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CO CRYSTALS - A REVIEW

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ABSTRACT

The use of co crystal are non-ionic supramolecular complexes and can be used to altered physical property issues such as solubility, stability and bioavailability in pharmaceutical development without affecting chemical composition of API. Pharmaceutical co crystals technology in active pharmaceutical ingredient (API) crystallizations is as an enabling technology to bring improved pharmaceutical products to the marketplace as well as for improved drug delivery. Pharmaceutical co crystal is more thermodynamically stable than crystal form of drugs. The recent advancement in the co crystal development arises the possibility to produce material by designing with an improved physical property. Co crystal not only provides a technique for improvement of physicochemical property but also provide opportunity to the researchers of pharmaceutical companies regarding intellectual property. Dissociation of the API from its excipient in Co Crystals prior to reaching the site of action is desirable for pharmacological activity. The crystalline solid forms with improved physical properties may impact the pharmaceutical intellectual property landscape. Co crystals high throughput provides information on relationship between formation and chemical structure of the API and conformers. Factors affecting Co Crystals stability are reported and a co crystal is only expected to form if it is thermodynamically more stable than the crystals of its components.

Keywords: Co crystal, Hydrogen bonding, Novel approach, Solubility, Bioavailability Aspects.

INTRODUCTION:

Co Crystals are defined as multiple component structures whose components interact by non-covalent interactions such as hydrogen bonding or other weak intermolecular interactions rather than by ion pairing. An important approach to understanding and designing Co crystals is to employ supramolecular synthesis; in particular exploitation of supramolecular heterosynths [1]. In the framework of co crystals, supramolecular synthesis is a relatively low-risk strategy, as the approach employs theories of molecular recognition and self-assembly rather than creating covalent bonds.

A solid form can exist in two forms. They are amorphous and crystalline forms. Solid dosage forms

are mostly chosen as oral drug delivery systems in crystalline form a solid can exist as polymorphism, hydrate form, solvate form or co crystal forms as shown in Fig. 1. Chemists and engineers in the pharmaceutical industry prefer to deliver crystalline forms of their active compounds, mainly due to the characteristic stability of crystalline materials and the well-established impact of crystallization processes on purification and isolation of chemical substances.

The solid dosage forms of a drug (e.g. tablet, capsule, powder) are the most marketed and convenient forms as they are simple, easy to administer and make, and stable, while offering accurate dosage. Traditional drug product development comprises a sequence of unit operations involving complex material and process

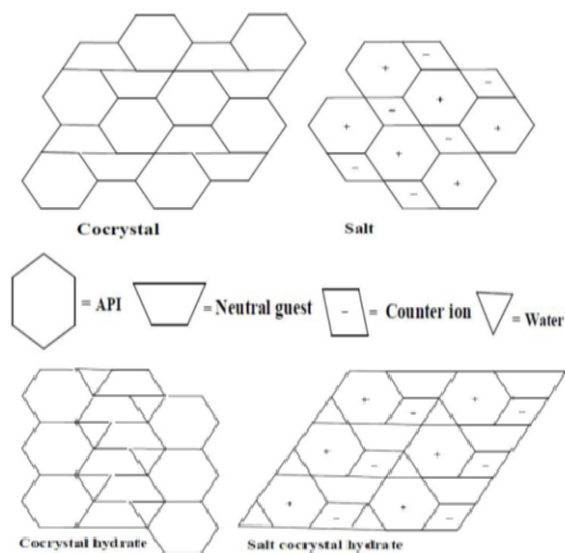


Fig. 1: Representation of a co-crystal, salt, co-crystal hydrate and salt co-crystal hydrate.

engineering activities, often empirically based. However, it is desirable to simplify the process of solid dosage form development for better control of the product quality and performance. This needs a thorough understanding of the interrelationships between solid-state structures, properties, performance and processes at a fundamental level, as has been discussed under the concept of the materials science tetrahedron [2].

Drug molecules can also crystallize with other guest molecules to form multicomponent crystals such as hydrates, solvates, salts and co crystals. Fig. 2 shows the possible solid forms of single and multicomponent crystals.

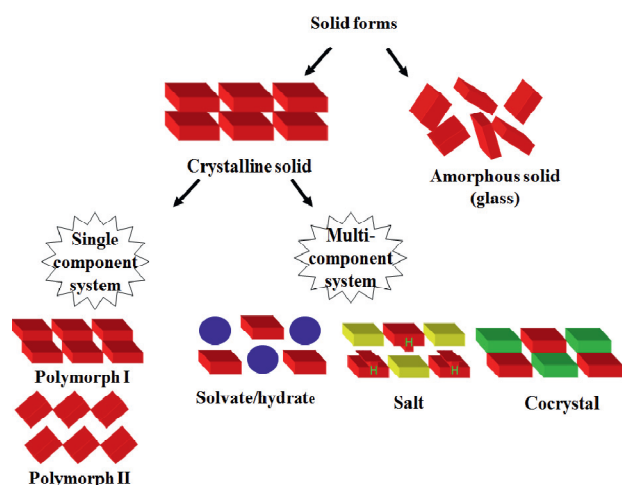


Fig. 2: Possible solid forms of a drug substance. Red, blue, yellow and green represent drug, water/solvent, counter ion, and co former molecules, respectively.

Co crystals and Salts:

To date, a universal and agreeable definition of what constitutes a co crystal is still unavailable. Within the academic literature, various parameters have been applied to the definition of what is and is not considered a co crystal, however, one broad commonality that is agreed upon is that all co crystals are crystalline materials comprised of at least two different components (or commonly called multicomponent crystals). Now, one's opinion as to what constitutes a "component" can be dramatically different, for example, solid, liquid, or gas and/or neutral or ionic species, etc., and this is usually where the differences in definitions arise. Furthermore, the use of "pharmaceutical co crystal" is commonplace and usually applied when an API is one of the molecules in the multicomponent crystal. Even though there are limitations with the co crystal definitions currently found in the literature, we do not see it necessary to complicate the existing debate by generating yet another definition for what constitutes a co crystal. In this review, the co crystalline examples presented herein will possess the following criteria [3].

- (1) An API, neutral or ionic form along with a neutral co former, held together through noncovalent, freely reversible interactions.
- (2) A co former, which may or may not be pharmaceutically acceptable.
- (3) And at least one measured physicochemical property. A pictorial description of possible multicomponent systems, including co crystals, salt co crystals, and salts along with their respective hydrates and solvates are displayed in Fig. 3.

Advantages of co crystal approach:

Co Crystals having several advantages such as no need to make or break covalent bonds, as compared to amorphous solids it is stable crystalline form, theoretical ability of all types of drug molecules such as weakly ionizable/non ionizable to form co crystals, the existence of numerous potential counter molecules such as food preservatives, pharmaceutical excipients, additives, and other API. Only solid form that is designable via co crystal engineering patentable expanding IP selections and can be produced using solid state synthesis green technologies high yield, no solvent or by products [10].

Solubility and bioavailability aspects of co crystal formation

Pharma industry use amorphous dispersions, co crystals, or salts to improve solubility. However, the interest in co crystals is gaining energy as co crystals can improve the dissolution rate and bioavailability of

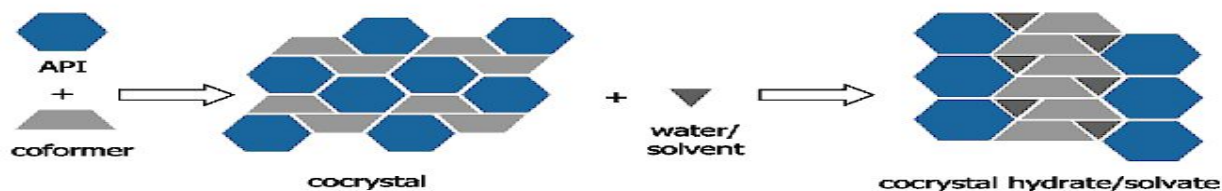
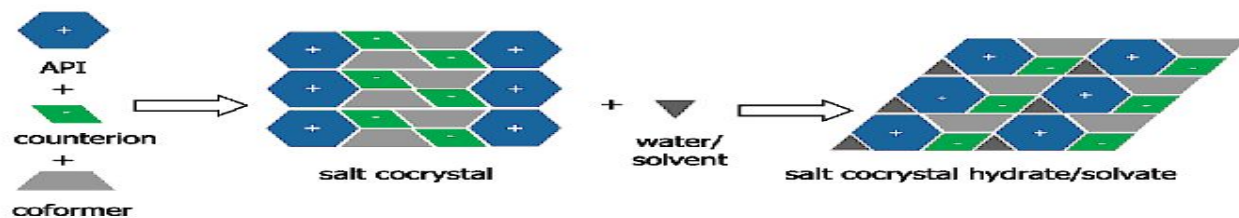
Example 1**Example 2****Example 3**

Fig. 3: Pictures displaying the more common solid-state strategies and their respected components.

Definitions of a Co Crystals

Cocrystal definitions	Authors
“A molecular complex that contains two or more different molecules in the same crystal lattice”	Stahly GP 2007 [4]
“Multi-component solid-state assemblies of two or more compounds held together by any type or combination of intermolecular interactions”	Bhogala BR and Nangia A 2008 [5]
Crystalline material made up of two or more components, usually in a stoichiometric ratio, each component being an atom, ionic compound, or molecule”	Childs SL and Hardcastle KI 2007 [6]
“Compounds constructed from discrete neutral molecular species...all solids containing ions, including complex transition metal ions, are excluded”	Aakeroy CB and Salmon DJ 2005 [7]
“Made from reactants that are solids at ambient conditions” “Structurally homogeneous crystalline material that contains two or more neutral building blocks that are present in definite stoichiometric amounts”	
“Synonym for multi-component molecular crystal”	Bond AB 2007 [8]
“A crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions, often including hydrogen bonding”	Jones W <i>et al.</i> , 2006 [9]

poorly soluble drugs. The sympathetic of the influence of co crystal components properties on the co crystal solubility is important to engineer Co Crystals with modified solubility. Co crystal approach uses solvates/hydrates and eutectics as a means to improve the solubility of poorly soluble compounds particularly Non-ionisable compounds. Solubility data have been reported as kinetic (or apparent) solubility or equilibrium solubility [11].

Polymorphism of co crystals

Co Crystals exhibit polymorphism. Most commonly, API's have hydrogen-bonding capability at their external which makes them more disposed to polymorphism, especially in the case of co crystal solvates which can be known to have different polymorphic forms. However, co crystal is only constant within a limited area of the phase diagram. Co Crystals of API with common pharmaceutical excipients becomes interesting as a tool to tune up solubility and absorption. Bisphosphonates (e.g. alendronate, risedronate, ibandronate) widely used in clinical practice are indicated for the treatment and prevention of osteoporosis. Their gastrointestinal adsorption is only about 1% due to their high hydrophilicity.

Screening of co crystals

The ultimate goal of co crystal screens is to discover a solid form of an API with improved physical properties. From this perspective, an efficient co crystal screening protocol can be split into three phase:

- ✓ Co crystal design;
- ✓ Co crystal screening and
- ✓ Co crystal selection.

General guideline for co crystal screening

Step-1 Design:

- ✓ Evaluation of physico-chemical properties of the free drug
- ✓ Defining the scope of screening
- ✓ Selection of co- crystal formers

Step-2 screening:

- ✓ Solvent-based crystallizations (e.g., slurry conversion, evaporation, antisolvent addition)
- ✓ Solid-based techniques (e. g., co-grinding, crystallization from the melt).

Step-3 selection:

- ✓ Solid-state characterization (structure, composition, physico-chemical properties, stability)

Solution based methods

- ✓ Large number of variables to test in search of conditions to nucleate and grow co- crystals: choice of solvent (where co crystal is less soluble form)
- ✓ concentrations
- ✓ temperature, cooling rates
- ✓ evaporation rates

Mechanisms and key factors that control co crystal formation:

Solution-phase mediated:

- ✓ **Nucleation** of co crystal is reliant on super saturation solvent selection, Stoichiometric reactant concentrations, where co crystal is less soluble form (similar Saturation), or
- ✓ **Nonstoichiometric** reactant concentrations, where co crystal is less soluble form (Dissimilar saturation).

Pharmaceutical co crystals:

An approach available for the enhancement of drug stability, dissolution and bio availability is through the application of crystal engineering to co crystals, generally referred to as molecular complexes. The physicochemical properties and the bulk material properties of the API can be modified, at the same time as maintaining the intrinsic activity of the drug molecule. Pharmaceutical co crystal formation is developing as an attractive alternative to polymorphism, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form design. The intellectual property suggestions of creating co crystals are also highly relevant.

The key difference between solvates and co crystals is the physical states of the individual components .At room temperature if one component is liquid then the crystals are assigned as solvates. While if both components are solids at room temperature then the crystals are called as co crystals. Though, co crystals have a propensity to be a product of more rational design and more stable, predominantly as the co crystallizing agents are solids at room temperature.

The key payments associated with approach of co crystallization to alter the properties of pharmaceutical solids are the hypothetical ability of all types of drug molecules to form Co Crystals including weakly ionisable and non-ionisable, and the presence of frequent, potential counter-molecules, including preservatives, food additives,

pharmaceutical excipients as well as other drugs, for co crystal synthesis. Major advantage for the pharmaceutical industry is co crystal synthesis which may offer is an opportunity to address intellectual property (IP) issues by spreading the life cycles of old API.

Mechanism for co crystal synthesis

Amorphous phases generated by pharmaceutical processes lead to co crystal formation during co grinding and storage. The mechanisms underlying moisture uptake generated co crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid) when solid mixtures with co crystal reactants were exposed to deliquescent conditions involve

- (i) Moisture uptake,
- (ii) Co-crystal aqueous solubility,
- (iii) Solubility and dissolution of co-crystal reactants,
- (iv) Transition concentration.

A molecular-level mechanism for two cases of mechanochemical co-crystallization via halogen bonds was reported and was based on the observation and structural characterization of intermediates that appeared in early stages of the reaction. The mechanism arises from the competition of strong and weak intermolecular halogen bonds of the N...I and S...I type and involves the initial formation of finite molecular assemblies, held together via N...I bonds that subsequently polymerize into infinite chains by cross-linking through S...I bonds. Co-crystallizations of exemestane and megestrol acetate improved initial dissolution rates compared to the respective original crystals. The mechanism of dissolution enhancement varied. With exemestane/maleic acid co-crystal, fine particle formation resulted in enhancement, whereas with megestrol acetate /saccharin co-crystal, enhancement was due to the maintenance of the co-crystal form and rapid dissolution before transformation to the original crystal [12].

The mechanisms of conversion of crystalline drugs to Co Crystals and factors affecting co crystal stability were reported. Co former solution concentration controlled the formation and stability of different stoichiometry co crystals. Studies with 1:1 and 2:1 carbamazepine-4-aminobenzoic acid co crystals indicated that the co crystal richer in co former was found more stable at higher conformer concentration. Co crystallization also occurred in solid mixtures of co crystal reactants. Co Crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with various carboxylic acid co formers were formed due to moisture sorption and

deliquescence in reactant mixtures. In the solid-state, co grinding carbamazepine with saccharin or nicotinamide formed co-crystals.

Crystal engineering and supramolecular chemistry in co crystal formation

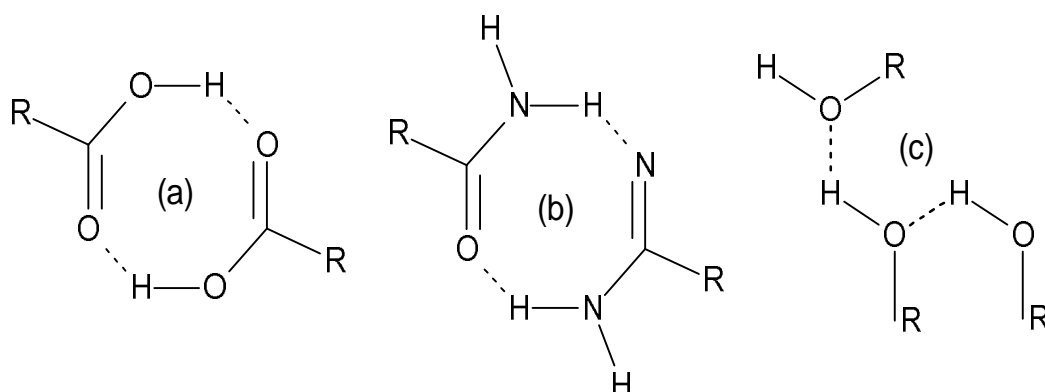
A pharmaceutical co crystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure. Crystal engineering affords a paradigm for rapid development of pharmaceutical co crystals. It can be defined as an application of the concepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are actual manifestations of self-assembly. Co crystals are constructed from intermolecular interactions such as Vander Waals contact forces, π - π stacking interactions, and hydrogen bonding [13].

Crystal engineering involves modification of the crystal packing of a solid material by changing the intermolecular interactions that regulate the breaking and formation of noncovalent bonds, such as hydrogen bonding, van der waals force, π -stacking, electrostatic interactions, and halogen bonding. The term supramolecular synthon is frequently used in the research field of co crystals. It is defined as structural units within supramolecules which can be formed and/or assembled by known conceivable interactions. Supramolecular synthons are spatial arrangements of intermolecular interactions and the overall goal of crystal engineering is therefore to recognise and design synthons that are robust enough to be interchanged between network structures. This ensures generality ultimately leading to the predictability of one, two and three dimensional patterns formed by intermolecular interactions. Representative examples of pharmaceutically acceptable co crystal formers that are able to cocrystallise with APIs include carboxylic acids, amides, carbohydrates, alcohols, and amino acids. The most common supramolecular synthons utilised in pharmaceutical co crystals are shown in Fig. 4.

Physicochemical properties of co crystals

Physical and chemical properties of co crystals are of great importance to the development of APIs. The overall motivation for investigating pharmaceutical co crystals as an alternative approach during drug development is the adjustment of the physicochemical properties to improve the overall stability and efficacy of a dosage form. Physicochemical properties, such as crystallinity, melting point, solubility, dissolution, and stability, have been studied extensively by researchers. Some key physicochemical properties of pharmaceutical co crystals are summarised as following.

Supramolecular homosynthons



Supramolecular heterosynthons

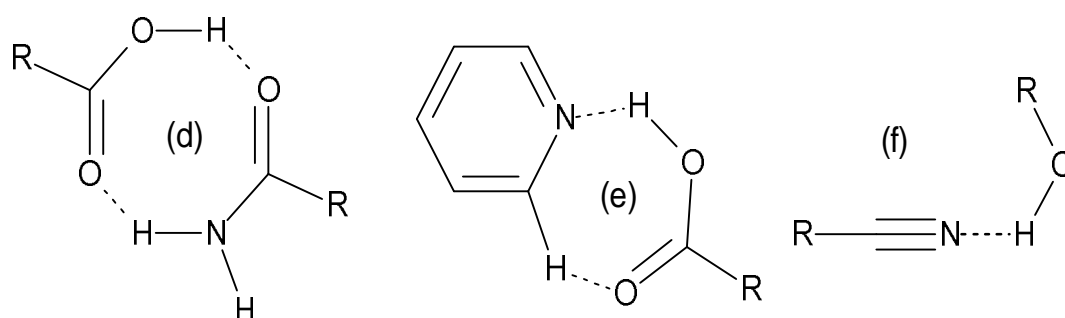


Fig. 4: Showing examples for supramolecular homosynthons (a) Carboxylic acid dimer (b) primary amide dimer (c) alcohol homosynthon chain; supramolecular heterosynthons (d) Carboxylic acid---primary amide (e) Carboxylic acid---pyridine (f) Cyano---Alcohol.

1. Melting point

Melting point is the temperature at which the solid phase is at equilibrium with the liquid Phase. It is a fundamental physical property and an important consideration during solid drug development. There are complex correlations between the melting point of pharmaceutical product and its process ability, solubility and stability. Much research work has been carried out to investigate if the melting point of a co crystal changes with respect to the individual components and if the melting points can be estimated and modulated within a series of co crystals. For example, the melting points of co crystals to the API AMG517 (an insoluble small molecule VR1 vanilloid receptor 1) antagonist) and their respective co formers showing that all these co crystals have a melting point that fell between the melting point of the API and their correspondent conformers.

2. Stability

Stability is a very important parameter when evaluating the properties of a pharmaceutical co crystal. Usually, the stability testing of a newly developed co crystal includes four aspects: relative humidity stress, thermal stress, chemical stability, and solution stability. The relative humidity stress test is used to identify the best storage conditions for the product because the amount of water present in the co crystal can lead to quality deterioration. It was found that better performance of the co crystals was displayed during water sorption/desorption experiment. For example, negligible amount of water was sorbed by indomethacin saccharin co crystals in dynamic vapour sorption and desorption experiments Co crystals of glutaric acid and 2-[4-(4-chloro-2-fluorophenoxy) phenyl] pyrimidine-4-carboxamide sorbed less than 0.08% water up to 95% relative humidity over repeated

sorption/desorption cycles. Results showed that these co crystals are stable with respect to moisture under normal processing and storage conditions. Thermal stress and chemical stability are relatively less studied areas about co crystal properties.

3. Solubility

Solubility is another important parameter for evaluating the properties of a pharmaceutical co crystal. Traditional methods for improving solubility of poorly water-soluble drugs include salt formation, solid dispersion (emulsification), and particle size reduction (micronisation). However, there are practical limitations with these techniques [14]. Researcher tried to improve the solubilities of two APIs, exemestane (EX) and megestrolacetate (MA), in which two novel co crystals, exemestane/maleic acid (EX/MAL) and megestrol acetate/saccharin (MA/SA), were prepared from organic solutions with different particle sizes.

4. Intrinsic dissolution

Intrinsic dissolution measures the rate of dissolution of a pure drug substance from a constant surface area, which is independent of formulation effects and measures the intrinsic properties of the drug as a function of dissolution media, e.g. pH, ionic strength and counter-ions. The sample used in the intrinsic dissolution test is pressed into a disk or pellet, which should be no form change upon pressing and the disk, needs to remain intact during the experiment. Most of the APIs studied for co crystallisation are classified as BCS (Biopharmaceutics Classification System) class II drugs, which have high permeability and low solubility. Thus, intrinsic dissolution rate is a good indicator for in vivo performance of APIs. One co crystal example, a low solubility API, 2-[4-(4-chloro-2 fluorophenoxy) phenyl] pyrimidine-4 Carboxamide, was cocrystallized with glutaric acid to achieve 18 times higher intrinsic dissolution rate.

5. Bioavailability

In pharmacology, bioavailability is a measurement of the extent to which a drug reaches the systemic circulation. The ultimate goal for co crystal investigation is to improve the bioavailability of an API. Animal bioavailability is an important parameter to consider when preparing new forms of a compound. There are limited numbers of animal bioavailability studies on co crystals. The co crystal of glutaric acid and 2-[4-(4-chloro-2 fluorophenoxy) phenyl]-pyrimidine-4- Carboxamide (PPPA) was used to demonstrate an improvement in the oral bioavailability of the API in dogs. Another pharmacokinetic study on the indomethacin-saccharin co crystal also shows an improved bioavailability of the co crystal over the pure API, indomethacin.

Design strategies of pharmaceutical co crystal

Pharmaceutical co crystal design and preparation is a multi-stage process. In order to get a desirable co crystal 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 co formers. As explained before, these intermolecular interactions include van der Waals contacts, π - π stacking interactions, and the most common interaction in co crystal structure of the hydrogen bonding.

The next step is to choose a co crystal former. The primary request for a co former is to be pharmaceutically acceptable, for example, pharmaceutical excipients and compounds classified as generally as safe (GRAS) for use as food additives. Co former selection is the crucial step for designing a co crystal. During the design process, there are lots of worthwhile reference resources, including both empirical and theoretical resources, such as Cambridge Structural Database (CSD), hydrogen bond theories, and many empirical conclusions. CSD is valuable tool to study intermolecular interactions in crystals. A supramolecular library of co crystal formers has been developed based on the information of CSD, within this library a hierarchy of guest functional groups is classified according to a specific contribution to a crystal packing arrangement, which is dependent on the functionalities contained on the host molecule. As a general guideline, the hierarchy of the supramolecular synthons within a range of common functional groups can be utilised. According to these studies, certain functional groups, such as carboxylic acid, amides, and alcohols are particularly amenable to the formation of supramolecular heterosynthons [14].

Methods of preparation of co crystals:

Formation of co crystals shows the reprehensibly difficult situation with regard to preparation it has been recognised to take 6 months to prepare a single co crystal of appropriate quality for single X-ray diffraction analysis. This is incompletely as such a heteromeric system will only form if only form if the non-covalent forces between two or more molecules are stronger than between the molecules in the consistent homomeric crystals. Co crystal design strategies are still being investigated and the mechanism of formation is distant from being understood. Co crystals can be prepared by solid and solvent based techniques. The solvent based techniques involve solvent evaporation, slurry conversion cooling crystallization and precipitation. The solid based techniques involve net grinding, solvent-assisted grinding and sonication 80° to 85°.

(a) Co crystallization from Solution:

The two components must have similar solubility for solution Co crystallization; otherwise the component which has least soluble will precipitate out entirely. On the other hand similar solubility of two components alone will not promise success. It has been recommended that it possibly useful to believe polymorphic compounds, which exist in more than one crystalline form as crystallizing components. If a molecular compound exists in numerous polymorphic forms it has showed a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Therefore the possibility of conveying such as a component into a different packing arrangement in coexistence with another molecule is improved.

Co crystal from small scale preparation has been described. Scale up crystallization was carried out in a water jacketed glass crystallization vessel and temperature was controlled by a circulating water bath. Teflon blade and overhead stirrer with a glass shaft were attached to vessel ports and also a reflux column, digital thermometer were attached. The API and co crystal former were added to vessel and were dissolved in ethanol/methanol solvent and heated to 70^oc under reflux for one hour. To induce precipitation of co crystal, temperature was decreased at a rate of 10^oC in a stirred. Literature to improve solids recovery decrease the additional temperature.

(b) Co crystallization by Grinding:

The product developed when preparing Co Crystals from grinding is usually consistent with that attained from solution. This may specify that patterns of hydrogen-bond connectivity are not characteristic or determined by non-specific and uncontrollable effects of solvent or crystallization conditions. Many co crystal materials can be prepared from both solution co crystallization and solid-state grinding, some can only be prepared by solid-state grinding where as some can be prepared by solution co crystallization. For instance, in the co crystallization of 2, 4, 6-trinitrobenzoic acid and indole-3-acetic acid, different crystal forms were prepared from solution when compared with grinding co-crystallization [15].

Dissatisfaction in Co Crystals formation by grinding co crystallization possibly due to incompetence to generate suitable co crystal arrangements rather than due to the stability of the initial phases. The reason for the successful formation of co crystal from solution but not from grinding may be of solvent addition in stabilizing the supramolecular structure. Even though formation of co crystal by solid-state grinding has been established for a moment and a late 19th century report is commonly cited as the initial reference to such a

procedure, the current technique of liquid assistant grinding has been shown to improve the kinetics and facilitate co crystal formation and as lead to increased consideration of solid-state grinding as a method for co crystallization.

(c) Co crystallization by Slurry conversion:

Investigations in slurry conversion were carried out in different organic solvents and water. 100 to 200 ml of Solvent was added and the resulting suspension was stirred at room temperature for few days. After few days, the solvent was decanted and the solid product was dried under a flow of nitrogen for few minutes. The remaining solids were then characterized using PXRD analysis

(d) Co crystallization by addition of antisolvent:

This is one of the precipitation methods for co crystallization of the co-former and drug. In this method, solvents include buffers (pH) and organic solvents. For example in preparation of Aceclofenac-chitosan co- crystals, in which solution of chitosan was prepared by soaking chitosan in glacial acetic acid for few hours. By using high dispersion homogenizer the drug was dispersed in chitosan solution [16]. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.

(e) Sublimation:

If a compound is adequately volatile at accessible vacuum pressures it can be crystallized. This technique is often used in the purification of crude mixtures. Crystals may form from a fusion, or by sublimation; but crystallization almost always takes place from solution.

(f) Melting:

Melts have generated an interest in co crystal formation. By simply melting two co crystal formers together and cooling, a co crystal may be formed. If a co crystal is not formed from a melt, a seed from a melt may be used in a crystallization solution in order to afford a co crystal.

(g) Seeding:

A seed crystal of the same or a similar material is added to a supersaturated solution in order to induce the growth of single crystals of a certain form as the solution evaporates [17].

Characterization of Co Crystals

Characterization of Co Crystals involves both structures (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction) [18] and physical properties (e.g. melting point apparatus, differential scanning calorimetry, thermo gravimetric analysis).

The analytical prospective of NIR spectroscopy for co-crystal screening using Raman spectroscopy as a comparative technique has been reported [19]. A compound-sparing, automated and green differential scanning calorimetric technique was developed for fast co-crystal screening which established the formation of Carbamazepine - Nicotinamide co-crystals. Single crystals of the 1:1 co-crystal of piracetam and gentisic acid obtained via slow evaporation from acetonitrile solvent. Co-crystal or prepared via grinding or slurring in water was characterized by IR, melting point, DSC, Powder XRD and single crystal XRD.

Co crystal characterization is an important constituent part within Co crystal research. The basic physicochemical properties of co crystal can usually be characterized by powder X-ray diffraction (PXRD), single crystal X-ray diffraction (SXRD), infrared spectroscopy (IR), Raman spectroscopy, differential scanning calorimetry (DSC), solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), and terahertz spectroscopy.

1. Single crystal X-ray Diffraction

SXRD is a basic characterization technique for determination of the solid state structure of co crystals at an atomic level. However, the problem is that a single pharmaceutical co crystal which is qualified for SXRD testing cannot always be produced. Therefore, PXRD are utilized more frequently to verify the formation of co crystals [13].

2. Raman Spectroscopy

Raman spectroscopy is a spectroscopic technique used to study vibrational, rotational, and other low frequency modes in a system, which has been demonstrated to be a powerful tool for distinguishing isostructural phase. There are many applications using Raman spectroscopy to identify characteristic peaks of co crystal products [13].

3. Scanning Electron Microscope

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 which provide information about the sample's surface topography. It is applied to determine the co crystal micrograph and particle size in many examples [13].

4. Terahertz time-domain-spectroscopy (THz-TDS)

Terahertz time-domain-spectroscopy (THz- TDS) has emerged as a versatile spectroscopic technique, and an alternative to powder X-ray diffraction in the

characterization of molecular crystals. It has been demonstrated that terahertz spectroscopy has the ability to distinguish between chiral and racemic hydrogen bonded co crystals that are similar in molecular and supramolecular structure. The investigation of the co crystal of theophylline with chiral and racemic forms of co formers using PXRD and Raman spectroscopy suggested that THz-TDS is comparable in sensitivity to diffraction methods and more sensitive than Raman to changes in co crystal architectures [13].

Crystallography:

X-ray crystallography is the study of crystals and their structure by means of the diffraction of X-rays by the frequently spaced atoms of crystalline materials. When an X-ray beam is directed at a crystalline sample, the atomic structure of the lattice causes the X-rays to be scattered in a defined manner creating a diffraction pattern. The electron density in the crystal may be deduced from this diffraction pattern, enabling an accurate molecular structure to be determined.

To understand this theory further and precisely determine crystal structures it is useful to have a general knowledge of crystal structures and their interaction with X-rays [20].

(a) Crystal structures:

Crystalline solid compounds are highly ordered structures; the molecules are arranged in an exactly regular array that is repeated by translation in three dimensions. Consequently crystal structures consist of structural units that are stacked side by side in all directions, thus forming a lattice in which the molecules in the repeated structural units are thought of as points. The lattice is considered to be infinitely large.

The lattice points connect to form unit cells a unit cell is the smallest group of atoms which has the overall symmetry of a crystal structure. The entire lattice can be built up by repetition of the unit cell in three dimensions. Depicts a unit cell; it is a parallelepiped defined by sides of length a , b and c , and three angles α , β , γ . The number of molecules in the unit cell is given as Z ; the number of molecules in the asymmetric unit is given as Z .

(b) Crystal Systems:

Due to restrictions imposed by reflection and rotation symmetry on the unit cell parameters, there are only seven types of crystal systems possible.

Lattice Types:

Within these seven crystal systems there are two possible lattice types: primitive and non-primitive. A

primitive lattice (P) only has lattice points at the corners of the unit cell, whereas a non-primitive lattice also has points on the faces or within the unit cell as well as on the corners. Non-primitive lattices may be side-centered (A, B or C), face-centered (F) with a lattice point at the centre of each face, body-centered (I) with a lattice point at the centre of the unit cell, or in the special case of trigonal rhombohedral, doubly-centred at $(\frac{1}{3}, \frac{1}{3}, \frac{2}{3})$ and $(\frac{2}{3}, \frac{2}{3}, \frac{1}{3})$.

X-rays:

X-rays were discovered by German physicist Willhelm Conrad Roöntgen in 1895; they are a form of electromagnetic radiation of wavelength $\sim 1\text{\AA}$ found between ultra violet and gamma rays in the electromagnetic spectrum. In 1912 Max von Laue recognised the ability of X-rays to be diffracted by crystalline solids. This is possible due to the wavelength of X-rays being of the same order of magnitude as the interatomic distances in crystals. X-rays are produced by bombarding a molybdenum or copper target with a beam of accelerated electrons. The absorption of the high-energy electrons in the metal target results in a release of radiation over a continuous range of wavelengths called the Bremsstrahlung. On impact with the metal target the energetic electrons also expel some of the inner 1s electrons of the metal causing an electron from an outer 2p or 3p orbital to drop down to fill the gap. The excess energy is released as an X-ray photon. The desired X-ray radiation can be selected from the range of wavelengths by passing the radiation through a monochromator such as a graphite crystal.

Cambridge Structural Database:

Established in 1965, CSD is an important tool for the solid-state chemist. The database records bibliographic, 2D chemical and 3D structural information for organo carbon compounds studied by X-ray and neutron diffraction. Given the huge amount of data available, there are many research applications including crystal packing studies, crystal engineering, conformational analysis, structural correlation, and statistical analysis, intermolecular interactions, crystal structure prediction and polymorphism. The CSD permits statistical analysis not only of molecular structure but also of packing motifs. Functionalities that are common or of special interest can therefore be studied in terms of how they associate with themselves or other functionalities [21].

PHARMACEUTICAL CO CRYSTALS AS INTELLECTUAL PROPERTY:

Compared to other types of solid forms, Co Crystals possessed particular scientific and regulatory advantages, and alongside these advantages were

intellectual property issues which give Co Crystals with exclusive opportunities and challenges. Researchers accounted the importance about patents on pharmaceutical Co Crystals to the pharmaceutical industry. The worth of Co Crystals to the pharmaceutical industry should become clearer, mostly with respect to several relevant legal and regulatory issues, as products containing co crystal technology come out from pharmaceutical development pipelines onto the market.

Regulatory classification of pharmaceutical co crystals

In this context, FDA has issued a preliminary guidance for industry. Such regulation can have a big impact on the application of Co Crystals in the pharmaceutical industry (innovators and generic companies) paving the way to the use of Co Crystals of APIs for new chemical entities and generic products. Co Crystals should be classified within the Agency's current regulatory framework as dissociable "API-excipient" molecular complexes which should be treated as a drug product intermediate (with the neutral guest compound being the excipient).

Applications of co crystals

Compared to other solid-state modification techniques employed by pharmaceutical industry, Co crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, neutraceutical co crystals), drug delivery (solubility, bioavailability) and Chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co crystallization.

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