A Tool on Pharmaceutical Cocrystal to Enhance the Drug Properties Those Comes Under BCS Class II and IV
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DOI: 10.36347/SAJP.2019.v08i09.001 | Received: 21.09.2019 | Accepted: 28.09.2019 | Published: 30.09.2019

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Abstract

In pharmaceutical field various types of dosage forms are present and discovered continuously but some dosage form have some solubility, stability or any other issues as per BCS classification system so these problem are overcome by using the formation of some solid dosage form like pharmaceutical cocrystals. During formation of pharmaceutical cocrystal molecules structure are important like hydrogen bonding, Crystal Engineering, Van der Waal’s Interactions, Interaction involving π-system, Van der Waal’s Interactions, and Supramolecular synthon etc. In supramolecular synths certain types of bonding between the functional group like acid-acid, acid-pyridine, pyridine-pyridine etc. Formations of cocrystal are different techniques based on requirement of study. Basically use solvent evaporation, solvent assisted grinding, hot melt extrusion, slurry method, anti-solvent, cooling method etc. use to form pharmaceutical cocrystals. In pharmaceutical cocrystal contain API and Cocrystal coformer are present and these final cocrystal characterized by the different techniques like SCXRD, PXRD, DCS, FTIR and NMR. Cocrystal is basically important to improve the solubility, bioavailability, stability, and dissolution rate of pharmaceutical dosage form.

Keywords: Cocrystal, BCS classification, coformer, SCXRD, PXRD, FTIR, NMR.

INTRODUCTION
The study of solid state chemistry of pharmaceutical solid focuses on all disciplines right from drug discovery to successful marketing. A clear understanding of the molecular structure can lead to a better design and control of the drug performance. Moreover, interest in the subject of pharmaceutical solids stems in the part from FDA’s substance guideline that states “appropriate” analytical procedures to be used to detect polymorphic, cocrystals, hydrated or amorphous forms of the drug substance. Solid forms are usually more stable than liquid counterpart.

The main factors which affect the oral route absorption are aqueous solubility, physical/chemical stability, and permeability. The fundamental parameters, i.e. aqueous solubility and gastrointestinal permeability which define oral drug absorption are used on the basis of BCS classification scheme. These biopharmaceutical classes are defined as below figure.

Solubility and permeability parameters defined by FDA and according to it, ‘A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1-6.8 at 37 ± 1°C’ and ‘A drug substance is considered to be highly permeable when the systemic Bioavailability or the extent of absorption in the humans is determined to be 85 percent or more in to the administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract ) or in comparison to an intravenous reference dose.[1]’
Types of solids forms

Solid is one of the four fundamental states of matter (the others are liquid, gas, and plasma). Solids molecules are closely packed. These are characterized by structural rigidity and resistance to changes in the shape or volume. Unlike a liquid, or a solid object does not flow to take on the shape of its container, nor does it expand to fill the entire volume available to it like a gas does. All atoms in a solid are tightly bound to each other, either in a regular geometric lattice (crystalline solids, which include metals and ordinary ice) or irregularly (an amorphous solid such as common window glass). Solids cannot be compressed within the little pressure whereas gases can be compressed within little pressure because in gases molecules are loosely packed.

In materials science, polymorphism is the ability in a solid material to exist in more than one form or crystal structure. Polymorphism can potentially be found in the any crystalline material including polymers, minerals, and metals, and is compare to allotropy, which refers to chemical elements. Most pharmaceutical molecules are polymorphic. Polymorphism is an ability of a chemical compound to crystallize depending on the crystallization conditions in different crystal structures alias polymorphs. Molecules in the crystal structure of Polymorphs are bonded by weak interactions (H-bridges, Van-der Waals forces, π-π interactions).

Amorphous materials have an internal structure made up of inter connected structural blocks. These blocks can be similar to the basic structural units found in the corresponding crystalline phase of the same compound. Whether a material is liquid or solid depends upon the primarily connectivity between its elementary building blocks so that solids are characterized by a high degree of connectivity whereas structural blocks in fluids have lower connectivity.

In pharma industry, the amorphous drugs are shown to have higher bioavailability than their crystalline counter parts due to the high solubility of amorphous phase. Moreover, certain compounds can undergoes precipitation in their amorphous form in vivo, and they can decrease each other's bioavailability if administered together.
Based on $\Delta pK_a$ value also suggested that the compound will be salt or cocrystal. It is generally accepted that the reaction of an acid with a base will be expected to form a salt or a cocrystal, if the $\Delta pK_a (\Delta pK_a = pK_a^- (base) - pK_a (acid)[19]$ is greater than 2 or 3 then salt will be form and, as Nangia[20] noted, a smaller $\Delta pK_a$ (less than 0) will almost exclusively result in cocrystal formation. The majority of crystalline acid-base complexes have a $\Delta pK_a$ value of less than 1 or greater than 3 and with very few exceptions will fall into either the cocrystal or salt categories.

Crystal Engineering

The term ‘Crystal engineering’ was discovered by pepinsky in year 1955. According to pepinsky, “Crystalization of the organic ions with a metal-containing complex ion of suitable sizes, charges and solubility’s result in structures with cells and symmetries determined chiefly by the packing of complex ions. These cells and symmetries are to good extent controllable; hence crystals with advantageous properties can be engineered.”

Crystal engineering is an interdisciplinary area in chemistry, which bridges, chemistry and crystallography. In the present decade, research is mainly focused on controlling the directionality and strengths of the intermolecular interaction in the design of molecular crystals. A. I. Kitagorodskii gave the definition of the molecular crystal which state that, “Within a molecular crystal, it is possible to identify groups of atoms such that for every atom of a group, at least one inter atomic distance within this group is significantly shorter than the smallest inter atomic distance to an atom in another group[4].” He invoked a question, “molecule to crystal,” he stated that packing of molecular solids was largely governed by the considerations of size and shape, so-called principle of packing.

Today, X-ray crystallography is a matured science and has a far reaching impact on material characterization. The structural insights obtained from the crystal structure analysis led to unprecedented developments in the electronic devices, mineralogy, geosciences, material science, and pharmaceuticals. Detailed knowledge of the accurate structural information of APIs is a prerequisite for rational drug design and synthesis of new chemical entities for the development of new medicine. As research progressed with time, the focus shifted to multicomponent molecular cocrystals. The knowledge obtained from the analysis of the crystal structures is used for the selection of coformer in cocrystal design. In a crystal, molecules are associated with a specific pattern of non-covalent interactions such as hydrogen bonds, halogen bonds [5], and $\pi$-stacking. Over the past century, single crystal X-ray diffraction has proven to be an important tool for the unambiguous determination of crystal structures, and thus, assisted in ground breaking analysis of material properties. Concerning cocrystals, structural characterization (a) Establishes the reliability of cocrystal design strategy, (b) Reveals hydrogen bond preferences of the functional groups, and (c) Provides insights into structure property correlation. Crystal engineering is a concept of great application and scope. Presently, it focuses on more practical applications such as pharmaceutical cocrystals and high energy materials, etc. Figure-2. Crystal engineering involved the modification of crystal packing in a solid material by changing the intermolecular interactions [6].

![Fig-2: Typical hydrogen bonds utilized in crystal engineering](image)

Non covalent Interactions

Non covalent interactions are ubiquitous in chemistry and are the primary source of stability for many molecular complexes in biological, pharmacological, Chemical, physical, and material sciences, etc. while traditional chemistry focuses on the covalent bond, crystal engineering and supramolecular...
chemistry exploit the non-covalent interactions which hold molecules together in a crystal lattice. These forces include hydrogen bonding, metal coordination, hydrophobic forces, Van der Waal’s forces, π-π interactions and electrostatic effect.

Hydrogen Bond

Hydrogen bonds are electrostatic and play an essential role in stabilizing the molecular aggregates. Nernst first introduced the phenomenon of hydrogen bond formation in 1891[7]. Bernel and Huggins proposed the term “hydrogen bond” in the year of 1935-36[8]. In the year of 1939, Linus Pauling defined the hydrogen bond as “under certain conditions, an atom of hydrogen is attracted by rather strong forces to two atom instead of only one, so that it may be considered to acting as a bond between them.” The more elaborate and expanded definitions were given by many scientists as the increased interest of research in this field, which include Pimentel and McClellan [9], IUPAC stated that “the hydrogen bond (designated as D-H---A, where acceptor A and donor D are electronegative atoms) is an attractive interaction between a hydrogen atom from a fragment or molecule D-H in which D is more electronegative is that H, and an atom or a group of atoms A, in the same or different molecule where there is evidence of bond formation”. Depending on the nature of the donor and acceptor atoms which constitute the bond, their geometry, and environment, the energy of a hydrogen bond can vary between 1 and 40 kcal/mol. The hydrogen bond is not a simple interaction but a complex conglomerate of at least four component interaction types electrostatics (acid/base), polarization (hard/soft), van der Waals (dispersion/repulsion) and covalency (charge transfer). It is neither a strong van der Waals interaction nor a weak covalent bond. It is not even a strong directional dipole-dipole interaction. For geometrical parameters of hydrogen bond see figure-3.

This interaction characterized through X-ray diffraction, neutron diffraction, NMR, FT-IR and RAMAN spectroscopy. Three types of hydrogen bond exist very strong, strong and weak (table 01)[11]. Because of this dual nature (very strong/weak), it attract many scientists all over the world. Hydrogen bonds are electrostatic interactions, but the proportions of electrostatic character can vary. A more expanded proposed definition of a hydrogen bond is as “any interaction X-H---A with a shallower energy/distance dependence should be termed as a hydrogen bond”.

Table-01: Classification of Jeffrey [11] for strong, moderate, and weak hydrogen bonds (the numerical data are guiding values only)

<table>
<thead>
<tr>
<th>Interaction type</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond length [Å]</td>
<td>Strongly covalent</td>
<td>Mostly electrostatic</td>
<td>Electrostatic/dispersive</td>
</tr>
<tr>
<td>H--A</td>
<td>1.2 to 1.5</td>
<td>1.5 to 2.2</td>
<td>&gt; 2.2</td>
</tr>
<tr>
<td>Lengthening of X-H</td>
<td>0.08 to 0.25</td>
<td>0.02 to 0.08</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>X-H versus H--A</td>
<td>X-H = H--A</td>
<td>X-H &lt; H--A</td>
<td>X-H &lt;&lt; H--A</td>
</tr>
<tr>
<td>X--A [Å]</td>
<td>2.2 to 2.5</td>
<td>2.5 to 3.2</td>
<td>&gt; 3.2</td>
</tr>
<tr>
<td>Directionality</td>
<td>Highly</td>
<td>Moderate</td>
<td>too much deviation</td>
</tr>
<tr>
<td>Bond angles [°]</td>
<td>170-180</td>
<td>&gt; 130</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Bond energy [kcal/mol]</td>
<td>15 to 40</td>
<td>4 to 15</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Relat.IR shift Δ νXH [cm⁻¹]</td>
<td>25%</td>
<td>10 to 25%</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>H downfield shift [ppm]</td>
<td>14 to 22</td>
<td>&lt; 14</td>
<td></td>
</tr>
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</table>
**Interaction involving π-system**

π-system are important building blocks in supramolecular assembly because of their versatile noncovalent interaction with various functional groups. Electrostatic factors play a dominant role in most intermolecular binding interaction. Two types of π-binding forces aromatic-aromatic interaction, which can be considered a specific case of π-π interaction, and C-H–π interaction. Intermolecular and intramolecular C-H–π interactions.

**Van der Waal’s Interactions**

In molecular physics, the van der Waal’s forces, named after Dutch scientist Johannes Diderik van der Waals [12] is distance dependent interaction between atoms or molecules. Unlike ionic or covalent bonds, these attractions are not a result of any chemical, electronic bond, and they are comparatively weak and more susceptible to being perturbed. Van der Waals forces include attraction and repulsions between atoms, molecules, and surfaces, as well as other intermolecular forces (figure-4).

**Supramolecular synthons**

Supramolecular synthons are the basic building blocks in crystal engineering. The term ‘synthon’ was firstly introduced by E. J. Corey [13] in the year 1967 to simplify the synthesis of complex molecules and natural products in a review article entitled “General Method for Construction of complex molecules”. He specified synthons as “structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operations”. Synthon is considered as a part of the molecules which contains required information about the bond connectivity and/or stereo chemical information [14]. Synthons strategies are beneficial in the synthesis of a complex molecules and this method is known as “Retrosynthesis [15]”. Similarly, crystal engineering is the solid state equivalent of supramolecular synthesis, where Desiraju derived and modified the term of “supramolecular synthon”. And these are defined as the “structural units within supramolecular which can be formed and/or assembled by known or conceivable intermolecular interactions”. It is more advantageous to use synthons strategy as it provides a simplified view of an understanding of the crystal structures. Zaworotko[16] sub-classified synthons in two categories as homosynthons and heterosynthons on the basis of interacting functional groups. When supramolecular synthons is formed between the same functional group, it is called a homosynthon, and it is called heterosynthon when formed between two different functional groups. Heterosynthons including acid-amide, acid-pyridine, phenol-pyridine, phenol-amine, amino pyridine-acid, amide-pyridine-N-oxide and sulphonamide-pyridine-N-oxide are well explored in crystal engineering. Synthon formation depends on the strength of interactions. 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 homosynthon should be present in the API and coformers. In supramolecular synthons approach, steps involved in the developing cocrystals are as follows.

- Choosing the target molecule (API).
- Finding the complementary functional groups which are capable of forming a hydrogen bond. (Coformer selection).
- Methods of Preparation.
In pharmaceuticals, constant and consistent attempt to develop active pharmaceutical ingredient (API) cocrystals with suitable cocrystal excipients is gaining widespread research interest because cocrystals have been shown to offer physicochemical property enhancement which includes solubility, bioavailability, compressibility, stability, hygroscopicity, crystallinity, etc. compared to their native drugs. Despite its widespread popularity, there is a considerable debate surrounding its definition, and different authors have used different parameters to define what cocrystal is. However, most agree with the general statement, “A cocrystal is a crystalline solid containing at least two different neutral molecular components that are solids under ambient conditions and present in definite stoichiometric ratio”. The recent definition for cocrystal proposed by FDA in the draft guidance, “Cocrystals are crystalline material composed of two or more different molecules, typically active pharmaceutical ingredients (API) and cocrystal former (coformers), in the same lattice [17]”. According to FDA guidance, coformer is a component that interacts non-ionically with the API in the crystal lattice, that is not a solvent (including water), and is typically non-volatile. The first reported cocrystal is quinhydrone by Friedrich Wohler in 1844, which is a cocrystal of quinone and hydroquinone. He mixed yellow quinone with the colorless hydroquinone and obtained a green crystalline material which he named as ‘green hydroquinone’. He carried out elemental analysis and concluded that green hydroquinone contained 1:1 ratio of quinone and hydroquinone. 50 years later, in 1893, Ling and Baker renamed green hydroquinone as quinhydrone. Finally, in the year of 1958, it was interpreted from XRD studies that quinhydrone is cocrystal of quinone and hydroquinone and they are connected with each other by O—H---O interactions. Many cocrystals are discovered after quinhydrone and some were discovered by the chance and others by screening techniques. The first reported drug-drug cocrystal between pyrithyldione and propyphenazone was patented in 1937 and crystal structure published in 2011. The first report on pharmaceutical cocrystal recognized between chloral hydrate and betaine (CHOBTN) has appeared in the US market well before in 1963.
Coformers can be chosen from the any other chemical but are usually restricted to excipients already used in the same drug products to avoid additional safety studies. Chemicals that can be registered as generally recognized as safe (GRAS) by the FDA are also popular coformer choices because many of them have substantial amounts of available safety data.

Physicochemical properties of the pharmaceuticals can be improved by obtaining cocrystals using cocrystallization techniques. Cocrystallization with pharmaceutically acceptable (GRAS) compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, compaction behaviour, and hygroscopicity.

**Bending of organic crystals**

Bending is observed in the organic crystals when the packing is anisotropic in such a way that the strong and weak interaction patterns occur in nearly perpendicular directions. Pharmaceutical cocrystals have attracted phenomenal interest in recent years for their potential for improving the physicochemical properties of drug substances. Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical cocrystals can enhance other essential properties of the APIs such as flowability, chemical stability, compressibility and hygroscopicity.

Cocrystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry ratio, which are solids at room temperature and these are held together by weak interactions, mainly hydrogen bonding. In cocrystals at least one component is molecular and a solid at room temperature i.e. coformer and other forms are supramolecular synthon with a molecular or ionic API.

**Cocrystal Synthesis**

To design cocrystal, principles of crystal engineering are generally utilized. For designing the pharmaceutical cocrystal having desired physical and chemical properties, it is necessary for to select the suitable cocrystal coformer (CCF) which can form a cocrystal with the active molecules. Ascertaining possible hydrogen bonding sites in API and choosing the right CCF that has complementary hydrogen bonding groups is critical in cocrystal design strategy. Besides crystal engineering aspects, the success of a cocrystallization experiment also depends on the several controlling factors, such as a solvent of crystallization, the stoichiometry of the cocrystal components, solubility of cocrystal components, temperature of crystallization and solvent of crystallization. The design of cocrystal involves the formation of supramolecular homo/hetero synthons between the cocrystal components, for e.g. acid-acid, amide-amide, acid-aromatic N, acid-amide, amide-pyridine, etc. Cambridge Structural Database survey that in the cocrystal formation heterosynthon dominates over the homosynthon. A number of methods for cocrystal preparations are available in the literature which includes grinding (neat/liquid assisted), solvent evaporation, solvent diffusion, anti-solvent method, slurry crystallization, freeze-drying, hot melt extrusion and ultra-sound assisted crystallization. The mostly used traditional method for cocrystallization is solvent evaporation method, where two solid compounds are dissolved in a stoichiometric ratio and allowed for

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Table 02 Difference between Excipient and Cocrystal Coformer

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Cocrystal Coformer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supposed to be chemically inert.</td>
<td>Participate in intermolecular interaction.</td>
</tr>
<tr>
<td>Do not become the part of the crystal structure</td>
<td>Become the part of Cocrystal structure</td>
</tr>
<tr>
<td>Involved in final dosage form.</td>
<td>They need further processing steps to be in final dosage form.</td>
</tr>
</tbody>
</table>

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Fig-6: (a) Molecular packing diagram of hydroquinone-quinone 1:1 cocrystal sustained by strong O–H…O synthons (b) pharmaceutical cocrystal 1:1 of chloral hydrate and trimethylglycine betaine interact each other through dimeric O–H…O hydrogen bonds[18]
solvent evaporation at ambient conditions. However, there has been an active and increasing demand for the clean and environmentally friendly processes that focus on green methods of conducting chemical reactions in the absence of solvents. Amongst all method, cocrystal synthesis by mechanochemical, i.e., grinding method has proven superior. These methods have emerged as a useful and alternative technique to the traditional solvent method for the pharmaceutical cocrystal synthesis and production. The grinding method provides a way to avoid the effects of solubility and solvent competition which can’t be avoided in solution based approaches. It has been driven by the fact that pharmaceutical cocrystal synthesis is largely due to the formation of supramolecular interaction that primarily due to the creation of supramolecular synths that can be broken and reformed under mild mechanical conditions. The mechanism of cocrystal formation through grinding method would include molecular diffusion, eutectic composition, and cocrystallization mediated by an amorphous phase. The significant advantage with grindings is faster reaction rate, high yields, and product crystalline.

However, there have been a number of reports presenting incomplete crystallization using dry/neat grinding. Liquid assisted grinding has, therefore, gained considerable favor because of the possibility of providing dramatically improved productivity via the addition of only catalytic amounts of solvent to a typical grinding process. More recently, another advanced solvent free continuous manufacturing method, hot melt extrusion (HME), has also emerged as an easy to scale alternative for mechanochemical cocrystal synthesis. It is a process of pumping raw material with a rotating screw under elevated temperature through a die into a product of uniform shape. This process employed for the synthesis of high quality pharmaceutical cocrystals. This technology is in its early stage, and more studies are required to understand the mechanism of cocrystal formation.
Characterization Techniques
X-ray Crystallography
X-ray crystallography is a technique used for the determining the atomic and molecular structure of a crystals, in which the crystalline structure cause a beam of incident X-ray to diffract into many specific directions. By measuring the angles and intensities of these diffracted beams, a crystallographer can produce a three dimensional picture of the density of electrons within the crystal.

Powder X-ray diffraction
Powder diffraction is a scientific technique use for the X-ray, neutron or electron diffraction on powder or microcrystalline samples for structural characterization of materials. An instrument dedicated to performing such powder measurements is called as powder diffractometer. Powder diffraction stands in contrast to single crystal diffraction techniques, which work best with a single, well ordered crystal. Identification is performed by comparison of the diffraction pattern to a known standard or to a database such as the International Centre for Diffraction Data Powder Diffraction File (PDF) or the Cambridge Structural Database (CSD).

Single crystal X-ray diffraction
These are oldest and most precise method of X-ray crystallography is single-crystal X-ray diffraction, in which a beam of X-rays strikes in single crystal, producing scattered beams. When they land on a piece of film or other detector, then these beams make a diffraction pattern of spots, the strengths and angles of the beams are recorded as the crystal is gradually rotated. Each spot is called as reflection, since it corresponds to the reflection of the X-rays from one set of evenly spaced planes within the crystal.

Differential Scanning Calorimetry
Differential Scanning Calorimetry, or DSC, are the thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. In DSC both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for the DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. Reference sample should have the well-defined heat capacity over the range of temperatures to be scanned.

DSC is used for the study of liquid crystals. As some forms of matter go from solid to liquid they go through the third state, which displays properties of the both phases. These anisotropic liquid is also known as liquid crystalline or mesomorphs state. Using DSC, it is possible to observe the small energy changes that occur as matter transitions from a solid to the liquid crystal and from a liquid crystal to an isotropic liquid.

NMR
In principle behind NMR is that many nuclei have spin and all nuclei are electrically charged. If an external magnetic field is applied, an energy transfer is possible between the base energy to the higher energy level (generally a single energy gap). The energy transfer takes place at a wavelength that corresponds to the radio frequencies and when the spin returns to its base level, energy is emitted at the same frequency. The signal that matches this energy transfer is measured in many ways and processed in order to yield an NMR spectrum for the nucleus concerned.

Two main types of NMR: $^1$H and $^{13}$C NMR

$^1$H NMR: It is used to determine the types and number of hydrogen atoms present in a molecule.

$^{13}$C NMR: It is used to determine the type and number of carbon atoms in a molecule. When significant portions of a molecule lack C-H bonds, little information is forthcoming by $^1$H NMR. For example, the following diagram pair of isomers (A & B) which display similar proton NMR spectra. But can be differentiated by $^{13}$C NMR.

Application
CONCLUSION

In recent study in Pharmaceutical field various barriers are arises during formulation or after the formulation like solubility issues, stability, dissolution, Manufacturability, Bioavailability etc. so these problems are overcome by formulating the pharmaceutical new solid forms like Pharmaceutical cocrystal and it will be helpful to overcome like theses problem. Pharmaceutical Cocrystals are increasing the basically solubility and dissolution rate of drug those drug are present in BCS class II and IV class. So the pharmaceutical cocrystal is helpful in enhancement of drug properties.

REFERENCES