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PHARMACEUTICAL CO-CRYSTAL: A TECHNIQUE FOR ENHANCEMENT OF PHYSICOCHEMICAL PROPERTIES OF DRUGS

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ABSTRACT

In development of new product major constraints are poor aqueous solubility and low oral bioavailability. Crystallization emerge as potential technique for enhancement of solubility of poorly aqueous soluble drugs also helps to improve physicochemical with preserving the pharmacological properties of the API. Cocrystals are solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates/hydrates nor simple salts. It is multicomponent system in which one component is API and another is called coformer. Coformer selection is the main challenging step during cocrystal synthesis, so various screening methods for the selection of coformers was explained. This article also summarizes differences between cocrystals with salts, solvates and hydrates along with the implications and limitations of cocrystals. It also provides a brief review on different methods of cocrystal formation and characterization technique of cocrystals.

KEYWORDS: Pharmaceutical cocrystals, Cocrystallization, Coformers, Solubility, Stability, Bioavailability, Dissolution, Grinding, Supramolecular synthons.

INTRODUCTION

Pharmaceutical cocrystals are solids crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. Thus, it is a multiple component crystal modified by intermolecular interaction such as hydrogen bonding, van der waals force, π–π interactions, and halogen bond between an active pharmaceutical ingredients (drug) and coformer.[1,2]

As a promising formulation, pharmaceutical cocrystals can improve some of the physicochemical properties of APIs, such as the solubility, dissolution rate, bioavailability, and stability, without altering their inherent chemical structures.[3,4,5] Meanwhile, the guidance for industry regulatory classification of pharmaceutical cocrystals announced by the U.S. Food and Drug Administration (FDA) claims that cocrystals, as a drug product intermediate or a fixed-dose combination product, should substantially dissociate before reaching the site of pharmacological activity.[6,7]

Actually, cocrystals are metastable solids because of their weak intermolecular interaction and easily dissociate into their respective components in solution.[8,9]

It is essential to explore the detailed behaviours of pharmaceutical cocrystals between their dissolved and dissociated processes, which will be beneficial to advance the development and application of pharmaceutical cocrystals.

Pharmaceutical cocrystal solubility commonly comprises a dissolution–dissociation process, and its evaluation is based on kinetic solubility, thermodynamic solubility, and the intrinsic dissolution rate. Kinetic solubility usually indicates a dynamic process such that the concentration fluctuations vary with time during cocrystal dissolution and depends on parameters such as the surface area, particle size and distribution, fluid dynamics, and experimental apparatus.[10] However, thermodynamic solubility focuses on the dissolved extent of the cocrystal when all the cocrystal components achieve dynamic equilibrium in the solution phase entirely.[11] The intrinsic dissolution rate concentrates on how the powder compacts affect the drug dissolution under a constant temperature and surface condition, which will contribute to approximately simulating the *In-vivo* behaviours of drug formulation.[12]

The process of solvation is a vital factor for the cocrystal dissolution–dissociation process in the human gastro-intestine that is related to coformer solubility, the type and concentration of surfactants, and the ion concentration in dissolution media. In addition, cocrystal solubility is influenced by the strength of the crystal lattice that is associated with the crystal stacked form and intermolecular distances of API and CCF.[13]

Difference between cocrystals, salt, solvates and hydrates

USFDA defined the cocrystal, salt and polymorphs in the draft guidance. The polymorphs are defined as the compound which are present in the different crystalline forms such as solvates or hydrates (also known as pseudopolymorphs). Polymorphs have different lattice arrangement and also, they have different physicochemical properties due to their crystal lattice structures. Salts are the compounds which are formed by complete transfer of proton from one compound to another.[14,15,16,17] Salts and cocrystals can be differentiated based by a proton transfer from an acid to base. A complete transfer of proton takes place between acid-base pairs, whereas, no proton transfer occurs during cocrystal formation. Two components are bound to each other by non-covalent interactions such as hydrogen bonding, π-π stacking, van der Waal forces. A prediction can be made by ΔpKa value whether cocrystals are formed or not. It is generally accepted that a salt will be formed if the ΔpKa value is greater than 3 and ΔpKa value less than 0 will lead to the formation of cocrystals. This parameter is not accurate to predict the formation of cocrystals in solids between the ΔpKa values 0 and 3 but the possibility of salt formation will increase when the ΔpKa increases.[18,19] Cocrystals and solvates can be differentiated based on their physical state of the components. The compounds which are liquid at room temperature are called as solvates. Whereas those compounds which are solid at room temperature are called as cocrystals. If the solvates contain water as a solvent in their crystal lattice then they are known as hydrates.[20] Solvates/hydrates are commonly formed during the cocrystallization via solution or liquid assisted grinding[21] and they can alter physicochemical properties of API's. Stability of solvates will be different from unsolvated forms because of presence of solvent in crystal lattice. Solvates/hydrates are quite unstable, because they lose solvent/water at high temperature and low humidity during storage and the physiochemical properties will be different for hydrated/dehydrated forms.[22] Different polymorphic cocrystals and solvates of caffeine and anthranilic acid were prepared by using different solvents via liquid assisted grinding. [23]

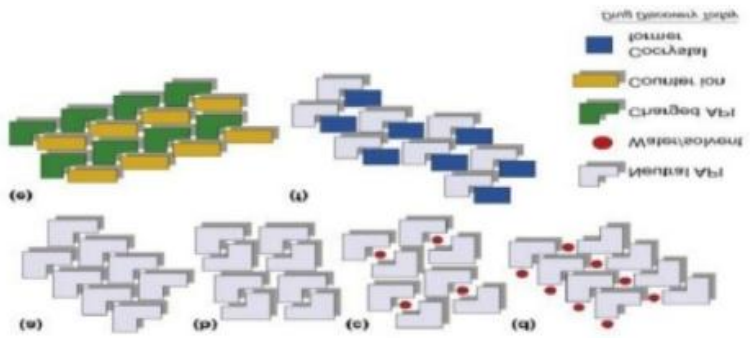

Fig. 1: Schematic representation of (a) pure API; (b) polymorphs of API; (c) clathrates solvates/hydrates of API, (d) solvates/hydrates of API, (e) salt of API, (f) pharmacetutical cocrystals of API.

Pharmaceutical cocrystal design strategies

Pharmaceutical cocrystals have rapidly emerged as a new class of API solids demonstrating great promise and numerous advantages. Much work has focused on exploring the crystal engineering and design strategies that facilitate formation of cocrystals of APIs and cocrystal formers. In order to get a desirable cocrystal product of an API with limited aqueous solubility, the first step is to study the structure of the target API molecule and find out the functional groups which can form intermolecular interaction with suitable coformers. Intermolecular interaction includes van der waals forces, p-p stacking and most common hydrogen bonding.[14]

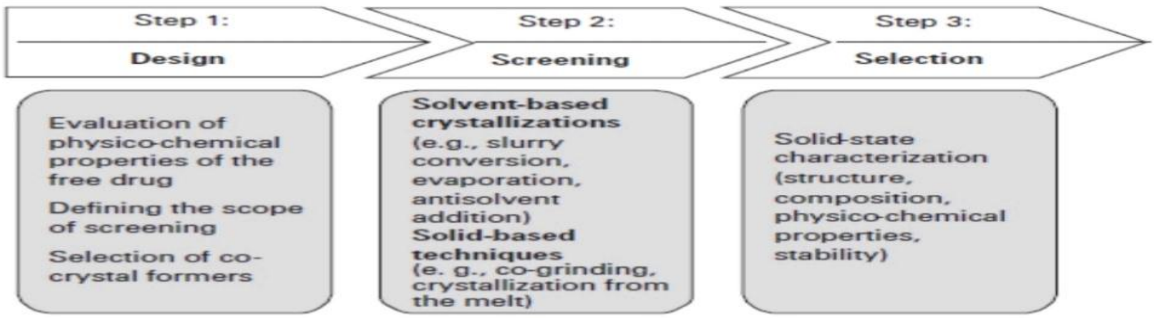

Fig 2: A general guideline for Cocrystal design and screening.

★ **Selection of appropriate co-formers**

The co-former can be anything like amino-acid, vitamin, excipient, preservative, minerals and other API too.[24] Sometimes co-formers can be neutraceuticals which will have additional beneficial along with API.[25] One of the main challenges in pharmaceutical co-crystal development is the selection of co-formers that are compatible with a particular API.[26] For selection of suitable coformer and screening of cocrystals, researchers have used some different knowledge based approaches which include supermolecular synthon, hasen solubility parameter, Cambridge Structure Database (CSD), *pKa* based models, hydrogen bonds, Fabian's method etc.

Supramolecular Synthon Approach

A pharmaceutical cocrystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure.[14,26] The term synthon was coined by Corey and defined as "structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions".[26,27] A supramolecular synthon is a pattern that is composed of molecular and supramolecular elements. When crystal patterns repeat regularly, the pattern of interactions can be called a supramolecular synthon.[14,15]

Supramolecular synthons are further categorized into:

(a) Supramolecular homosynthon: composed of identical self complementary functionalities

(b) Supramolecular heterosynthons: composed of different but complementary functionalities.[14,15,27]

Single-component or compounds containing the functional groups can be sustained by supramolecular homosynthons whereas; supramolecular heterosynthons can dominate in the presence of other competing functional groups. This concept may be better explained with the help of following fig.

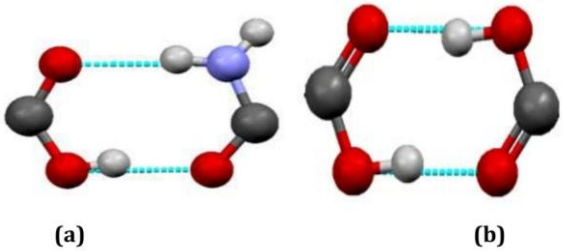

Fig. 3: Types of supramolecular synthons.

a) Supramolecular homosynthon [In this case between two carboxylic acid groups]

b) Supramolecular heterosynthon [In this case between carboxylic acid and amide group]

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

1. Homosynthon formed between carboxylic acid dimer
2. Heterosynthon formed between carboxylic acid group and pyridine
3. Homosynthon formed between amide dimer
4. Heterosynthon formed between carboxylic acid group and amide Group
5. Heterosynthon formed between alcohol and ether group.

Generally heterosynthon are more robust than homosynthons. e.g. acid–amide heterosynthons favored over both carboxylic acid and amide homodimer.[27,28,29] The ability to form the supramolecular homosynthons of functional groups was amides>acids>alcohols. The supramolecular homosynthons should be broken and lead to formation of heterosynthons when other groups were present in the complexes.[15,30]

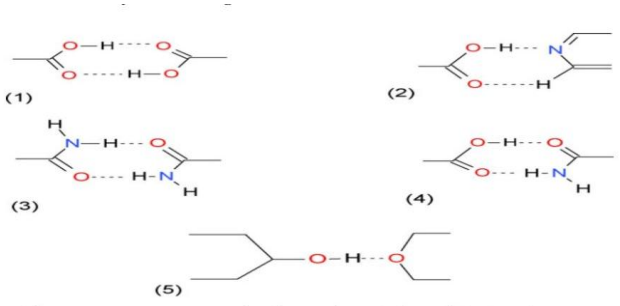

Fig. 4: Typical hydrogen bond in crystal engineering.

Supramolecular heterosynthons are generally more favoured than homosynthons, e.g., the acid- amide and the acid-pyridine heterosynthons are commonly used as compared to carboxylic acid and amide homodimers.[29]

The most common supramolecular synthons in Crystal Engineering are:-

★ **Hansen Solubility Parameter**

Miscibility of a drug and coformer, as predicted by Hansen Solubility Parameters (HSPs), can indicate cocrystal formation and guide cocrystal screening. Predicting the miscibility of cocrystal components using solubility parameters can guide the selection of potential coformers prior to exhaustive cocrystal screening work.[14,26,31.]Cocrystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry, which are solids at room temperature and are held together by weak interactions, mainly hydrogen bonding. By definition, cocrystals are miscible systems at a molecular level. It is therefore hypothesized that an indication of the miscibility of the component molecules in the solid state could predict the likelihood of cocrystal formation.[26, 31]The concept of a solubility parameter was introduced by Hildebrand and Scott, who proposed that materials with similar values would be miscible.[26,32] The Hansen solubility parameter (HSP) model, which was developed later, is based on the concept of dividing the total cohesive energy into individual components (dispersion, polar and hydrogen bonding).[26,31,33] The solubility parameters (i.e. cohesion energy parameters) can be used to carriers the physicochemical properties such as solubility, melting point, etc. of a material.[26,31,34]The cohesive energy is the sum of the forces (van der waals interactions, covalent bonds, hydrogen bonds and ionic bonds) that hold the material intact.[26,31] The cohesive energy per unit volume is termed the cohesive energy density (CED). The CED can be used to calculate the solubility parameter (δ) based on regular solution theory restricted to non-polar systems, as follows

$$\delta = (CED)^{0.5} = (\Delta E_V / V_m)^{0.5} \qquad (1)$$

Where,
EV is the energy of vaporisation
Vm is the molar volume
δ is measured in units of $(J/cm3)^{0.5}$, or $(cal/cm3)^{0.5}$

Attempts have been made to extend the Hildebrand and Scott approach to include polar systems and strongly interacting species. One of the most widely accepted approaches, using HSPs, proposes that the total force of the various interactions can be divided into partial solubility parameters, i.e. dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h). These partial solubility parameters represent the possibility of intermolecular interactions between similar or different molecules. The total solubility parameter (δ_t), also called the three-dimensional solubility parameter, can be defined as follow

$$\delta t = (\delta^2_d + \delta^2_p + \delta^2_h)^{0.5} \qquad (2)$$

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

As other method requires practical knowledge, the group contribution method is a commonly used theoretical method that only requires knowledge of the compound's chemical structure to calculate the HSPs. The partial solubility parameters can be calculated using the combined group contribution methods of Van Krevelen–Hoftyzer and Fedors as follows:[26,31,35,36]

$$\delta_d = \frac{\sum_i F_{di}}{\sum_i V_i}$$

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

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

Where,
i is the structural group within the molecule, Fdi is the group contribution to the dispersion forces, Fpi is the group contribution to the polar forces, Fhi is the group contribution to the hydrogen bonding energy, Vi is the group contribution to the molar volume.

It was demonstrated that the two components should be miscible if total HSPs difference was<7MPa0.5, otherwise immiscible 68. Another method estimates the miscibility of two components if the difference is ≤5 MP0.5 between two substances which are supposed to be cocrystal formation. The predicted miscibility of drug/coformer systems by Hansen SPs was correlated with miscibility predicted by DSC and possible structure of cocrystals was determined confirmed by findings of FTIR & PXRD.[26]

★ **Cambridge Structural Database**

The Cambridge Structural Database (CSD) is a repository for small molecule crystal structures. Scientists use single-crystal x-ray crystallography to determine the crystal structure of a compound. Once the structure is solved, information about the structure is saved but in CSD scientists can search and retrieve structures from the database. Scientists can use the CSD to compare existing data with that obtained from crystals grown in their laboratories. The data gathered in the CSD for every passage can be considered in three classes. Firstly, there is the text-based (and sometimes numeric) information, containing the bibliography (i.e. full literature reference, where

appropriate), chemical names and formulae, some experimental information about the crystal structure determination procedure, and any other information that may be available (e.g. compound's use, colour and shape of crystals, etc.). Secondly, there is chemical connectivity information in the form of a 2D structural diagram which is the basis of much of the sophisticated search mechanisms for the CSD System. Thirdly, there is the crystallographic information, consisting of unit cell dimensions and space group, and atomic coordinates. In this third category where the true value of the database lies.[26,15]

★ Hydrogen Bond

The success of cocrystal design by utilizing hydrogen-bonded supramolecular synthons clearly shows the importance of hydrogen bond in forming cocrystals. After metal co-ordination bonds and ionic interactions (e.g. dipole-dipole) the strongest interactions in crystal engineering are hydrogen bonds. Due to the strength, directionality, and ubiquitous presence of hydrogen bonds in organic molecules, it is also termed as the 'key-interaction' in crystal engineering. For most pharmaceutical cocrystal structures, hydrogen bonds take an important role in directing intermolecular recognition between an API and a coformer molecule. A graph-set notation system introduced by was used widely to describe and label hydrogen bond motifs.[26,37,38] In the graph-set system four principal motifs are used: chains (C), dimers (D), rings (R), and intramolecular hydrogen bonds (S), as descriptors of hydrogen-bonded molecular solids. Additionally, the following guidelines were proposed to facilitate the design of hydrogen bonded solids: (1) all good proton donors and acceptors are used in hydrogen bonding; (2) if six-membered ring intramolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen bonds (3) the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation, form intermolecular hydrogen bonds to one another.[26,37]

★ pKa rule

Cocrystals or salts formation can be predicted by proton transfer between acid and base. The formation of salts or cocrystals can be predicted by determining the ΔpKa=[pKa (base)–pKa (acid)]. It is generally accepted that proton transfer will occur from acid to base if the difference in the pKa values is greater than 2 or 3. A smaller ΔpKa value (less than 0) indicates the formation of cocrystals whereas higher value (more than 2 or 3) indicates the formation of salts.[15,18,19] But the intermediate value of ΔpKa between 0 and 3 was unable to give a clear cut distinction between cocrystals and salts. A co-crystal to salt continuum exists between 0<ΔpKa < 3 values.[15,18,19,39]

The nature of hydrogen bonding (neutral or ionic) during the formation of cocrystals between polycarboxylic acid and bipyridine compounds was analyzed with different compounds in the ΔpKa range -2.5 to +2.5 and predicted that the carboxylic acid-……..pyridine (OH…….N) interaction will be neutral if ΔpKa less than 0 and interaction will be ionic (N+-H …….O -) when ΔpKa more than 3.75. The nature of the hydrogen bond would be intermediate i.e. (O- H N and/or N+-H ….O-) when the ΔpKa between 0 and 3.75 values.[15,19]

The formation of ionized and non-ionized complexes was predicted by calculating the pKa values (ΔpKa) and a linear relationship was found between ΔpKa and probability of proton transfer between acid-base pairs. Cruz Cabeza (2012) calculated the difference in aqueous pKa values (ΔpKa) for 6465 crystalline complexes containing acid-base pairs and separated the complexes in three zones on the bases of ΔpKa values. In Zone 1 (ΔpKa<-1), about 99.1% crystalline complexes were observed non-ionized i.e. no transfer of proton whereas in zone 3 (ΔpKa>4), 99.2% crystalline complexes were found to be ionized i.e. complete transfer of proton. But in zone 2 (-1 < ΔpKa > 4), both ionized and non-ionized crystalline structures were observed. The relative occurrence of ionized complexes increases linearly with increasing the ΔpKa values. It was observed that during the salt formation, probability of proton transfer between acid –base pairs increased 17% with increase in one ΔpKa values from ~ 10% at ΔpKa= -1 to ~ 95% at ΔpKa= 4. It would be found that the ΔpKa rule is widely used for designing the formation of salts and cocrystals.[15,40]

Fabian's method

Different sets of reliable cocrystal forming structures were extracted from the CSD and the molecular descriptors (single atom, bond and group counts, hydrogen bond donor and acceptor counts, size and shape, surface area and molecular electrostatic) were calculated for each molecule. On the basis of calculated molecular properties, the database described pairs of molecules that were able to form cocrystals. The strongest descriptor correlation was related to the shape and polarity of cocrystal formers.[15,41]

COSMO-RS

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

For screening of suitable coformers for an API, COSMO-therm software based on COSMO-RS fluid phase thermodynamic approach was used to describe the miscibility of coformers in super cooled liquid (melt) phase.[15,42] COSMO-RS thermodynamics is based on the statistical physics of interacting molecular surface segments. The polar and hydrogen bond interaction energies are quantified based on the surface screening charge densities, which result from a

quantum chemical continuum solvation calculation.[15,43,44]

Due to its ability to treat mixtures at variable temperatures and to compute accurate solvation energies based on first- principles, it has become very popular in chemical engineering and in wide areas of physical and medicinal chemistry. COSMO-RS being a fluid phase thermodynamics model, we can compute a virtually liquid mixture of the cocrystallization components and obtain the excess enthalpy of stoichiometric m:n mixtures, typically 1:1 mixtures, created out of the pure components A and B:

Hex = HAB – mH pure,A – nHpure,B

Hpure and HAB represent the enthalpies in the pure reference state and in the m:n mixture respectively. Hex contains all enthalpic contributions and is not limited to hydrogen bonding interactions, though those may be separated from the overall enthalpy by COSMOtherm. In our on-going studies we found that the excess enthalpy Hex is a superior descriptor to the pure hydrogen bonding interaction. Compounds with Hex<0 are strongly interacting in solution (equivalent to a negative deviation from Raoult's law) and prefer the mixture enthalpically over their pure liquids. We demonstrate that Hex corresponds nicely with an increased probability of forming cocrystals. Since it is plausible to assume, that such liquid phase enthalpic preference will also certain in a mixed crystal, i.e. in a cocrystal of the components, it is plausible to use the liquid phase excess enthalpy as a guide for cocrystal screening. Within several other applications in many areas of chemistry, chemical engineering and pharmaceutical chemistry, COSMOtherm has been proven to be a valuable tool for solvent screening, i.e. for screening for a suitable solvent for a given solute X.[15,43,44,45]

Synthon matching

Synthon matching is the computational theory used to investigate the intermolecular interactions in the crystal structure and is an important tool for the cocrystal screening. The major limitation of this approach is that *in-vivo* properties of cocrystals cannot be determined exactly. This synthon approach is used to estimate the possibility of hydrogen bond formation between API and coformer.[46,47] Over the past few years, various methods have been evolved to determine the intermolecular interactions in crystal structures qualitatively and quantitatively, such as the conformational similarity index for proteins, graph set analysis for hydrogen bonds, Voronoi-Dirichlet polyhedral for crystal packing, continuous symmetry measures, and the Hirshfeld surface by using computer programs such as ESCET, COMPACK, TOPOS, Crystal Explorer, and dSNAP, respectively.[46,48]

Physicochemical Properties Can Be Altered With Cocrystal Techniques

The alteration in molecular structure assemblies may lead to change in physical properties. The expected changes in physicochemical properties would occur such as solubility, melting point, stability, tabletability, bioavailability and permeability.[49]

[1] Solubility

As solubility affects the absorption and bioavailability of drug so solubility enhancement is essential phenomenon in case of pharmaceutical research.[49]Solubility is an important parameter to investigate the formulation of poorly soluble drug. Traditional methods for improving solubility of water soluble drug include salt formation, solid dispersion (emulsification), particle size reduction (micronisation) and so amongst which cocrystallization has been used by several researchers.[50] Co-crystal of ionized drug Co-crystal solubility is mainly depending on solution pH. The prediction of this can be done by calculation based on degree of ionization and dissociation equillibria of cocrystals.[49,51,52]

[2] Melting point

Melting point is a physical property of solids, which is used to determine the purity of the product with sharp melts and narrow ranges.[46,23] The solid having low melting point in comparison with other solid shows lowered susceptibility to degradation.[49] The melting point of a drug is also related to its solubility, stability, tabletability, flow property and processability of drug formulation. The melting point of cocrystals in general, differ from those of the individual components due to changes in molecular interactions, composition and structure compare the melting points of some drugs, coformer and corresponding of pharmaceutical cocrystals.[50] Melting point contributes a major consideration during formulation of cocrystals. Cocrystals with high melting point are usually required but they have poor aqueous solubility whereas low melting point cocrystals have stability, so, further study within this area is required.[46]

[3] Permeability

Drug absorption and distribution of drugs mainly depends upon the permeability of drugs across the biological membrane. Permeability study of hydrochlorothiazide and Cocrystals with different coformers was studied by using Franz diffusion cells. The amount of drug flux in all cocrystals was higher as compared to pure drug except for sccinamide cocrystals. Cocrystals permeability was improve due to formation of hetrosynthon between drug and coformer.[46]

[4] Bioavailability: Bioavailability is defined as the rate and extent of pure drug that reach into systemic circulation.[46,54] Low oral bioavalibility of APIs is one of the major challenges in development of formulation,

which help of cocrystallization one can enhance or improve the bioavailability of API. Many researchers has been enhanced the bioavailibility of different drugs with conversion in cocrystal form.[56] For ex. Pinky et. al formulated cocrystals tablets dosage form of clarithromycine to enhance the bioavailability. As clarithromycin in BCS class II drug author prepared cocrystals by using Urea as coformer by solvent evaporation method. Developed tablet Formulated and evaluated. Author, concluded that the formulated tablets of clarithromycin cocrystals showed improved solubility and *In-vitro* drug release profile as compared to marketed tablet, and thereby increase oral bioavalibility and therapeutic effects.[49]

[5] Stability

Stability study is extremely important during the development of new dosage formulation.[53] During cocrystallization there is alteration in molecular assemblies that changes the mechanical properties of solids. For this reason study of stability of polymorphic cocrystals is major concern for investigators. Several stability should be performed during development of pharmaceutical cocrystals such as relative humidity stress, chemical stability, solution stability and photostability study.[46] Temozolamide (TMZ) - succinic acid, TMZ-malic acid, and TMZ-tartaric acid cocrystals, an anticancer drug, are known to be more stable at pka 2-6 than the pure drug with temperature 40°c and relative humidity after week except TMX-succinic acid and TMZ-oxalic acid. This stability pattern was revealedusing PXRD. [2,55]

Methods Used For Cocrystal Preparation

Cocrystals can be prepared by liquid based technique and solid based technique.

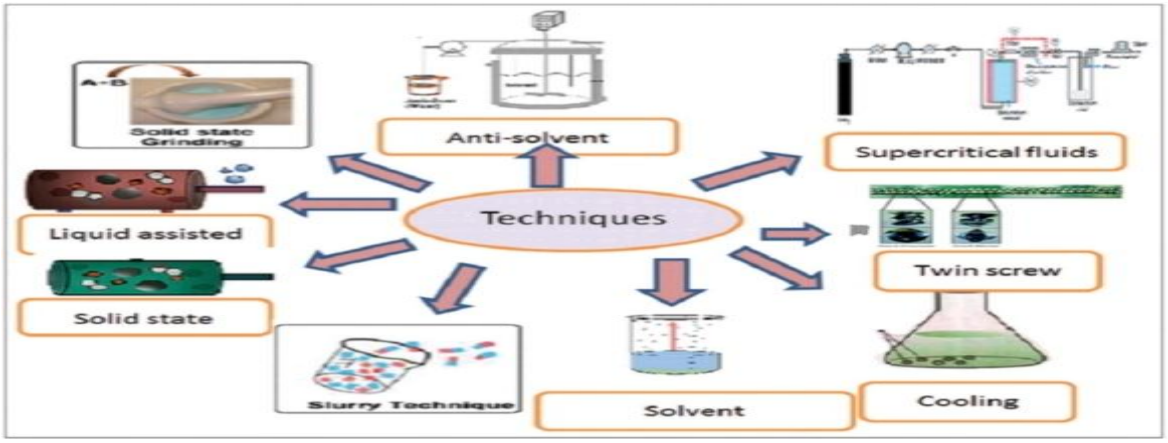

Fig. 4: Techniques of cocrystal formation.

[I] Liquid- based method: The liquid - based method involved solvent evaporation,[56] slurry conversion method,[57] solvent drop grinding,[46] Liquid assisted grinding,[58] antisolvent method,[59] reaction crystallization method,[60] ultrasound-assisted solution technique,[61] supercritical fluid atomization technique,[62] spray drying technique.[63]

1] Solvent evaporation method: This is most conventional technique of cocrystallization which includes super saturation of solution by evaporation, cooling and addition of solubility changing solvent or substance.[49] In this method both API and coformers are dissolved with a continuous stirring in a boiling solvent until the final volume becomes small. This boiling solution is allowed to cool slowly to form cocrystals in either open air or in hot air oven. During the process of dissolution, the functional moiety in the API and coformer interchange with each other to form new hydrogen bonds which is most widely used by many researchers. For ex. glutonic acid cocrystals. Norfloxacin cocrystals were synthesized with Isonicotinamide, malonic acid and malefic acid as coformers.[49]

2] Slurry conversion method: It is one of the easiest technique for the crystallization process where cocrystal formation take place.[2] Slurry is prepared by addition of solvents in the mixture of API and suitable coformers.[15] The solvents is decanted and solid material is dried and characterized by different methods for evaluation. This method is selected for the preparation of cocrystals when the drug and coformer should be stable in the solvent. Cocrystal of aspirin designed with 4,4-Dipyridil as a coformer by using slurry crystallization method. However the yield obtained was not sufficient as compared with solvent drop grinding method.[49,64] The major disadvantage of this method is that it requires large amount of solvent.

3] Solvent drop grinding: Solvent drop grinding is emerging step in advancement of polymorphic selectivity in various models of cocrystals.[49] In solvent drop grinding technology the API and coformer are taken in equimolar ratios and these equimolar ratios are grind in a mortar and pestle to this addition of few amount of solvent. The solvent used behave as a catalyst which enhance crystal formation. This technique is also suitable for the synthesis of amorphous cocrystals. This method is advantageous than solid state grinding in terms of yield, ability to control polymorph production, better product crystallinity, and a larger scope of cocrystal form.

4] Liquid - assisted grinding: Beside providing faster rate of cocrystal formation than dry grinding, it is more reliable and suitable method as well.[2] Is commonly used method to form cocrystals. It is know to be ecofriendly method for industrial level production due to less amount of solvent used.

5] Antisolvent method: In this method coformer and active pharmaceutical ingredient (API) was precipitated or recrystallization using buffers (pH) and organic solvents as an antisolvent.[15]

6] Reaction crystallization method: Drug and coformer are solvated separately in either methanol or other suitable solvent and finally mixed together for crystal formation under its solubility limit. To determine stoichiometry of the complex precipitates are collected and examined by high-performance liquid chromatography.[2,65] The reaction is fast or very fast, and the mixing conditions influence the product size distribution.

7] Ultrasound - assisted solution technique: Ultrasound has been generally utilized for inciting nucleation in solution and co-crystallizing small molecules.[27] In this technique, API and cocrystal former are dissolved together in a solvent and the solution is kept in a sonoreactor to form the solution turbid. Cold water is supplied during the sonication to maintain the constant temperature of sonicator and prevent fragmentation. The solution is kept overnight for drying. Pure cocrystals were obtained by this method and the purity of cocrystals can be assessed by using x-ray diffraction study.[15,66]

8] Supercritical fluid atomization technique: A recently emerging technology in pharmaceutical industry, utilize supercritical fluids. Supercritical fluids use offers additional advantages compared to the other co-crystal production methods.[15] This method is most useful technique for crystal preparation and to prevent the thermal degradation of compound.[2] In this technique, solid sample is dissolved in a suitable solvent (organic or inorganic) which is injected into a supercritical fluid (under high pressure) resulting in a large decrease in solution density forming cocrystals.[2,68] In supercritical antisolvent (SAS) method, the cocrystals are prepared from solution by the antisolvent effect of supercritical fluid.

Advantages of supercritical fluid technology

1. Rapid one step processing.
2. Moderate operating temperature, has made supercritical fluids a fascinating technology specially for heat sensitive materials.
3. It minimizes the use of hazardous and toxic organic solvent. [15]

Limitaion of supercritical fluid technology (SFT)

The elevated pressure required, high maintenance cost and requirement of the acessories/auxiliary equipments limits the use of SFT for most of the pharmaceuticals. Therefore, it seems that this technique can not completely substitute the conventional techniques as it is not applicable for processing of all pharmaceuticals.[15,67]

9] Spray drying technique: It is very commonly employed method for the preparation of cocrystals because of its quick, continuous, and single step process.[2] In this technique, solution containing API and coformer is allowed to evaporate over hot air stream.[2] Spray drying process will offer a unique environment for the preparation and scale-up cocrystals.

[II] Solid-based technique: It generally includes solid phase grinding, melt extrusion, and melts crystallization. In this method, API and coformer are melted and mixed together, resulting in the cocrystal formation in a fixed stoichiometric ratio. It is basically not suitable for thermolabile moiety, but it is easy, scalable, and continuous process.[2]

1] Grinding method: Over past few years grinding methods have been widely used method and found to be superior than other methods (solution or melt). Grinding techniques are of two types: neat or dry grinding and wet grinding.

a) Neat grinding (dry grinding)

In dry grinding, drug and coformer are mixed together in a stoichiometric ratio and ground them by using either mortar and pestle or ball mill. Nowadays, planetary milling systems are also available in a laboratory scale.[15,69]This method requires one or both reactant having sufficient vapour pressure in solid state.[14]The examples of cocrystals prepared by this method are carbamazepine-nicotine amide, piracetam-citric acid, and piracetam-tartaric acid.[50]

b) Wet grinding

Wet Grinding was performed in a similar manner that of neat grinding by addition of some drops of solvent in the mixture.[15,70,71]

2] Hot melt extrusion method

In this technique, API and coformers are transferred into a fixed controlled temperature system where they are melted and form cocrystals of new moiety.[2,72,] This technique is not suitable for thermolabile drugs because both drug and coformer should be mixed in a molten state. In this method, API and coformer are mixed in their molten state to enhance their surface contact without the use of solution (solvent), for example, pyrazinamide cocrystals.[2,76]

Evaluation and Identification of Co-Crystals

1] Fourier-transform infrared spectroscopy: It is widely used process for the prediction and determination of chemical conformation, intermolecular interactions, and communion study between API and coformers. This method is quick, non-destructive, prone to changes in

molecular structure and can also detect a functional group.[2]

2] Differential sacanning calorimetry: It is used for the determination of cocrystal formation, determined by the existence of exothermic crest followed by endothermic crest in the DSC spectra.[2,76] The cocrystal formation is determined by the presence of crest (peaks) present in the compound. It is also useful for determining the melting point, polymorphic nature, glass temperature, heat of fusion, and exothermic or endothermic behavior of a compound or a molecule.[2,77]

3] Terahertz time-domain-spectroscopy (THz-TDS): Is an alternative tool to PXRD for the characterization of cocrystals. Chiral and racemic molecular and supramolecular structures can be distinguished by terahertz spectroscopy.[15,79] Terahertz spectroscopy was used to distinguish the identical molecular structure cocrystals of theophylline with different coformers (such as malic acid and tartaric acid) which were present in chiral and racemic forms.[15,80]

4] PXRD: PXRD is a characterization technique for the determination of solid - state structure of cocrystals at an atomic level. However, the problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, PXRD are utilised more frequently to verify the formation of cocrystals.[50] The PXRD pattern obtained from diffractometer were compared to each other for analysing the structure of cocrystals. It deals with the study of crystalline behaviour of a powder or a drug sample. Bolla et. al. carried out analysis of acematacin cocrystals using these analytical techniques. They revealed the crystalline cell dimension, purity, structure, and texture of this bulk sample.[2,81]

5] Raman spectroscopy: Is a tool for observation of crystallization process. It is used to differ coated between polymorps, salts, cocrystals, solid solutions and hydrated salts.[15,82]]There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystals products.[15,83,84,85]

6] Scanning electron microscope: Scanning electron microscope is the instrument used to determine the particle size and morphological analysis of cocrystals. A high energy electron beams scan the atoms that provide the information about the sample surface's topography.[46,86,87,88]

7] Dissolution study: Dissolution study is used to determine the amount of drug release with time in dissolution medium and predict the in vivo performance of the formulation.[46] The drug samples can be collected in the suitable quantity at predetermined time interval and can be examined with the help of suitable means like HPLC or UV.[46,89,90]

8] Solubility study: Can be assessed by Higuchi and Connors method for solubility determination. The solubility of pure drug, physical mixture and cocrystals can be determined in water or suitable medium given in the referred pharmacopoeia. Drug sample and medium should be added in a conical flask, and should be shaken for 24h at room temperature on rotary flask shaker. The entire samples should be protected from light by wrapping the flask by aluminium foil if the drug is sensitive to light. After 24h samples are filtered through Whatman filter paper and aliquots are suitably diluted and assayed by HPLC or UV at suitable wavelength.[26,46,91]

9] Stability study: Stability study provides the information about shelf life of drug products under different storage conditions. Drugs products should be kept in glass vials under variable environmental factors (such as humidity, temperature, light) for different intervals of time. After that, the samples are analysed for thermal study, drug release study, XRD study and FTIR study and compared with the results obtained before stability study.[46,92]

Regulatory Views

Co-crystal has increased huge significance in the pharmaceutical industry with the presentation of regulatory rules. In 2013, the FDA was the principal regulatory organizational to distribute direction on the regulatory classification of co-crystal.[27,93] Various approach have been used for coformer selection and screening of cocrystals, however each compounds has its own limitation. Mainly, those compounds should be used as coformers which are listed as GRAS by USFDA and EAFUS database but Gras status does not guarantee its use as cocrystal forming agents.[46] Development, screening and evaluation of new cocrystals of drugs require a lot of time and energy; however, various researchers have used some knowledge based approaches for selection of coformers, designing and screening of cocrystals, as highlighted in various sections.[26,46,55,94]

The fundamental criteria for the patentability of any innovation are novelty, utility and non-obviousness. Patent filing of cocrystal is related with their particular chemical composition, supermolecular systems in crystal structure and beneficial properties. Fruitful characterization of co-crystal and the evaluation of their pharmaceutical and biopharmaceutical properties are prime contemplation for successful patenting. The count of patents conceded to co-crystals and their techniques for preparing are panding yearly.[27,93]

Future Prospective

The co-crystallization technique is most beneficial for some drugs which undergo degradation because of certain condition such as basic or acidic environment or deficient of basic or acidic group for the formation of salt. Nowadays researchers are showing more interest towards co-crystals due its impeccable advantages. It

will be nothing unexpected if co-crystals become most significant in the pharmaceutical market.[26,95]

CONCLUSION

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

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