals versus salts

Sometimes co-crystals and salts may be confused. The understanding of fundamental difference between salts and co-crystals is very important for both preformulation studies and chemical/pharmaceutical development aspects<sup>6</sup>. Salts and co-crystals can be considered as opposite ends of multi-component structures. Salts formation is a three-component system having an acid, base and one or more solvents involving acid-base reaction between the API and an acidic or basic substance. Co-crystals are used as an alternative to salts when these cannot be formed because of the absence of ionisable sites in the API. Co-crystals are formed using a drug, a co-crystallizing agent and an appropriate solvent<sup>6</sup>.

### Need of Co-crystals

Co-crystals can improve the physical and/or chemical properties of an API like solubility, melting point, bioavailability, stability, dissolution rate without making or breaking the covalent bonds. Salts formation is also one of the techniques to improve the solubility of an API. But salts formation requires the acidic, basic or ionisable site whereas cocrystals can be prepared regardless of presence of acidic, basic or ionisable group in an API<sup>10,14</sup>.

### CHEMISTRY OF CO-CRYSTALS

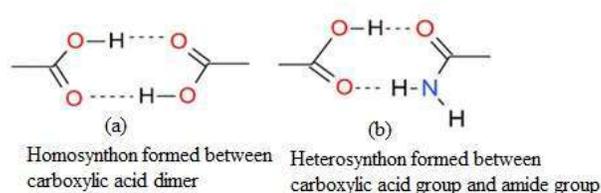
Co-crystals are formed to improve solid state properties of an API without affecting the intrinsic structure by approach of crystal engineering. Crystal engineering involves modification of the crystal packing of a solid material by changing the intermolecular interactions that regulate the breaking and formation of non-covalent bonds<sup>1,5,10,15</sup>.

### Supramolecular synthon:

The term supramolecular synthon is used in the field of research of cocrystals was given by Corey in the context of organic chemistry and defined as “structural units within super molecules which can be formed and/or assembled by known or conceivable intermolecular interactions”. The hydrogen bond has been the most important interaction in cocrystal because of its strength and directionality<sup>9</sup>.

### Supramolecular synthons are further divided into

- (a) Supramolecular Homosynthon: Made up of identical self-complementary functionalities
- (b) Supramolecular Heterosynthon: Made up of different but complementary functionalities



**Figure 2. Type of supramolecular synthons**

### Halogen bonding:

However, halogen bonding (XB) is a non-covalent interaction that is in some ways analogous to hydrogen bonding (HB), and it may be therefore be used as a practical tool for co-crystal synthesis. In HB, a hydrogen atom is shared between an atom, group, or molecule that “donates” and another that “accepts” it. In XB, it is a halogen atom (X) that is shared between a donor atom (D) and an acceptor (A)<sup>16</sup>.

### $\pi$ - $\pi$ interactions:

With respect to the interactions involved in the co-crystals, they can be divided into two classes: the first class exhibit the substructures generated through hydrogen bonding acting individually; the second class is dominated by the combination of the substructures along with the rest of these weak forces to build a supramolecular framework<sup>17</sup>.

### CO-CRYSTAL FORMER (COFORMER) SELECTION:

The selection of the coformer for an API is the most important step in co-crystallization. Coformer interact with an API through non-covalent interactions including hydrogen bonding,  $\pi$ - $\pi$  stacking and Van der waals forces. Coformers are the pharmaceutically acceptable (GRAS) compounds which may be excipients or another drug that does not affect pharmacological activity of API but can improve its physicochemical and pharmacokinetic properties. It can have similar solubility with an API and should contain certain functional groups like carboxylic acid, amides, amines and alcohols<sup>24</sup>.

**Table 1: List of Co-former**

<i>trans</i> -cinnamic acid	2,5-dihydroxybenzoic acid	2-hydroxybenzoic acid	glutaric acid	sorbic acid
glycolic acid	<i>trans</i> -2-hexanoic acid	L- (+)-lactic acid	benzoic acid	succinic acid
ketoglutaric acid	L- (+)-tartaric acid	4,4'-bipyridine	maleic acid	glutaric acid
2,4-dihydroxy benzoic acid	1-hydroxy-2-naphthoic acid	4-hydroxybenzoic acid	salicylic acid	malonic acid
DL-tartaric acid	<i>trans</i> -1,2-bis(4-pyridyl) ethylene	terephthalaldehyde	L-tartaric acid	glycolic acid
fumaric acid	5-nitroisophthalic acid	benzoquinone	saccharin	nicotinamide

#### METHOD FOR PREPARATION OF CO-CRYSTALS

There are many reported methods for co-crystal preparation as follows:

**Solution Evaporation method:** In this technique, the API and coformer are dissolved in same solvent separately with suitable stoichiometric ratio. Both the solutions are mixed together and completely evaporated. Solvent residue is removed by vacuum oven at 30°C for 48 h. The major disadvantages of this method are that it requires large amount of solvent and its limited scalability<sup>23</sup>.

#### **Solution Cooling crystallization:**

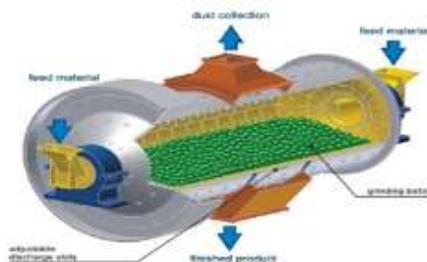
In this method, an equimolar proportion of an API and suitable coformer are dissolved in organic solvent by heating at 65°C and refluxed for 1 h with continuous stirring. Then the solution is cooled to room temperature and the co-crystals are formed in the reaction vessel during the cooling process. Co-crystals obtained are collected by filtration, washed twice with solvent and dried at 30°C for 48h in vacuum oven<sup>24</sup>.

#### **Solid state grinding:**

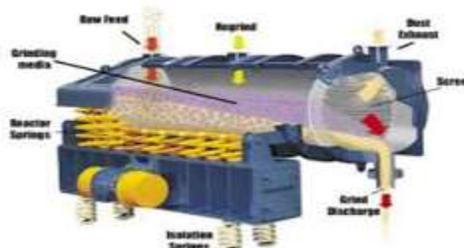
In this method, materials are mixed, pressed and crushed. This method is also called as dry grinding, consisting of mixing the stoichiometric co-crystal components either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill<sup>6,15</sup>.



A) Mortar and pestle



B) Ball mill



C) Vibratory mill

**Figure 3. Instruments for grinding method****Liquid Assisted Grinding Method:**

This is the modified technique of grinding technique also known as solvent-drop grinding or wet granulation involving addition of a small amount of suitable solvent to the ground mixture of a drug and the crystallizing agent to accelerate cocrystallization. This method has proven to be an effective method for achieving good polymorphic control of co-crystals. Limitations of liquid-assisting grinding include the fact that it is a small-scale technique, requires high energy consumption<sup>15</sup>.

**Slurry conversion:**

In this method, small amount of solvent is added to the compound and co-crystallizing agent and the resulting suspension is stirred at room temperature for some days. After some days, the solvent is decanted, and the solid material is dried under the flow of nitrogen. The major disadvantage of this method is that it requires large amount of solvent<sup>6</sup>.

**Antisolvent addition:**

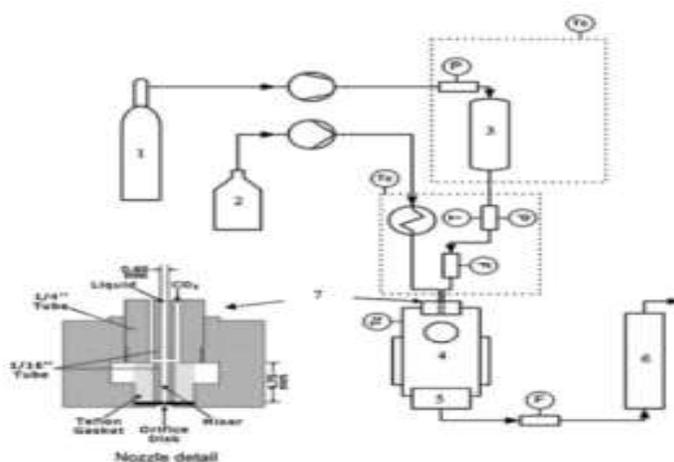
Here, co-crystallizing agent is dissolved in an appropriate solvent followed by addition of drug to this solution. The dispersion of co-crystallizing agent and the drug so formed is added to another solvent (antisolvent) to precipitate co-crystallizing agent on a drug. Disadvantages of this method are its lower performance compared to grinding that uses a solvent, as well as the large volume of solvent used<sup>6</sup>.

**Melting method:**

In this, co-crystals are formed by simply melting two co-crystal formers together and cooling. If a co-crystal is not formed from a melt, a seed from a melt may be used in a crystallization solution in order to afford a co-crystal<sup>3</sup>.

### Supercritical Fluid Technology:

Supercritical fluids offer additional advantages over classical methods. In this technique, an API and the co-crystallizing agent are mixed together by using magnetic stirrer after pressurizing with supercritical CO<sub>2</sub> in a high-pressure vessel. The generation of pure and dried new co-crystals can be achieved due to unique properties of supercritical fluids. Anti-solvent property of a supercritical fluid enables its use in precipitation of the co-crystals from the solution of an API and the cofomer<sup>6,20</sup>.



**Figure 4. Schematic diagram of the Supercritical fluid apparatus.**

(1) CO<sub>2</sub> cylinder; (2) liquid solution flask; (3) temperature-controlled CO<sub>2</sub> storage cylinder; (4) precipitator; (5) filter; (6) solvent trap; (7) detail of the nozzle cap. P, T, F: instruments for, respectively, pressure, temperature, and flow measurements. Tc is for temperature control and measurement

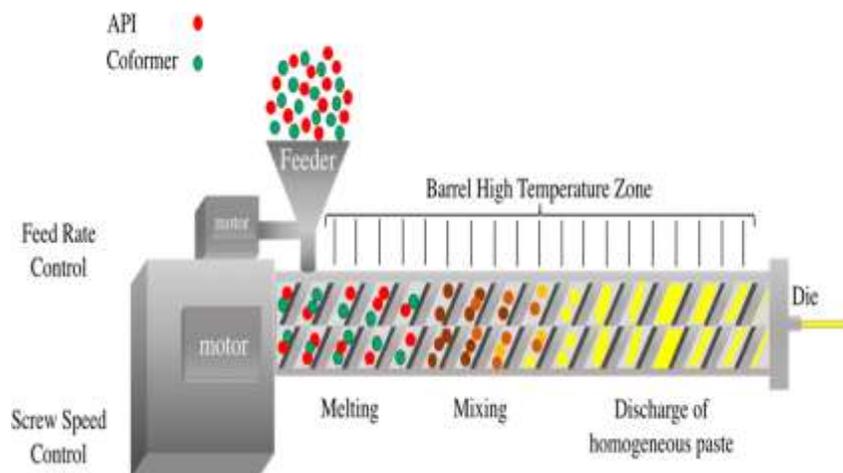
### Ultrasound assisted solution crystallization:

In this technique, an API and the co-crystallizing agent are mixed together in an appropriate solvent at a temperature. The resultant solution is then subjected to ultrasound pulse in a sonoreactor. This results in the formation of a turbid solution. Cold water is subjected during sonication to prevent fragmentation and after this turbid solution is left for overnight for drying of solvent<sup>15</sup>.

### Hot melt extrusion:

This specialist technique combines simultaneous melting and mixing of the target molecule and cofomer via the use of a heated screw extruder. Melting occurs, facilitating intimate mixing of the

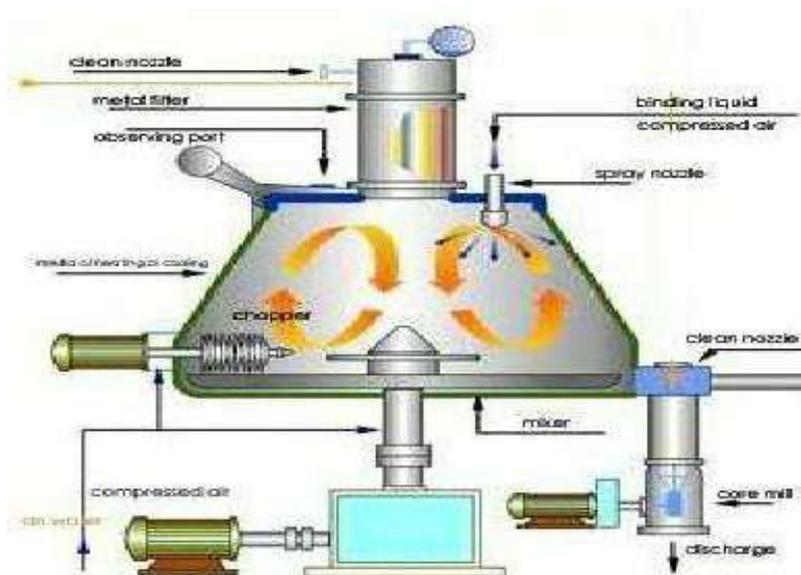
starting materials. The co-crystal nucleates directly in the melt, and pure co-crystal extrudate is isolated from the extruder continuously. The advantages of the method are elimination of the use of organic solvents, fast operating times, reduced waste<sup>25</sup>.



**Figure 5. Hot melt extrusion**

### High shear granulation:

This technique involves the agglomeration of powder particles via a liquid medium in the presence of a binder. Technically, the procedure is carried out in a high shear granulator, which imparts shear on the powder mixture through impellers and choppers<sup>25</sup>.



**Figure 6. High shear granulator**

### Freeze drying:

Freeze drying is multistep operation by means of drying accomplished by freezing of wet substance followed by ice sublimation directly to vapour by applying low partial pressure of water

vapour. Freeze – drying facilitates the formation of co-crystals through an amorphous phase developed while the solvent sublimates<sup>26</sup>.

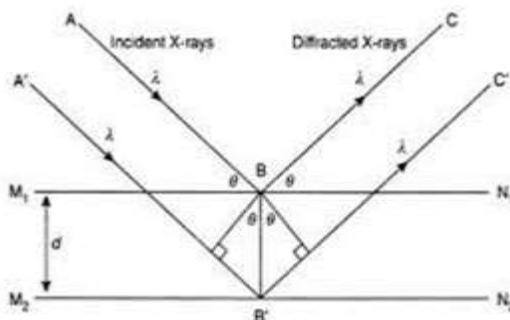


**Figure 7. Freeze dryer**

## CHARACTERIZATION OF CO-CRYSTALS

### **Powder X-ray diffraction:**

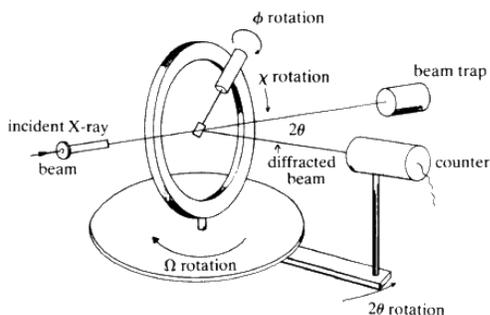
The X-ray powder diffractometer works on the principle of keeping the wavelength constant and varying the angle of incidence. This is due the fact that not all the molecules in the sample will be in the same orientation. By keeping the wavelength constant and varying the angle at which the beam “hits” the sample there is a greater chance that most, of the reflections which obey the Bragg equation will be detected<sup>4</sup>.



**Figure 8. X-ray diffraction**

### **Single crystal X-ray diffraction:**

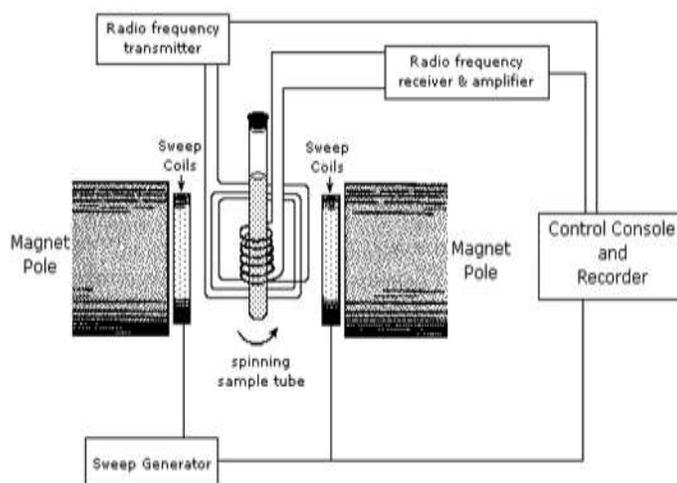
Single crystal X-ray diffraction study can provide unambiguous atomic positions and complete structural information. Single crystal X-ray diffraction may prove difficult on some co-crystals, especially those formed through grinding, as this method often provides powders. However, these forms may be formed often through other methodologies in order to afford single crystals<sup>8,20</sup>.



**Figure 9. Single crystal X-ray diffraction**

### **Nuclear Magnetic Resonance (NMR):**

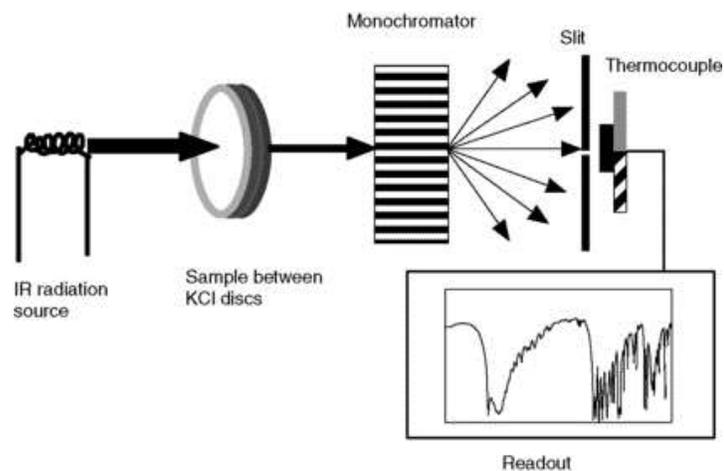
NMR studies give the chemical environment of the nuclei which is different in polymorphs because of magnetic non-equivalence. NMR peaks for the magnetically non-equivalent nuclei will differ in different polymorphs and can yield very useful information. NMR not only allows for non-invasive, element specific observation of different nuclei, but also facilitates the identification of chemically distinct sites based on NMR chemical shifts<sup>8,18</sup>.



**Figure 10. NMR instrumentation**

### **Infrared Spectroscopy (IR):**

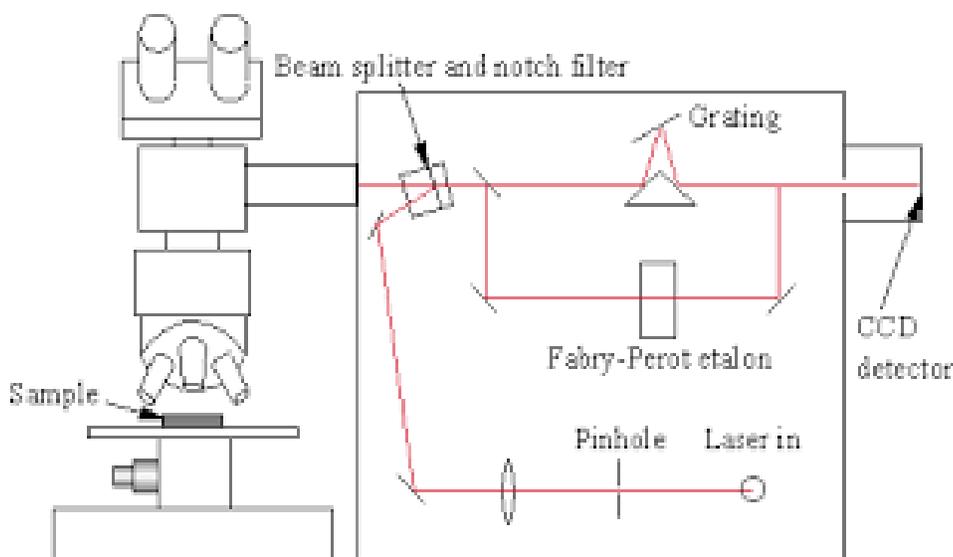
IR is a very common spectroscopic technique in determining the chemical conformation of compounds. It can be a very powerful tool in distinguishing co-crystals from salts when a carboxylic acid is involved in hydrogen bond formation<sup>18</sup>.



**Figure 11. IR instrumentation**

### Raman Spectroscopy:

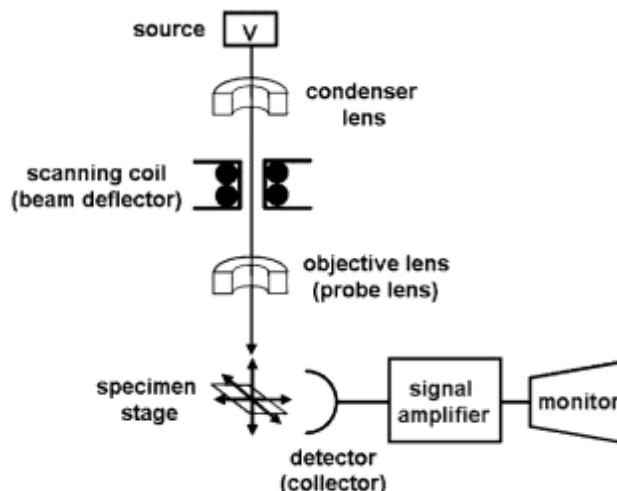
Raman spectroscopy is a spectroscopic technique that is used as a powerful tool for distinguishing isostructural phase. Technique is used for the study of vibrational, rotational and other low frequency modes in a system<sup>19</sup>.



**Figure 12. Raman instrumentation**

### Scanning Electron Microscope (SEM):

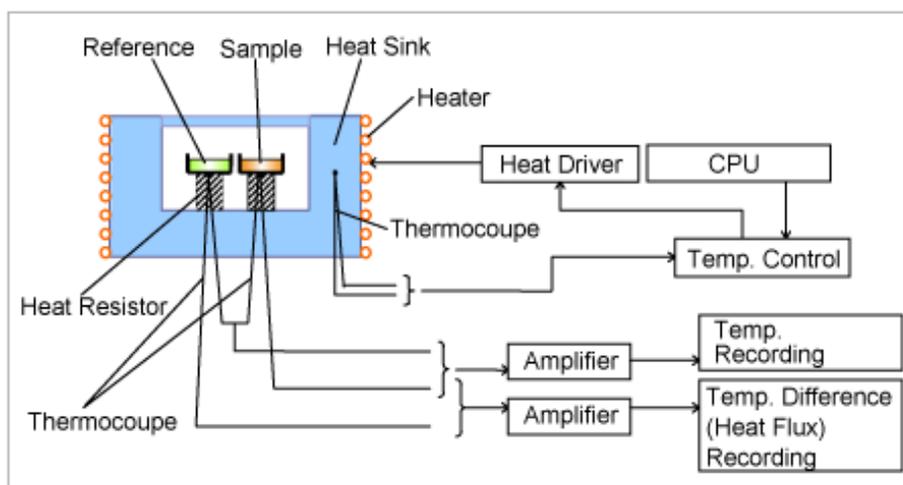
SEM is conducted to characterize the surface morphology of the particles with excellent ease and efficiency. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is applied to determine the co-crystal micrograph and particle size<sup>8,18</sup>.



**Figure 13. Scanning Electron Microscope**

### Differential Scanning Calorimetry (DSC):

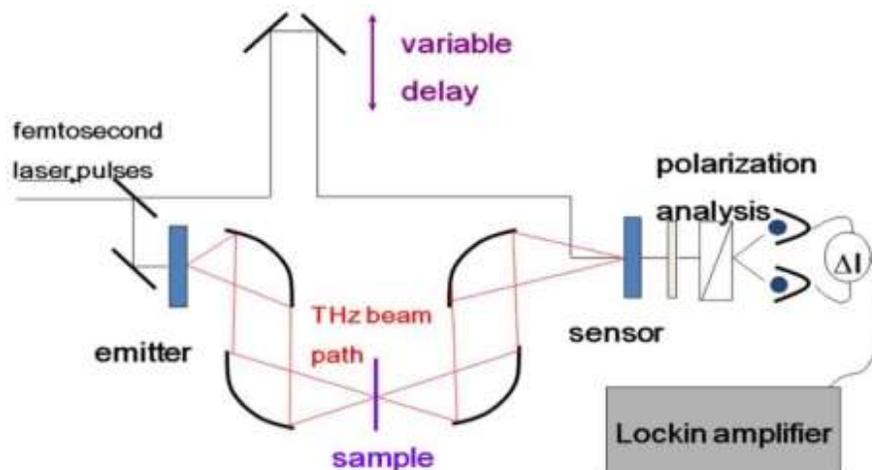
In this characterization technique, the two specimens in which one is the sample and the other is the reference are subjected to identical temperature and an environment which is heated or cooled at a controlled rate. DSC is most widely used technique for obtaining comprehensive melting point data and additional thermal data, such as the enthalpy of melting, heat of fusion and level of crystallinity<sup>8,18</sup>.



**Figure 14. Differential Scanning Calorimetry (DSC)**

### Terahertz time-domain-spectroscopy (THz-TDS):

Terahertz spectroscopy is an alternative to powder X-ray diffraction in the characterization of molecular crystals and used to distinguish between chiral and racemic hydrogen bonded co-crystals that are similar in molecular and supramolecular structure. THz-TDS is comparable in sensitivity to diffraction methods and more sensitive than Raman to changes in co-crystal architectures<sup>18,20</sup>.



**Figure 15. Terahertz time-domain-spectroscopy**

### PHYSICOCHEMICAL PROPERTIES ALTERED BY CO-CRYSTALS

The need of co-crystallization is to improve the physicochemical property of the drug. The altered physicochemical properties by this technique are as follows;

#### **Melting point:**

It is a fundamental physical property in which melting temperature shows the equilibrium between solid and liquid phase. The melting point of the co-crystal can be in between that of an API and coformer or can be lower than that of API and coformer. Hence, when lower melting point of an API is desired without causing covalent medication in it, then co-crystallization will be of suitable choice. DSC can be used to measure the melting point<sup>9,15,19</sup>.

#### **Relative Humidity Stress:**

It is found that co-crystals show minimum water uptake at higher relative humidity. Hence, degradation due to water is minimum and which results in stable forms of APIs<sup>9,20</sup>.

#### **Chemical Stability:**

Co-crystals shows chemical stability at slightly elevated temperatures<sup>9,10</sup>.

#### **Solution Stability:**

It is ability of the co-crystal to remain in the solution not readily crystallize. The vehicles used are water, buffer solutions, simulated gastric fluid, simulated intestinal fluid, formulation vehicles, etc. When solution stability is estimated using water as a vehicle then it is found that co-crystals containing coformers that have relatively high aqueous solubility converted into dihydrate whereas coformers that have relatively low aqueous solubility remained as co-crystals<sup>9,10</sup>.

#### **Solubility:**

It is found that co-crystals shows higher solubilities. Hence co-crystallization is a more favourable approach for a poorly soluble drugs having no ionisable group. Solubility is determined by two

independent factors; the strength of the crystal lattice and the solvation of co-crystal components. To increase solubility, one can lower the lattice energy controls solubility in solvents and/or increase the solvent affinity which plays a decisive role on the aqueous solubility of co-crystals. Co-crystals can influence both factors to different extents<sup>11</sup>.

#### **Intrinsic Dissolution:**

It measures dissolution rate without the effect of particle size. The aqueous solubility of the cofomers correlates with the aqueous solubility of co-crystal with benzoic acid being least soluble fumaric acid being intermediate soluble and succinic acid being the most soluble<sup>9,15,19</sup>.

#### **Bioavailability:**

The co-crystals are found to be more bioavailable than their parent form<sup>9</sup>.

#### **NEWER TRENDS IN CO-CRYSTALS**

The diverse crystallization techniques using different conditions give rise to the newer co-crystal forms. The newer trends include:

#### **Polymorphism in co-crystals:**

One proposed advantage concerning cocrystallization is lower tendency to polymorphism than respective cofomers. Just like salts, which can be polymorphic, cocrystal can also exhibit polymorphism. In general, polymorphs can be classified into different types. The advantage of these classifications is that the nature of polymorphism and the differences between alternative crystal structures are easily identified<sup>17</sup>.

#### **Synthon polymorphs:**

Polymorphs that differ in their primary hydrogen bond motifs or synthons can be classified as synthon polymorphs. Example of synthon polymorphs in single component crystals: Polymorphs of tetrolic acid in which the  $\alpha$ -form contains the acid-acid dimer synthon and the  $\beta$ -form contains a catemer synthon. Synthon polymorphism arising from different hydrogen bond synthons has also been reported in co-crystals<sup>13</sup>.

#### **Conformational polymorphs:**

Conformational polymorphism refers to the occurrence of different molecular conformations in different polymorphs. In general, flexible molecules with several degrees of torsional freedom and low-energy conformers are more prone to exhibit conformational polymorphism<sup>13</sup>.

#### **Packing polymorphs:**

Polymorphs can be classified as packing polymorphs when they differ in their overall three-dimensional crystal packing. A 2:1 cocrystal of benzoic acid with 2-aminopyrimidine was found to exist in two polymorphic forms<sup>13</sup>.

**Tautomeric polymorphs:**

When different tautomers of a compound crystallize in different crystal forms, they are termed as tautomeric polymorphs. In general, tautomerism occurs when the constitutional isomers of different hydrogen-atom connectivities are in dynamic equilibrium with one another<sup>13</sup>.

**Polymorphic cocrystal hydrates and solvates:**

A co-crystal hydrate involves 18-crown-6 and 3,5-dichloropicric acid (DCPA) existing two polymorphic forms. For a polymorphic co-crystal solvate, a methanol solvates of a co-crystal of 1,3,5-benzenetricarboxylic acid (BTA) with 4,4-methylenebis-(2,6-dimethylaniline) (MBDA) in a 1:1:1 molar ratio exists in two polymorphic forms<sup>13</sup>.

**Higher-order co-crystals:**

The screening of co-crystals for an API is usually targeted for two component crystals, that is, the drug and one coformer. The formation of hydrates or solvates, sometimes serendipitously, of two component co-crystals suggest the possibility preparing ternary, quaternary and possibly even higher-order co-crystals. Such structures can, in theory, significantly expand the solid-state landscape of drugs. However, research in this direction is still in the nascent stage and few examples have been reported, perhaps because of the relatively fewer attempts in preparing them. One strategy is to cogrind multiple compounds employing LAG. This approach allows the use of coformers without the challenge of dissolving multiple compounds in a solvent, which is a prerequisite for solution-bas crystallization<sup>17</sup>.

Hence, a much larger space is accessible for exploration than what solution crystallization can afford. Some design strategies have also been proposed, which can be used to guide the LAG experiments. One strategy is based on hydrogen bonding preference, where a ditopic base with two potential H-bond accepting sites to react with two acids of different strengths. A ternary co-crystal is formed when the stronger H-bond donor in the acid interacts with the stronger hydrogen bond acceptor site in the base and the weaker donor (acid) interacts with the weaker H-bond acceptor site. Another design strategy is to replace a weakly bonding molecule in a binary co-crystal with a molecular mimic. When a molecule in a binary co-crystal does not interact strongly with other molecules, that is, a space filler, another molecule that is similar in size and shape can replace it to form a ternary co-crystal without significantly disrupting the crystal structure<sup>17</sup>.

**Sweet Co-Crystals:**

Co-crystallization of an API is done by using a coformer which is one of effective artificial sweeteners fit for human use such as saccharin aspartame, acesulfame and sucralose, they are called sweet co-crystals. These sweeteners molecules are capable of forming co-crystals as they

have multiple hydrogen bond acceptors and donors. Saccharine is one of the most used sweeteners as a co-crystal former. Saccharine (pKa 2.2) is an acid being used in the pharmaceutical industry as a salt former and is generally regarded as safe material. Co-crystal formation with saccharine requires that the API has sufficiently low basicity, functional group complementarity and viable packing interactions (synthon compatibility)<sup>28</sup>.

Co-crystallization of API with sweeteners could solve the problem of un-pleasant taste, especially in paediatric formulations in addition to enhancement of other API properties. Detailed pharmaceutical, pharmacological and clinical studies are required to emerge this technique into the pharmaceutical industry<sup>28</sup>.

### **Nanocrystal:**

A nano crystal refers to any nanomaterial with at least one dimension  $\leq 100\text{nm}$  and it should be single crystalline. The drug nanocrystals are produced by bottom up techniques (with main focus on particle diminution by high pressure homogenization) for many new chemical entities of very low solubility. This also includes transfer of the liquid nanosuspensions to patient convenient oral dosage forms such as tablets and capsules. Nonlinear optical nanocrystals of aminonitropyridines with benzenesulfonic acids were reported, under microwave irradiation. These studies demonstrated the importance of organic nanostructures for supporting structure-preserving chemical transformations that were not possible in larger crystals<sup>27</sup>.

### **Synthesis of Nanocrystals**

Sonochemical synthesis: Sonochemistry describes preparation of co-crystals of nanometer scale dimensions. In this process the pharmaceutically active ingredients and co-former are dissolved separately in solvents and injected in an antisolvent at 0°C under ultrasonic radiation. After 15 s of sonication suspension is filtered<sup>27</sup>.

**Table 2: Reported studies of co-crystals**

<b>Drug</b>	<b>Coformer</b>	<b>Method of Preparation</b>	<b>Property which has enhance</b>
Olanzapine (Antipsychotic)	Nicotinamide	Solution method	Dissolution
Carbamazepine (Anti-epileptic)	Nicotinamide	Solution method	Solubility, dissolution, bioavailability
Fluoxetine (Anti-depressant)	Benzoic acid, succinic acid	Evaporation method	Dissolution profile
Caffeine (CNS stimulant)	Propionic acid	Solution method	Solubility
Theophylline (CNS stimulant)	Nicotinamide	Reaction crystallization method	Solubility
Aceclofenac (Analgesic, anti-inflammatory, anti-pyretic)	Chitosan	Anti-solvent addition method	Aqueous solubility, bioavailability
Ibuprofen (Analgesic, anti-inflammatory, anti-pyretic)	(RS)-2-(4-(2-methylpropyl) propionic acid	Solution method	Solubility
Ketoprofen (Analgesic, anti-inflammatory, anti-pyretic)	Cinnamic acid, Glutaric acid, maleic acid, malonic acid	Melting method	Aqueous solubility
Indomethacin	Saccharin	Solution cooling crystallization	Solubility, dissolution
Itraconazole (antifungal)	L- malic acid	Gas antisolvent cocrystallization method	dissolution
Piroxicam (Anti-inflammatory)	Resorcinol, methylparaben	Liquid assisted grinding (LAG) method	Dissolution
Adefovir dipivoxil (Antiviral)	Glutaric acid	Liquid assisted grinding (LAG) method	Dissolution
Hesperetin (Antioxidant)	Picolinic acid, nicotinamide, caffeine	Liquid assisted grinding (LAG) method	Bioavailability
Glipizide (Anti-diabetic)	Rosuvastatin calcium	Slurry Method, Solvent drop method, Solvent Evaporation Method	Solubility
Tadalafil	malonic acid	Slurry method, solvent evaporation method	Solubility, dissolution
Sildenafil citrate	Succinic acid	Reaction crystallization	Dissolution
Carbamazepine (Antiepileptic)	Itaconic acid	Evaporation method	Dissolution
Artesunate (Anti-malarial)	Nicotinamide	Evaporation method, Slurry Method	Bioavailability
Etravirine (Anti-viral)	Tartaric acid	Evaporation method	Solubility
Gliclazide	Tartaric acid, Succinic acid	Evaporation method	Solubility

Mefenamic acid (Anthranilic acid, anti-inflammatory, antipyretic, analgesic)	Nicotinamide	Melt crystallization method	Solubility
Aceclofenac (Analgesic, anti-inflammatory, anti-pyretic)	Nicotinamide	Neat Grinding method, Evaporation method	Solubility

## APPLICATIONS OF CO-CRYSTALS

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery as well as drug delivery by improving the solubility and bioavailability of poorly water-soluble drugs.

Application of co-crystals includes chiral resolution, enhancement of the physicochemical properties, drug development and diversity<sup>3</sup>.

## CONCLUSION

Co-crystallization offers one of the most promising approaches to improve physicochemical properties of APIs. A wide range of options exist to prepare cocrystals ranging from routine lab scale synthesis methods to potentially large-scale continuous production methods. This review offers standard descriptions and examples of established and emerging co-crystal preparation routes. As co-crystals continue to gain interest and prove their value, the range of demonstrated co-crystal application areas continues to expand. It is anticipated that co-crystals will become more and more routine in pharmaceutical development as their benefits continue to be demonstrated and routine routes of manufacturing are proven.

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