REVIEW ON COCRYSTALS AND ITS CONCEPT

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Abstract: -

A pharmaceutical cocrystal is a multicomponent system created by an active pharmaceutical ingredient (API) in ionic or non-ionic form and a cocrystal former (coformer) in a certain stoichiometry, resulting in supramolecular synthon. Pharmaceutical cocrystals can improve a variety of important factors in addition to solubility, dissolving rate, and physical stability. Three co-crystals of gefitinib have been prepared with highly soluble gallic acid (GAL), ascorbic acid (AA), pyridoxine (PYR) co-formers of GRAS status to improve its solubility, dissolution and finally bioavailability. Two methods are used for preparing cocrystal i.e. Free of solids/solvents and Developed on solvents. By Enhanced solubility and dissolution profile of drug, improvement the permeability of the drug, cocrystal, bioavailability, Increased drug residence time at the action site and Tabletability.

1. INTRODUCTION: -

Various groups of researchers have defined pharmaceutical cocrystals as essentially a multicomponent complex containing the active pharmaceutical moiety or API and the counter molecule in distinct stoichiometric ratios, held together by non-covalent interactions, -interactions, and halogen bonds. The formation of cocrystals is based on the unique concept of the establishment of non-covalent interactions, especially H-bonds between hydrogen charge carrier groups on two different functional groups, which would now be complimentary to each other. The active groups are present on both the therapeutic agent and the countering molecules, which in virtue of their involvement in co-crystallization, is also called a co-former. The co-former theoretically is any neutral molecule with the hydrogen donating or accepting functional groups, but is practically severely limited in choice.

The main advantage of cocrystals over other techniques is the flexibility and the versatility as the physical and chemical properties of an API can be altered and adjusted according to requirements by choosing an appropriate co-former belonging to generally regarded as safe (GRAS) status. It provides an opportunistic approach for the improvement in various physicochemical properties pertaining to enhancement of bioavailability. Pharmaceutical cocrystals can improve a variety of important factors in addition to solubility, dissolving rate, and physical stability and also such as chemical stability, mechanical properties enhancement, separation and purification and taste masking.

For example: -

Three co-crystals of gefitinib have been prepared with highly soluble gallic acid (GAL), ascorbic acid (AA), pyridoxine (PYR) co-formers of GRAS status to improve its solubility, dissolution and finally bioavailability. These novel co crystals have been characterized using different analytical techniques Hot stage microscopy (HSM) etc. and further subjected to solubility, dissolution, pharmacokinetics to assess the potential of this technique in

improvement of its physicochemical parameters. These novel cocrystals were characterized by crystal structure analysis was also performed using their PXRD patterns for structural insights. Further, evaluation studies involving solubility, dissolution, Log P, pharmacokinetic.

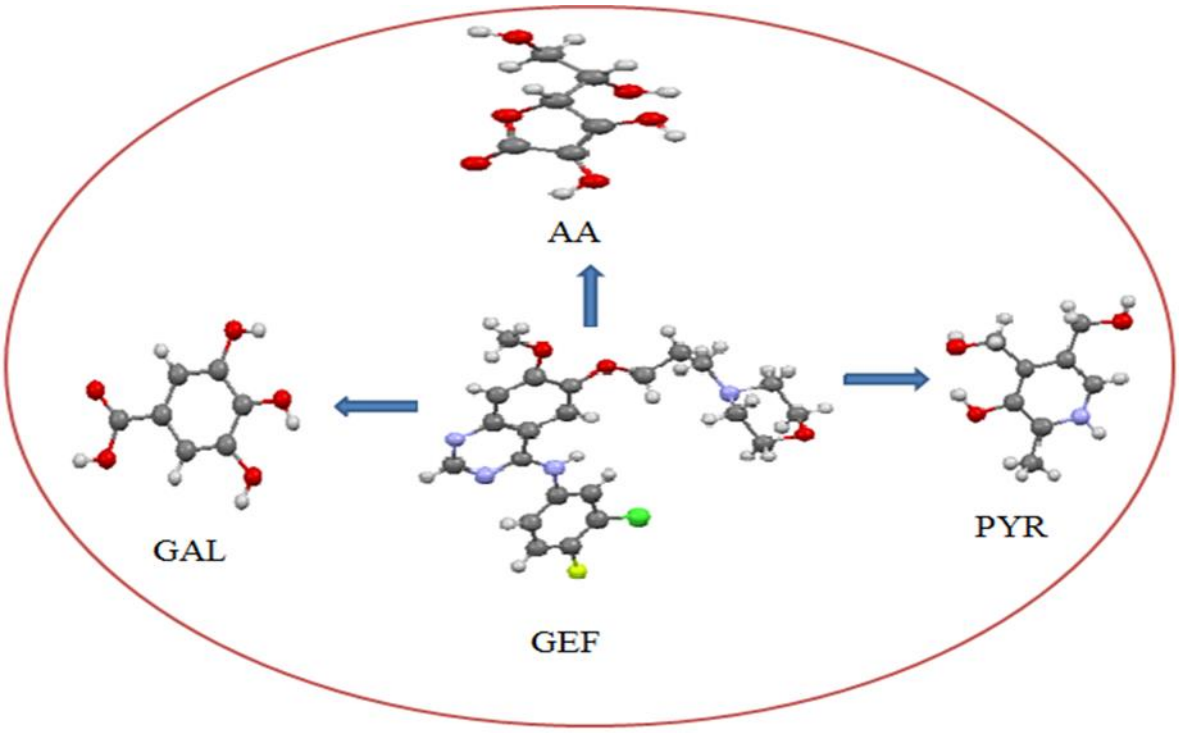


Figure 1: Structural representation of drug and coformers

2.REVIEW OF LITERATURE

A pharmaceutical cocrystal is a multicomponent system created by an active pharmaceutical ingredient (API) in ionic or non-ionic form and a cocrystal former (coformer) in a certain stoichiometry, resulting in supramolecular synthon. Class II and IV medications in the Biopharmaceutics Classification System (BCS) have minimal aqueous solubility and thus bioavailability. Because of their poor water solubility, most of these medicines are hydrophobic and cannot be produced into a pharmaceutical formulation (5). Using crystal engineering concepts to construct cocrystals of these molecules with water-soluble molecules is one way to improve the aqueous solubility of weakly water-soluble pharmaceuticals (which are generally called coformers).

R Pepinsky was the first to coin the phrase "crystal engineering" in 1955. It deals with growth and deign of crystalline solids with the aim of influencing crucial properties mainly solubility and stability of a drug product which in turn affect its bioavailability. It was defined by Desiraju G. The diverse solid forms (figure 2) that can be obtained by applying concepts of crystal engineering are polymorphs (single component form), solvates /hydrates (pseudopolymorphs), salts, co-crystal and eutectics (multicomponent forms). Solvates and hydrates are sometimes classified as multicomponent solids (6).

Different crystal versions of same Ingredient are referred to as polymorphs. This could be in the form of amorphous solvation or hydration. Solid drugs can be anhydrous or solvate/hydrate in their amorphous and crystalline forms. The term "solvate" refers to a solid that contains a solvent. Depends upon the nature of the solvent's intermolecular interactions with the

crystalline solid, the presence of residual solvent can have a significant impact on the crystalline structure. A hydrate is formed when the solvent is water. Solvates and hydrates often suffers from poor thermal stability and variable stoichiometric, whereas amorphous substances are usually unstable there by making these solid forms unlikely candidates for use as a drug product.

Therefore, multicomponent systems including cocrystals, salts and inclusion compounds have gained research interest for improvement of poor biopharmaceutical properties of API (7). Therefore, multicomponent systems including cocrystals, salts and inclusion compounds have gained research interest for improvement of poor biopharmaceutical properties of API.

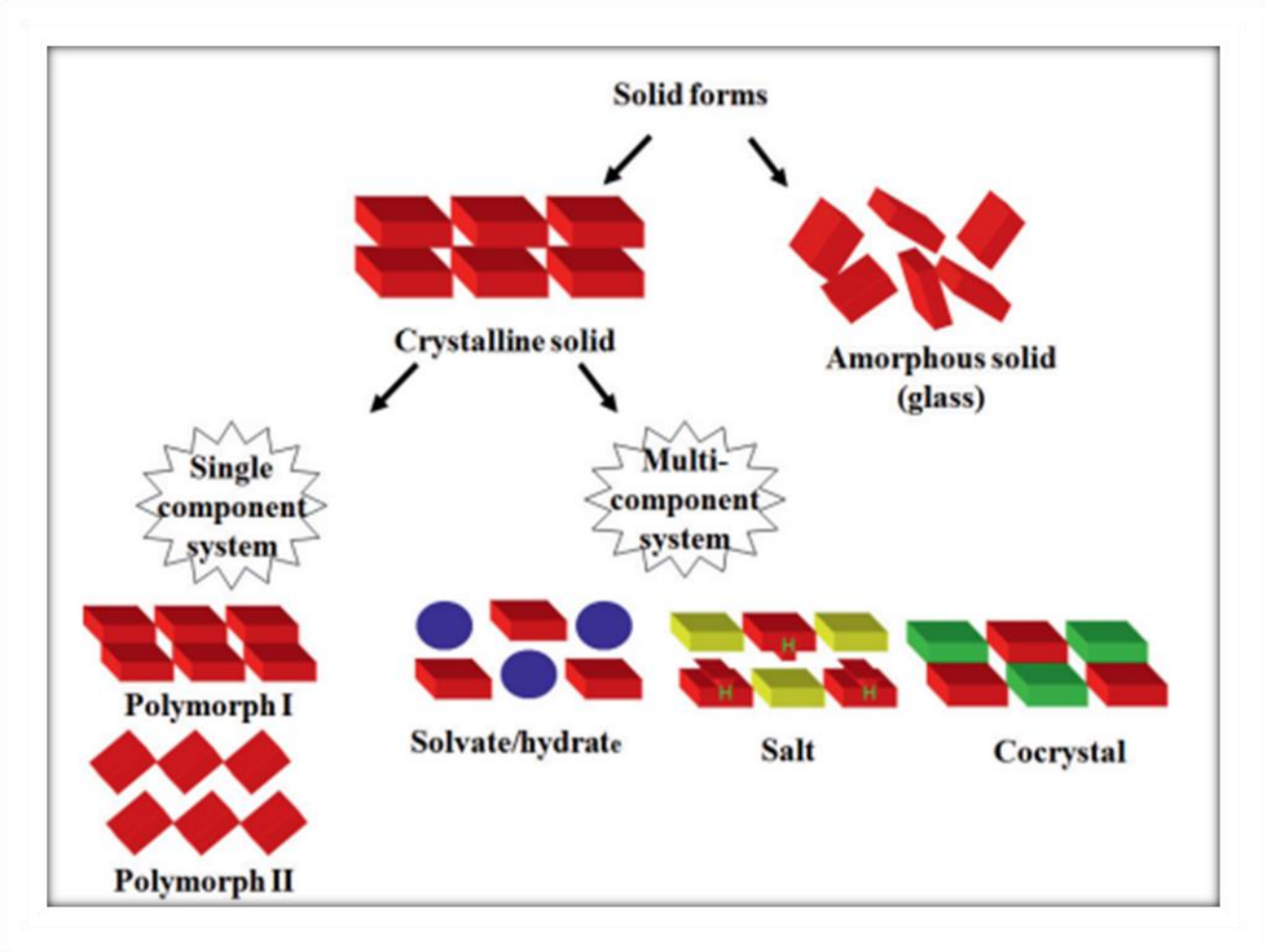
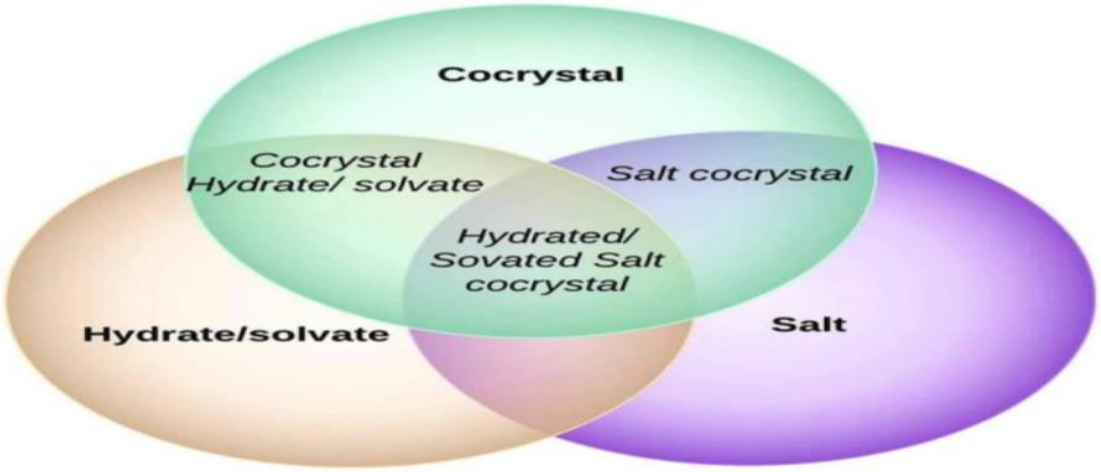


Figure 2: Diverse forms obtained via crystal engineering

2.1. Multicomponent solid forms

Hydrogen bonding, halogen bonds and other non-covalent interactions are of utmost importance in crystal packing. Crystal engineering involves intermolecular interactions such as hydrogen bonding, electrostatic interactions, Van-der Waals interactions, metal coordination bonds and π-π stacking. Salts are frequently used instead of free acids and bases in a pharmaceutical compound. According to this classification, solvate crystals contain a solid residue and a liquid residue (8). Salts have two ions, one of which is a solid, whereas cocrystals have two solid residues.



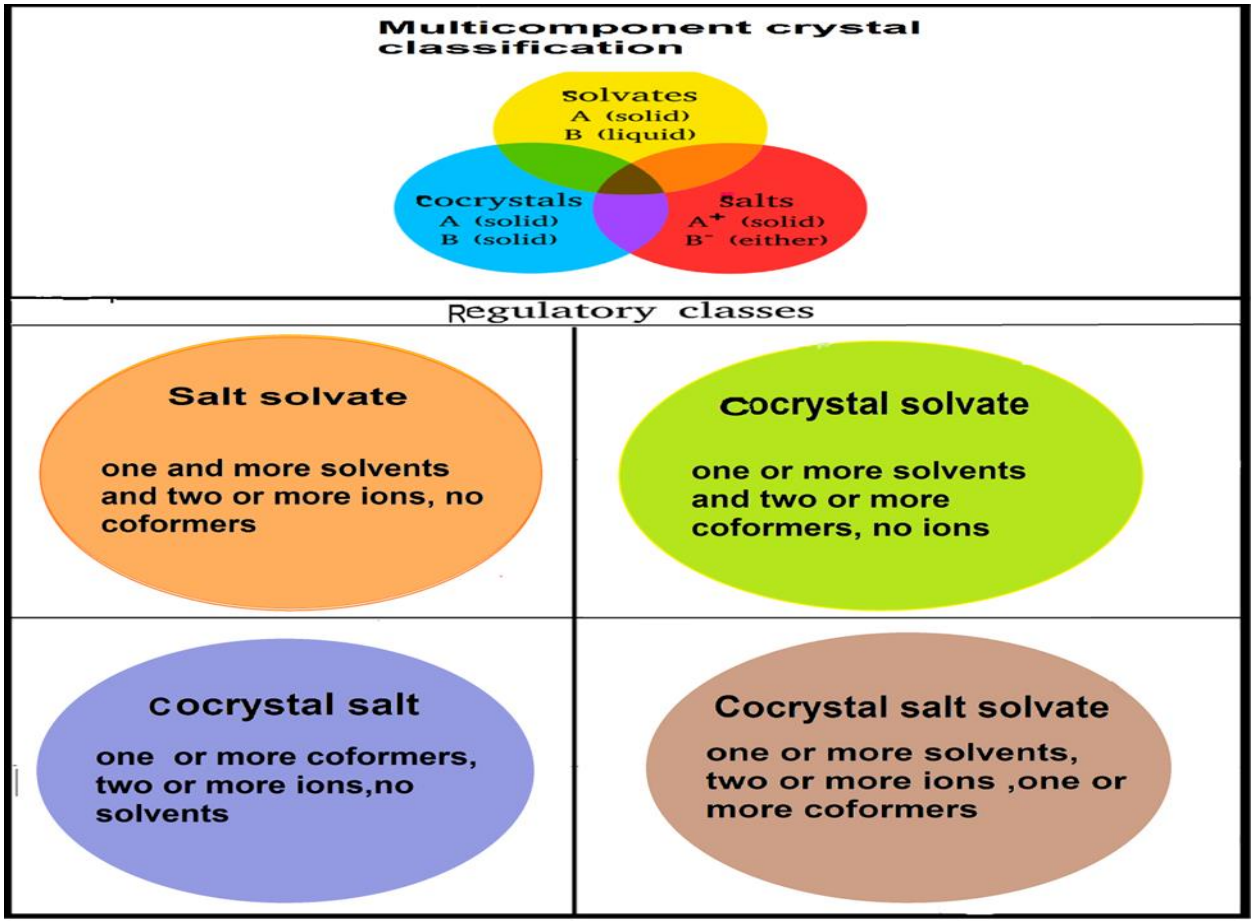


Figure 3: Multicomponent crystal

2.2. Interactions involved in cocrystallization: -

Intermolecular interactions playing the integral role in cocrystallization are non-covalent in nature. Halogen bonds are non-covalent intermolecular interactions that occur when a halogen atom interacts with atoms having lone pairs. The most prominent non covalent interactions among these are halogen hydrogen bonds and halogen bonds. They are intermediates between strong and weak hydrogen bonds. Hydrogen bonds are of utmost importance and are most

frequently used in cocrystallization for supramolecular synthesis as they have characteristics of strong and directional interaction, thus influencing the molecular assembly(9).

The components in a cocrystal exist in a definite stoichiometric ratio and assemble via non-covalent interactions such as hydrogen bonds, ionic bonds, π-π or van-der waal interactions (Table1) rather than by ion pairing. Cocrystal interactions such as hydrogen bonds, ionic bonds, π-π or van-der waal interactions rather than ion pairing. These non-covalent interactions offer tremendous scope for controlled modification of key pharmaceutical properties like habit, bulk density, compressibility and other bioactivity(10).

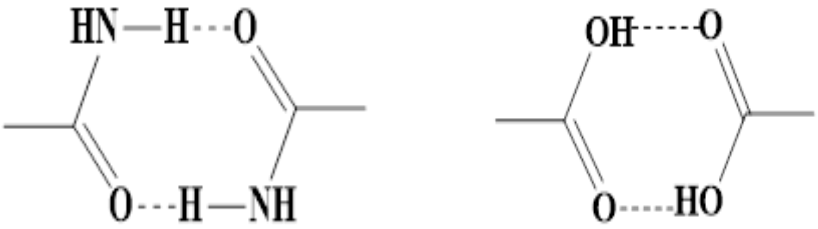
Interaction	Bond energies (kj/mol)	Building blocks	Products	Features
Covalent	200-400	Atoms	Molecules	H>TΔs MW:1-1000 kDa
Hydrogen Bond	4-120	Molecules	Supermolecules	H=TΔs MW:1-100 kDa
Dipole-Dipole	5-50	Molecules	Supermolecules	H=TΔs MW:1-100 kDa
π-π stacking	<50	Molecules	Supermolecules	H=TΔs MW:1-100 kDa
Vander Waals	<5	Molecules	Supermolecules	H=TΔs MW:1-100 kDa

Table1: Interactions involved in cocrystallization

2.3. Synthons designing

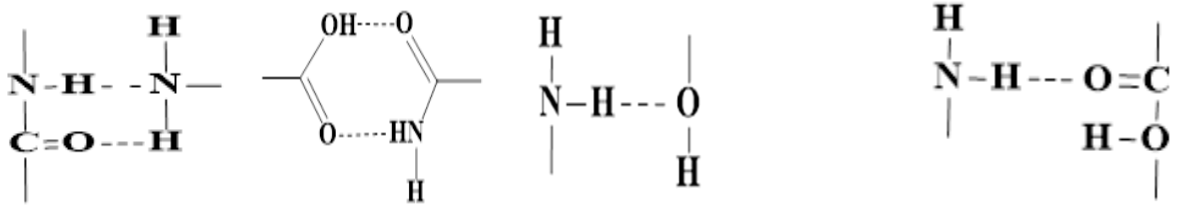
In multicomponent solid formation, supramolecular molecular crystal formation is critical. Synthons are the essential characteristics or kernel of a crystal structure that surround the crystal's core. The synthon is made up of molecular fragments and their supramolecular interactions (11). There are two types of supramolecular synthons:

Homosynthons: consisting of functional groups that are related.



Amide-Amide **Acid-Acid**

Heterosynthons: functional groups that are diverse but complimentary



Amine-Amine **Acid-Amide** **Amine-Alcohol** **Amine-Acid**

2.4. Cambridge Structural Database (CSD)

The CSD is a crucial tool for analysing crystal structures that are known. Since 1965, the Cambridge Crystallographic Data Centre (CCDC) has maintained a comprehensive database of the all reported organic as well as the metal–organic and the small-molecule crystal structures. X-ray and the precipitate investigation were incorporated in the CSD, along with cell characteristics, atomic coordinates, and refinement.

CCDC catalogues all the structures that have been deposited into the database. The structures are processed prior to their deposition into the database both the computationally and by the means of expert structural chemistry editors(13).

Four modules are involved in the CSD software namely:

1) ConQuest: searches frequency of occurrence of supramolecular synthons.
2) Mercury: visualization of crystal structures.
3) Vista: statistical analysis
4) PreQuest: database creation

It aids in the determination of the possibility of synthon formation among the two complimentary functional group units. In this manner, CSD supports the coformer selection criteria in the process of cocystallization (14).

2.5. Selection of coformers

A pharmaceutical co-crystal is a crystalline solid with a single structure that incorporates the two neutral molecules present. In an ideal world, the type of cocrystal former would be included in the current American Food and drug administration "Everything added to food in the United States" list, or approved as "Generally Regarded as Safe".

These include the hydrogen-bonding propensitya and coformers together with targeted drug molecules encompass the basic structural units, i.e., synthons, in the supermolecule (cocrystal).

Methods of Preparation of cocrystals

There are three types of the methods of effective kind of cocrystal preparation technologies in the use today:

(1) Free of solids/solvents.

(2) Developed on solvents.

The solvent choice is critical for solvent-based techniques, as any change in the solvent will alter the intermolecular interactions.

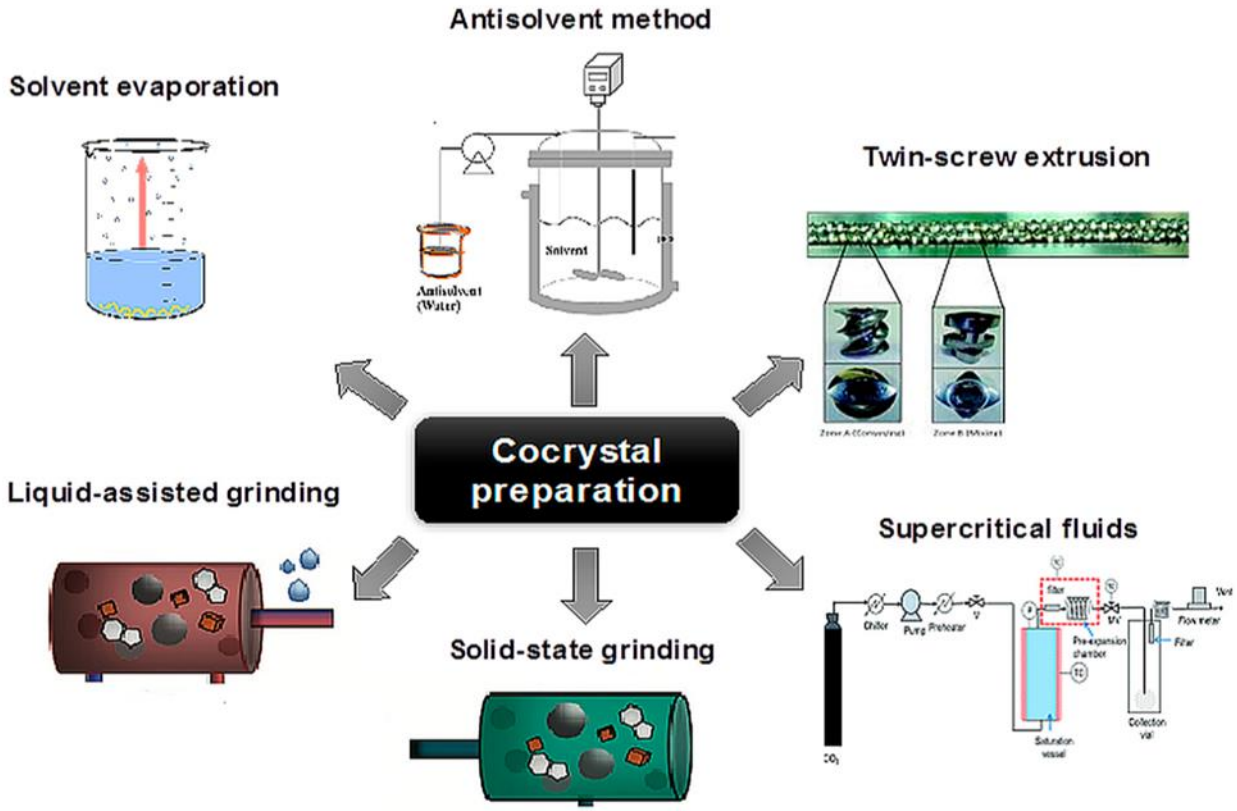


Figure 4: Different methods for preparation of cocrystals.

2.5.1. Solid/Solvent-free cocrystallization

Solvent- free cocrystallization involves the mixing of the components either manually or mechanically in defined stoichiometric ratio. In order to get cocrystals, the reactants are required to exhibit significant vapour pressures. The techniques covered under solvent-free cocrystallization are explained briefly in the following sections (16).

Mechanochemical methods: -

This approach is gaining popularity since it produces cocrystals mostly through grinding. Mechanochemical reactions are defined by the International Union of Pure and Applied Chemistry (IUPAC) as "chemical reactions generated by the direct absorption of mechanical energy." Stretching, grinding, and shearing are among the methods used to create reactive sites in this process. Based on the application of mechanical stress, which promotes interpenetration and reactivity by facilitating fracture and increasing surface area. In some circumstances, using a tiny amount of solvent might speed up the procedure. There are two types of grinding techniques: liquid assisted grinding and neat grinding (17).

1. Neat grinding method: -

Neat grinding entails combining stoichiometric cocrystal components and grinding them either manually with a mortar and pestle or mechanically with a ball mill or vibrating mill. One or both reactants must have significant solid-state vapour pressures for this approach to work (18). The neat grinding method has been used to successfully synthesis a variety of pharmaceutical cocrystals.

2. Polymer assisted grinding: -

Polymer assisted grinding (POLAG) method employs polymers to act as catalysts, either in hard or runny state, for mechanochemical cocrystal creation. This technique prevents the solvates creation which is the main matter of interest in liquid assisted grinding. Furthermore, it improves the bioavailability and dissolution rate of cocrystals (19).

3. Hot melt extrusion

This technique requires chemically inert hot melt extrudable excipients capable of producing a suspension of cocrystals entrenched in a matrix. These inert meltable excipients facilitate the formation of solid extrudate and catalyze the process of cocrystallization (20).

2.6. Matrix-assisted cocrystallization

This is a HME based cocrystallization method that includes the use of matrix with equimolar numbers of the components (coformer). The process starts with the mixing of the system with the medium material in the solid phase. Then, in the extrusion development, medium material either liquefies or softened and becomes fluid in the extrusion process (21). This leads to optimal mixing and grinding that facilitates cocrystallization. A catalytic role is played by the matrix solvent which is also responsible for the reduction in shear stresses produced meanwhile during extrusion. The final product comprised of solid state cocrystals embedded within a matrix (22).

2.7. Liquid assisted grinding

It was previously called as kneading, wet cogrinding and solvent drop grinding. The calculation of solvent in small amounts that serves as a chemical agent by rising the kinetics of the cocrystal formation, forms the basis for this method. The rate of cocrystal formation is higher in comparison to neat grinding. This method beholds the possibility of the formation of undesired solvates (23).

2.8. Solvent-based cocrystallization:

Cocrystal formation of hydrogen bonds between different functional groups produces a thermodynamically preferred product. The materials (API and coformer) are completely evaporated after being dissolved in a common solvent. This is the most commonly used technique for generating cocrystals (24). If the two components' solubilities differ, the component with the lesser solubility will precipitate. Solvent evaporation is a small-scale process for preparing cocrystals that does not require complex equipment and produces high-quality and pure cocrystals. However, this approach has two drawbacks: it requires a lot of solvent and has limited scalability.

1. Slurry crystallization:

This method involves synthesis of cocrystals through slurry crystallization that can be achieved simply by adding solvent to equimolar binary solid mixtures of cocrystals components. Major limitation of this technique is that huge volumes of solvent are required for crystallization (25).

2. Antisolvent cocrystallization:

A solvent that is less soluble in the compound is frequently added to the solution, promoting solid precipitation. Antisolvent crystallisation has been used to create carbamazepine-saccharin cocrystals. The resulting suspension is filtered, and the collected solid can be characterized by XRPD. The disadvantages of this method include its lower performance when compared to solvent-based grinding, as well as the large volume of solvent used (26).

3. Vapour - diffusion

In vapour-diffusion crystallization, the vapours of organic solvent enact the role of a catalyst. The concept of spontaneous cocrystallization acceleration produced by high aqueous humidity was the inspiration for this approach (27). Vapour digestion is a more environmentally friendly alternative to traditional solvent-based procedures, and it has the potential to replace mechano-chemical methods due to its low energy input.

4. Ultrasound assisted solution cocrystallisation (USSC)

Technique involves the use of ultrasonic waves for the mixing of components in the solvent. Use of ultrasonic waves in this method increases the rate of formation of cocrystals by enhancing the rate of dissolution of components. Reducing the amount of solvent makes the solution supersaturated and therefore increases the tendency of cocrystallization(28). Cocrystals of nano and micro size can be obtained by this technique.

2.9. Spray drying technique

The technique of spray drying is mainly used for amorphous and metastable materials where cocrystallization cannot be achieved by conventional methods. An amorphous phase intermediate is formed using this method and solvent evaporation occurs instantly due to the hot air, thus leading to cocrystallization. The cocrystals of urea-succinic acid in the stoichiometric relation of 1:1 and 2:1 have been successfully synthesized by this technique. However, these amorphous or metastable products are thermodynamically unstable thereby influencing the purity and the yield of the cocrystal (29). Supercritical fluid technology

Supercritical fluid technology allows a single-step generation of particles that are difficult or even impossible to obtain by conventional techniques. Different supercritical fluid techniques are being used these days and have been found to have additional advantages compared to the classical cocrystal production methods. The properties of different super critical fluids assist in generation of pure and dried cocrystals (30). The unique properties of different super critical fluids assist in generation of pure and dried cocrystals.

(i) Cocrystallization with supercritical solvent (CSS)
(ii) Supercritical antisolvent (SAS)
(iii) Atomized anti-solvent (AAS

2.10. Twin-screw extrusion

Twin-screw swelling involves the twisting of two parallel screws in opposite direction thus helping in effective mixing of the components and thereby leading to the synthesis of various multi-component forms. Even at low temperatures, the addition of a solvent may aid in the

formation of the products. This technique is a continuous process and can be used for scale up at higher levelsthus making it a promising choice for industries (31). This method has been used for the preparation of AMG 517-sorbic acid cocrystal.

3. Characterization techniques

There are numbers of established analytical techniques to characterize potentially new co-crystalline materials (figure 4). Differencial Scanning Calorimetry (DSC), Thermo gravimetric Analysis (TGA), Fourier Transform Infrared Spectroscopy (FT-IR), Powder X-ray Diffraction (PXRD), Single Crystal X-ray Diffraction (SXRD), Solid State Nuclear Magnetic Resonance Spectroscopy (ssNMR), and Field Emission Scanning Electron Microscopy are used to characterise the physicochemical properties (FESEM).

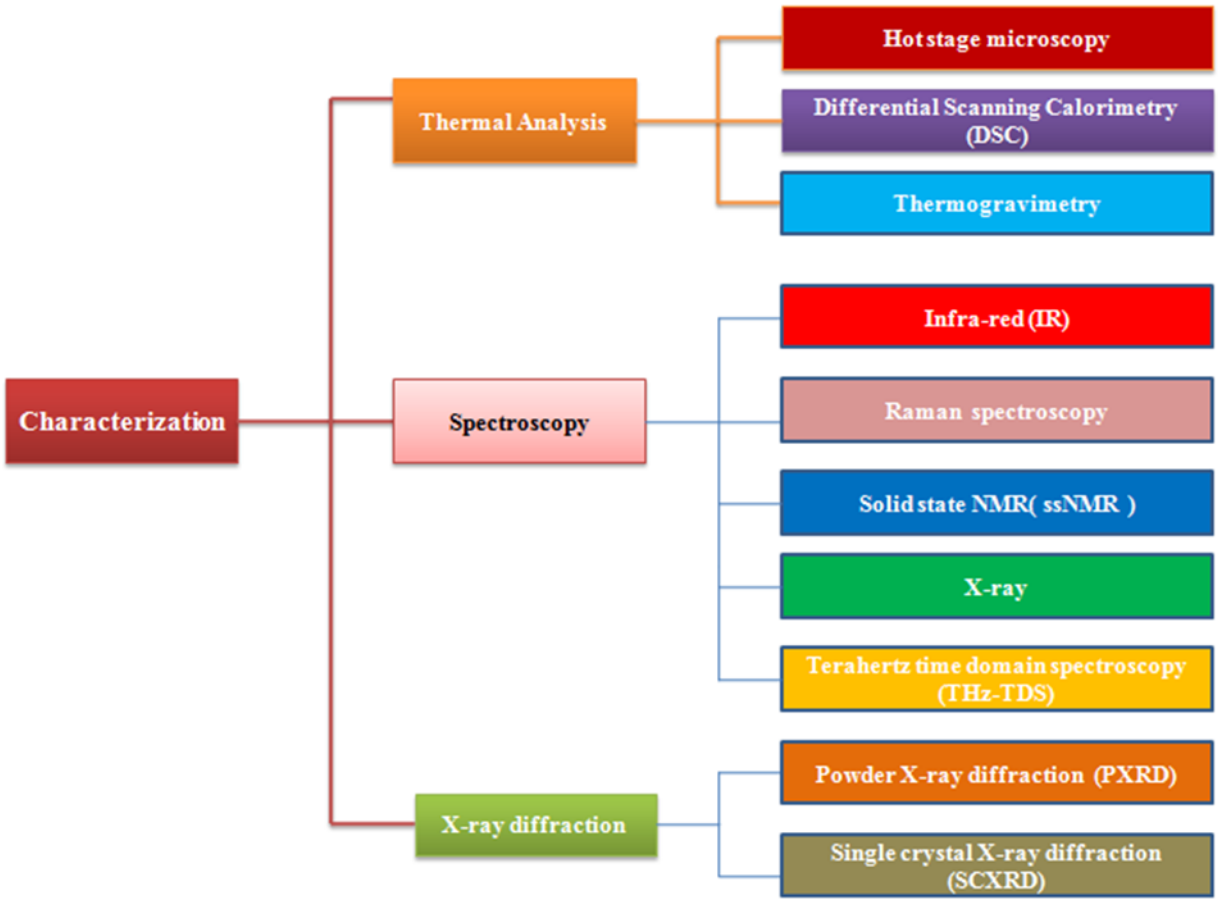


Figure 5: Characterization Techniques

3.1 Thermal analysis (DSC, TGA and HSM)

DSC, TGA, and HSM are regarded as the most important thermal characterization techniques for solid forms. They are used to characterise single and multicomponent amorphous and crystalline forms including crystals, cocrystals, polymorphs, solvates, and hydrates. DSC, TGA, and HSM are regarded as the most important thermal characterization techniques for solid forms (32). Besides the melting point of the compound it also reveals desolvation, solid-solid transitions crystallization point and heat capacity. DSC is moderately an easy and fast

method which provides the important information of the purity and phase transformation of the solid forms (33). The thermodynamic relationship between two polymorphs can be derived using DSC. On the other hand, TGA is used for affirmation of loss of mass in case of hydrates of solvates and also to check the degradation of the compound.

The advancement of DSC and TGA instruments has widened the domain of thermal analysis in following ways:

- Modulated DSC helps to identify reversible and irreversible transitions.
- TGA in conjunction with IR allows detection of solvents in hydrates/solvates.
- TGA along with DTA imparts the information regarding weight loss along with the heat flow information.

3.2 Infrared (FT-IR) and Raman Spectroscopy

Infrared and Raman spectroscopy are used to study vibrational, rotational, and other low frequency modes in a system. Infrared spectroscopic techniques can be powerful tools for distinguishing is structural phase of a chemical or physical system. The information of shifting in the wavenumber of some characteristic absorption peaks and change in peak intensity provides evidence of formation of multicomponent from like cocrystal (34). In case of eutectics there is no change in frequency or bands in FT-IR.

3.3 Solid state NMR (ssNMR)

Solid-state nuclear magnetic resonance (ssNMR) is a molecular structure determination approach based on NMR spectroscopy. SSNMR entails putting a sample in a media that has little or no mobility, such as a crystalline or powder state, a membrane-bound system, or an aligned solution. Among all the ssNMR techniques, 13C CP/MAS NMR spectroscopy is used widely for the description of objects. This method is non-destructive and helps to investigate the structural changes in solids. The weak hydrogen bonded forces that forms the supramolecular network of solids can easily be detected by ssNMR and thus, useful for characterizing polymorphs and cocrystals (35). The change in crystal structure creates the perturbation in the chemical situation around separately center which results in a distinctive range in solid state of each nucleus.

Besides this, it is used to estimate the purity of substance and to analyze the composition of mixtures. Even the FDA has also documented the utility of ssNMR for characterization the food or drug material (36). This technique has extreme importance in determining the existence of cocrystals in cases where single crystal X-ray diffraction is not possible.

3.4 Powder X-ray Diffraction (PXRD)

Any material in the world is composed of atoms which are related by interatomic promises, and the properties of the material are strong-minded by the exact nature of these interatomic bonds. PXRD exploits this property of crystalline material for comprehensive structure analysis at atomic resolution. (Tishmack et al., 2003) Modern development in the X-ray crystallography have made it possible to determine the structure of microcrystalline powder, thereby illustrating it to be substitutive approach for characterization (37).

3.5 Scanning Electron Microscopy (SEM)

SEM is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals and provide information about the surface topography (38). These signals include secondary electrons (that produce SEM images), backscattered electrons (BSE) diffracted backscattering electrons (EBSD) and heat.

3.6 Single crystal X-ray diffraction (SCXRD)

SCXRD is a powerful non-destructive system that offer energetic material not only of complete structural analysis but also the nature of the multicomponent form. This is an exclusive technique which can differentiate molecular structure of polymorphs and cocrystals. Moreover, it is a unique tool to distinguish salts from cocrystals (39). However, the time needed for acquisition of sample being analyzed quite long and requires sound knowledge for interpretation of data. Sometimes the molecular information is not feasible when the crystals are of not good quality.

3.7Hot-stage microscopy (HSM)

HSM is a technique that combines microscopy and thermal analysis to investigate the physical properties of solid materials as a function of temperature and time. When the drug crystals are heated, they undergo changes that are easily visible through a microscope. Thermal changes such as melting point, melting range, crystal growth, crystalline transformations, and so on can be visualized (40).

4. Scientific/Technological significance of Cocrystals

Physicochemical properties of drugs can be tailored by various approaches such as salt formation, micronization, solid dispersion, amorphous drugs and encapsulation. Cocrystals have the advantages of existing in stable crystalline form involving addition of GRAS status excipients or additives in formulations which overlay safer approach for drug development. Different formulations of pharmaceutical cocrystals are available in the market Viagra (Pfizer) to treat erectile dysfunction and pulmonary arterial hypertension (41). Pharmaceutical cocrystals can improve a variety of physicochemical qualities in pharmaceuticals, including melting point, tabletability, solubility, stability, bioavailability, and permeability.

4.1. Enhanced solubility and dissolution profile of drug

Solubility is an important metric to consider while researching poorly soluble medication compositions. Salt creation, solid dispersion, particle size reduction, and other methods have all been used to improve medication solubility, with cocrystallization being one of them. Cocrystallization uses the spring and parachute effect to improve the solubility of poorly soluble medicines. The spring and parachute concept (Figure 5) is an approach for improving the solubility and dissolution rate of poorly soluble medicines by exploiting supersaturation (42).

(1) The stable (crystalline) form is insoluble.

(2) Metastable species with a limited lifespan (i.e., the amorphous phase) has a high peak solubility but quickly decreases to the crystalline form's low solubility (within minutes to an hour).
(3) For a long time, highly soluble drug forms are retained in the metastable zone (usually hours).

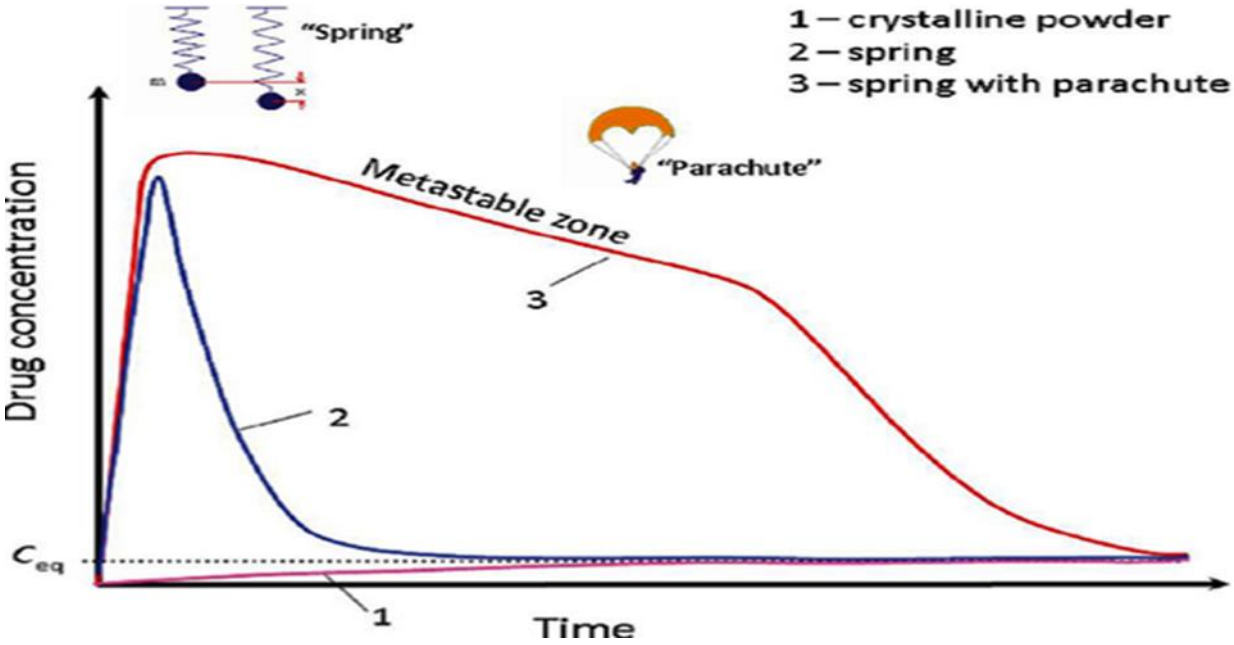


Figure 6: Spring and parachute concept

The impact of cocrystallization on drug solubility can be assessed by studying the technology's application on some drugs. For example, approximately fifty-three and hundered times enhancement caused in solubility profile of ketoconazole by synthesizing its salts and cocrystals respectively. Cocrystals of antitumor drug 6-mercaptopurine with nicotinamide also showed two times higher dissolution as compared to its pure drug. The solubility of pterostilbene was increased sixfold by combining it with piperazine (43).

4.2 Improvement of permeability of drug

Permeability of a BCS class-III drug, 5-fluorouracil, was enhanced by cocrystallization with different coformers such as 3-hyroxybenzoic acid and cinnamic acid. The partition coefficient influences drug permeability based on log P values (C log P) for the unchanged form of the drug. The formation of Hetero synthon between drug and coformer improved cocrystal permeability (44).

4.3 Bioavailability

Oral bioavailability of baicalein was increased by the formation of cocrystals with nicotinamide as indicated by 2.49 times higher peak plasma concentration (Cmax) and 2.80 times higher area under the curve (AUC) in rats compared to pure drug. Bioavailability is defined as the rate and extent of pure drug that reaches into systemic circulation.

4.4 Increased drug residence time at the action site:

Alteration of physicochemical properties can be in either directions i.e. there are example where instead of increase in solubility or dissolution profile of the drug, a decrease has also been observed. For instance, sulfacetamide a drug used as an antibiotic to treat ocular infections, have low residence time at its site of action due to its high solubility. Forming its cocrystals exhibited lower solubility than the reference drug and hence have increased residence time at site of action (45). This means this concept of cocrystallization can be applied to either extended release or immediate release formulation.

4.5 Tabletability:

Cocrystallization of the medication and the coformer can have an impact on crystal packing, tabletability, and compaction, all of which are significant criteria to consider throughout the preformulation investigation. The compaction behavior of paracetamol cocrystals including trimethyl glycine and oxalic acid was shown to be superior to that of the pure drug. The formation of cocrystals with 4-aminobenzamide and isoniazid improved the tabletability of resveratrol (46). Tabletability of cocrystals was higher than that of pure drug or coformers. Cocrystallization was used to change the mechanical characteristics of the API, and cocrystals of vanillin isomers with the same coformer had better tabletability than isomers and coformers.

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