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REVIEW ARTICLE: CO-CRYSTAL AND SELECTION OF ITS CO-FORMER

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ABSTRACT
Poor aqueous solubility and bioavailability of an active pharmaceutical ingredient are major problem in development of new product. Pharmaceutical co-crystals are new class of solid drugs with improved physicochemical properties. In this paper systematic overview of pharmaceutical co-crystals is provided. With special emphasis on difference between co-crystal, salt and solvate, preparation methods, physicochemical properties of co-crystal. As co-crystals are crystalline material made up of two or more components i.e API and co-formers, usually in a stoichiometric ratio, each component being an atom, ionic compound, or molecule. So brief overview on various co-former screening methodology including supra-molecular synthon approach which utilizes Cambridge structural database (CSD), Pka approach, Hansson solubility parameter are explain and correlate with co-crystal formation.

KEYWORDS: Pharmaceutical co-crystal, Crystal engineering, Solution co-crystallization, Supra-molecular synthon, CSD, Hansen solubility parameter.

INTRODUCTION

An Active Pharmaceutical Ingredient (API) can exist in variety of solid state forms, which include: polymorphs, solvates, hydrates, salts, Co-crystals and amorphous forms. Each form exhibits unique physicochemical properties that can profoundly influence the bioavailability, stability, manufacturability and other performance characteristics of the formulated API. Such diversity offers the opportunity of tuning key physicochemical properties of the pharmaceutical product without compromising the pharmacological activity of the API As the molecular structure preserved.

An Active Pharmaceutical Ingredient (API) exists mainly in two different types viz. crystalline and amorphous depending upon internal structure of compound. Other forms are polymorphs, hydrates and solvates.

Generally crystalline form is preferred as it is thermodynamically more stable but this form exhibits inadequate aqueous solubility and poor dissolution rate and hence results in poor oral absorption particularly in case of water insoluble drugs when given orally. Even though of high solubility, amorphous form is not preferred due to lack of stability. Since crystal form is crucial for the performance of the dosage form as the crystal form acts as the barrier for the drug solubility by showing low aqueous solubility, slow dissolution rate. Hence the nature of physical form of API and formulation tends to exhibit greatest effect on bioavailability parameter of water insoluble API that needed to be given in high doses.

Still there are various physicochemical and pharmaceutical processing related problems of crystalline API such as low aqueous solubility, low dissolution rate, low bioavailability, hygroscopicity, instability, poor compressibility. In order to solve these problems by retaining crystalline form various approaches are developed for API which includes preparation of Salt, Hydrate, Solvate, Polymorph, and Co-crystals etc.

Pharmaceutical Co-Crystals

Co-crystals, a class of compounds for which the principles of crystal engineering are utilized, have gained lot of recent attention owing to their amenability to design and their ability to tailor physicochemical properties. They represent class of compounds with large potential and play important part in chemical and pharmaceuticals especially in field of polymorphism.

Pharmaceutical co-crystals comprises of API and pharmaceutically accepted compounds.co- crystals are formed due to several types of interactions including hydrogen bonding, Van-der Wall's forces, and π-π interactions and Favorable geometries during self-assembly are responsible for the generation of supra-molecular networks. Co-crystals are multicomponent systems whose components interact by hydrogen

bonding or other weak intermolecular interactions rather by an ion pairing. A detailed understanding of supramolecular chemistry of the functional groups present in the given molecule is the first step in designing a co-crystal since it facilitates selection of molecules that contain the appropriate complementary functional groups. Here these complementary functional groups are referred as 'co-crystal formers'.

Table 1: Definition's of co-crystal.[10]

Author	Definition of co-crystal
Childs, S. L.	"crystalline material made up of two or more components, usually in a stoichiometric ratio, each component being an atom, ionic compound, or molecule"
Aakero¨y, C. B.	"compounds constructed from discrete neutral molecular species...all solids containing ions, including complex transition-metal ions, are excluded" "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"
Bond, A.	"synonym for multi-component molecular crystal"
Jones, W.	"a crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, often including hydrogen bonding"
Zaworotko, M. J.	"are formed between a molecular or ionic API and a co-crystal former that is a solid under ambient conditions"
Nangia, A.	"multi-component solid-state assemblies of two or more compounds held together by any type or combination of intermolecular interactions"

Table 2: Difference between co-crystal and salt form.

Co-crystal	Salt
Co-crystals can simultaneously address at multiple functional groups in single drug molecules.	Salt formation directed at single acidic or basic group.
Co-crystal formation may be employed for non-ionisable molecules	Salt formation can be employed for only ionisable molecules.
Ternary and quaternary structures are also possible in co-crystals	Binary structure only possible in salt formation

Table 3: Difference between co-crystal and solvate.

Co-crystal	Solvate
If both components are solid at room temperature crystals are designated as co-crystals.	If one component liquid at room temperature co-crystals are designated as solvates.
As co-crysatallising agents are solids at room temperature co-crystals are more stable.	Solvated crystals are often unstable and lead to de-solvation during storage

Proposed Mechanism for the Solubility Advantage of Pharmaceutical Co-Crystal

The dissociation of the hydrogen bonded co-crystal in the aqueous medium liberates the more soluble co-former into the solution, whereas the less soluble drug molecules aggregate as an amorphous phase because of the sudden crashing out from solution. These aggregates lack the long-range order and periodicity characteristic of the crystalline state. The amorphous phase gives peak drug solubility for a short period (the spring), which will gradually transform to metastable polymorph(s) and thereby extend the metastable zone width (the parachute effect). Finally, the drug will transform to the stable, insoluble polymorph, but by this time the bulk of the drug has been absorbed through the fast dissolving metastable state(s). The Ostwald's Law of Stages could stretch the metastable zone width to several hours. If the amorphous state directly transforms to the stable, crystalline form without the intermediacy of metastable polymorphs (dash arrow), the drug will exhibit spring effect.

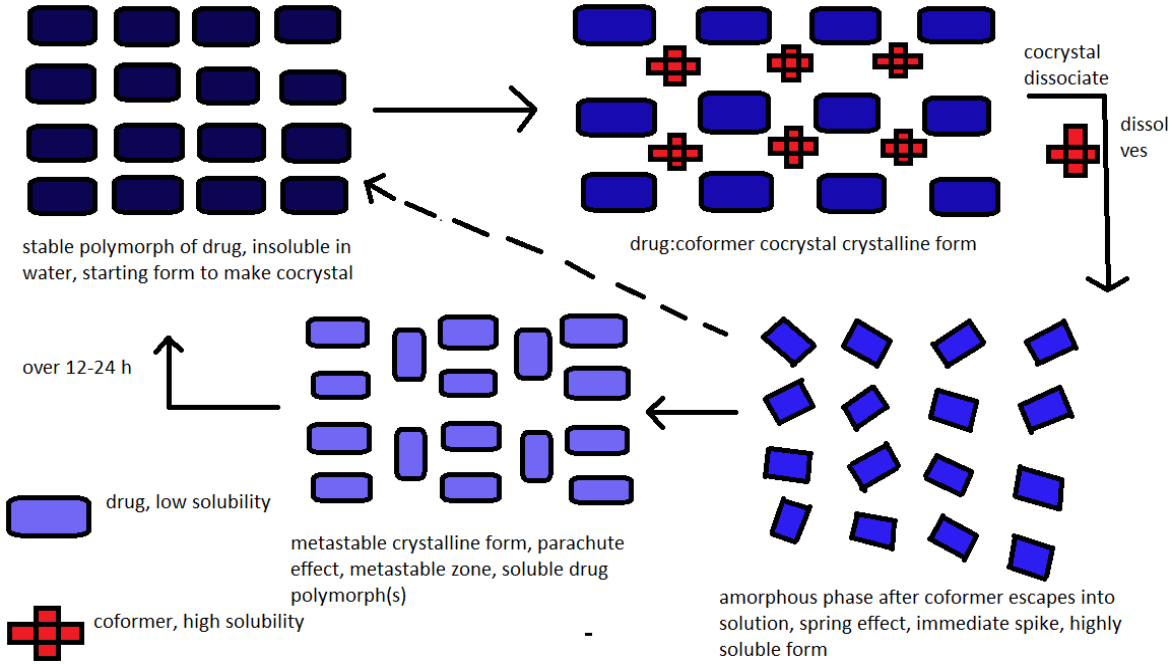

Fig. Mechanism for solubility advantage of pharmaceutical co-crystals.

Use of Co-Crystals To Alter Physicochemical Properties Of Active Pharmaceutical Ingredients (API).[5,8,9]

Melting point

Changing the Melting point of an API provides advantages in pharmaceutical processes; for example when a melted state of thermally labile API is desired during some processes such as hot melt extrusion, a Co-crystal with lower melting point than that of pure crystalline API will allow for melting at lower temperatures to avoid chemical degradation. The Melting point of API is altered buy Co-crystallization. However, higher melting point does not represent higher thermal stability. Co crystals may absorb or release heat before they finally melt, indicating the possibility of existence of phase change. The melting point of odd Co crystals are systematically higher than those of the evens since they have systematically higher packing efficiency interface between the layers in the structure. A series of DSC tests was carries out on the nonstoichiometric Co crystals of phosphodiesterase-IV inhibitor and L- tartaric acid. The Co crystals melting point is between L- lactic acid and phosphodisterase-IV inhibitor, increasing the percentage of phosphodisterase-IV inhibitor. The Co crystals with acid: base value of 0.5:1 has the best thermal stability, like no thermal transformation or other transition with endothermic or exothermic process exists, though it is not the Co crystals with highest melting point in this series. The above example shows that the melting point could be very dependent on the Co crystals formers. The melting point of Carbamazepine: nicotinamide(CBZ:NCT) and Carbamazepine: saccharin(SBZ:SAS) Co crystals lie In between melting point of the pure component phases. CBX: NCT melts at 156^{o}C and CBZ: SAS AT 177^{o}C. IT is interesting to note that there are no other thermal events prior to the melt of these co crystals.

Solubility and Dissolution rate

Solubility and Dissolution rate are very important properties to the pharmaceutical industries since the bioavailability of an API is often related to them. Compared with the original API, the solubility and dissolution rate of the Co crystal could be higher or lower. A series of dissolution profile experiments and solubility measurements about fluoxetine hydrochloride and its Co crystals is carried out in water at 22^{o}C. The solubility of fluoxetine HCL fumaric acid Co crystals is about 30% higher than those of fluoxetine HCL. The solubility of Fluoxetine HCL- succinic acid Co crystals is generally higher than that of fluoxetine HCL, but the value fluctuates as time goes. However the solubility of fluoxetine HCL-benzoic acid is only about 50% of that of fluoxetine HCL. Among these four solid phases fluoxetine HCL-succinic acid has highest dissolution rate. The dissolution rate of fluoxetine HCL-fumaric acid/benzoic acid are lower than fluoxetine HCL. The increased dissolution rate of this Co-crystals translated into plasma concentration values that were nearly three times higher than the API itself when drugs were dosed orally. Another example Co crystal showing enhanced solubility is Co crystal of the norfloxacin with isonicotonamide. It is has three times higher solubility than norfloxacin Co crystal.

Hygroscopicity

Hygroscopicity describes the stability of the solid drug in the presence of atmospheric moisture. The reports of Co crystal now generally presented less hygroscopicity than that of the original crystal. In the presence of Co crystal

of an API with phosphoric acid, compared with the API itself. The Co crystal has improvised chemical and physical stability to humidity. A systematic study on the Co crystal of caffeine with the several carboxylic acids showed that they generally have less hygroscopicity than caffeine. Among them, the crystal with oxalic acid even exhibits stability to humidity over period of several weeks. This Co crystal solid is reported as non-hygroscopic.

Increased resistant to hydrate formation

The stability of an API in the presence of atmospheric moisture is of concern to the pharmaceutical industry. A conversion of API into hydrate form could bring about undesirable physiochemical properties such as low bioavailability and also implicate the processing, formulation, packaging, and storage of the API. Various manufacturing methods such as aqueous granulation, spray drying, aqueous film coating and crystallization may bring the API into contact with water, thus providing the opportunities for hydrate formation. Even after an API has been formulated into a drug product, an opportunity for hydrate formation still exists. For example, if hydrated excipients are used, water redistribution within the dosage form could occur resulting into hydration of API itself. If the storage environment is humid, a hydrate could be formed. Thus special requirements are needed for manufacturing and handling of APIs that are hygroscopic, which could be difficult and expensive to maintain. Alternatively, Co crystallization could be used to solve this problem as in case of the caffeine and theophylline: a central nervous system stimulant and a bronchodilator respectively. Both APIs are stable below a certain critical relative humidity levels, but a higher relative humidity levels they transform into hydrate forms. However, upon Co crystallization with dicarboxylic acids such as oxalic acid, malonic acid, non- hygroscopic Co crystals were produced that can resist hydration under extreme relative humidity levels. Another example of this is the stability of carbamazepine Co crystals (nicotinamide and saccharin) when exposed to high relative humidity. Even though the pure carbamazepine anhydrous crystal transform into carbamazepine dehydrate when exposed to high relative humidity, but the Co crystals do not.

Improved compaction property for tableting

An understanding of APIs mechanical property such as its compressibility is essential for its development into a tablet form. Excipients are sometimes added to the formulation to enhance the tablet quality of the drug Paracetamol (Panadol), an analgesic and antipyretic drug has three unknown polymorphs: the most stable is form I and the least stable form II which has not yet been fully characterized. For is only the polymorph which exhibits the necessary compaction properties for direct tableting as it exhibits parallel molecular stacking, making it more favorable with respect to plastic deformation. However its lower stability makes it an impractical option for commercial use, therefore the current marketed form of paracetamol comprises of form I and excipients that prevent shipping and disintegration of the tablet. Recently attempts were made to produce alternative solid forms of paracetamol that are pharmaceutically acceptable, thermodynamically stable and share similar compaction properties to form II of paracetamol. Salt formation was unattainable due to lack of acidic and basic functionalities on the paracetamol molecule hence several Co crystals containing biologically safe conformer were produced, such as paracetamol theophylline Co crystals all which displayed superior compaction properties to form I.

Formulations of two APIs into one dose

The ability to formulate two pharmacologically complementary APIs into one single dosage is also of interest to the pharmaceutical industry, as this could potentially save resources in manufacturing, packaging, storing and may provide a more convenient dose to patients. An example of Co crystal that contains two APIs is that of sildenafil-acetylsalicylic acid. Sildenafil (viagra) is a drug used for the treatment of erectile dysfunction and pulmonary arterial hypertension, and acetylsalicylic acid (aspirin), a non steroidal anti inflammatory drug (NSAID) used to relive pain and inflammation, reduce fever (antipyretic) and for the treatment of cardiac diseases (antiplatelet). This Co crystal has been patented used for the treatment of cardiac diseases and male erectile dysfunction. It has also displayed favorable physiochemical properties which include higher dissolution rates to the marketed salt form of sildenafil.

Chemical stability[12]

Co crystal formation can also include the chemical stability of an API when chemical reactivity requires that reactant molecules be in suitable position in the solid state. For example, the single component CBZ polymorphs degrade by photochemical reaction, where the cyclobutyl dimer is one of the Main decomposition products. This reactivity depends upon crystals packing and the arrangement of molecules. Formation of cyclobutyl dimer requires alignment and a distance between azepine rings of less than or equal to 4.1 Asimilar to the solid state reactivity requirements for cinnamic acid polymorphs. CBZ Co crystal formation inhibits photo-degradation of CBZ by altering the molecular arrangements in the solid state and by preventing hydrate formation.

Methods of Co-Crystallization[1,2,3]

Solid based methods

Neat grinding (Co-grinding)

Grinding is generally used to obtain Co-crystals superior to that obtained from solution. This process includes the grinding of both of the active pharmaceutical ingredients (API) with that of Co crystal former (CCF) in a small mortar pestle made up of glass or suitable non- shedding material. This may indicate that hydrogen- bond connectivity patterns are not idiosyncratic or determined

by non specific and unmanageable solvent effects or crystallization conditions. Whilst many Co crystal materials can be prepared from both solution growth and solid state grinding, some can only be obtained by solid state grinding. Sometimes it is seen that during co crystallization, different crystals form are obtained from solution as compared with grinding. The process of co crystal formation by grinding also has some limitations such as failure to form co crystals by grinding due to inability to generate suitable co crystal arrangements rather than due to stability of initial phases. When Co-crystal formation has been successful from solution, but not form grinding, solvent inclusion in stabilizing the supramolecular structure may be a factor.

Hot melt extrusion (HME)

Extrusion is a process that involves forcing a raw material or blend through a die or orifice under set conditions such as temperature, pressure, rate of mixing and feed rate, for the purpose of producing a stable product of uniform shape and density. In this technique the API and CCF are mixed together and then fed into the hot melt extruder, with different extruder screw configurations and different extruder barrel temperature profile (at a varying temperature and screw speeds/ rpm) and are extruded for the specified period of time. Extruder screw configurations were selected to achieve a range of shear intensities. HME has been grown so steadily as an effective method of Co crystallization due to advantage of such as being a continuous, single step, solvent free and readily scalable process. The novelty of this work is a development f solvent free process. HME technology is used to produces a pharmaceutical Co crystal using a combination of controlled heat and shear deformation. As it is a continuous process and does not involve the use of extraneous ingredients like solvent, melt extrusions is a cost efficient, effective system.

Twin screw extrusion

Twin screw extrusion (TSE) of co crystal components is introduced as a scalable and solvent less process for manufacture of co crystals which obviates the need for solution crystallization and it has been demonstrated for the first time using caffeine and AMG 517 as model drugs. It is believed that, that TSE offers highly efficient mixing and close material packing, leading to improved surface contact between co crystal components facilitating co crystal formation without the use of solvent. Unlike other mechanical mixing procedures, TSE is a continuous process which lends itself to scalability. TSE may be considered as an efficient, scalable, environmentally friendly process for the manufacture of co crystals as compared to solvent crystallization methods.

Solvent based methods

Solvent drop grinding

The technique of adding small amounts of solvent during grinding process has been shown to enhance the kinetics and facilitate co crystal formation and as lead to increased interest of solid state grinding as a method for co crystal preparation. Solvent drop grinding involves grinding of two materials together and small quantity of solvent. The solvent used here is as a catalytic role, to enable the formation of co crystals not obtained by neat grinding and the solvent molecule will not exists in final product. Some co crystals could be prepared by both neat grinding and by solvent drop grinding, such as the co crystals of some carboxylic acid with trimethoprim and pyrimethamine. A series of experiments have been carried on to prepare co crystal of caffeine of theophylline with carboxylic acids and demonstrated that solvent drop grinding has higher successful rate than that of solid state grinding under certain conditions.

Anti solvent addition

This is one of the methods of precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient. Solvent include buffers (pH) and organic solvents. For example preparation of co-crystal of Aceclofenac using chitosan, in which chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. The dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.

Solvent evaporation/ Slow evaporation

This is one of the easiest technique of co-crystal formation. In this technique the API and CCF were added to this container. The solids were dissolved in solvents or mixture of solvents and then mixed thoroughly for specified time. Then after suitable time the solvents were allowed evaporate under controlled evaporation to induce co-crystal formation. After complete drying the co-crystals were left in the container. Then co-crystals were collected and formation of co-crystals was then confirmed by its characterization.

Slurry conversion

Slurry conversion is one of the most widely used methods utilizing the solvent. Slurry conversion experiments includes taking both components of study i.e. API and CCF in suitable container, different organic solvent and water is added to this I suitable quantity i.e. solvent (10-50 ml) was added and the resulting suspension was stirred at room temperature for some days. After some days, the solvent was decanted and the solid material was dried under flow of nitrogen for 5 min. the remaining solid were then recovered and formation of co-crystals is confirmed by characterization using suitable analytical technique.

Solution co-crystallization/ reaction crystallization

There is an important criterion for solution co-crystallization, that the two components (API and CCF) must have similar solubility, otherwise the least soluble component will precipitate out exclusively. It has been suggested that it may be useful to consider polymorphic

compounds, which exists in more than one crystalline form as Co-crystallizing components. If molecular compound exists in several polymorphic forms it has demonstrated a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Thus, the chance of bringing such a molecule into a different packing arrangement in coexistence with another molecule is increased. Clearly polymorphism does not guarantee the functionality of a compound to act as a co-crystallizing agent, whilst the ability of a molecule to participate in intermolecular interactions obviously plays a critical role.

Sonocrysallization (Co-crystallization by sonication)

"Sonication" and "Sonicate" refer to the application of sound including ultrasound. A solid paste may. A solid paste may be sonicate in variety of ways, such as continuously or by one or more pulses. Often one pulse of sonic energy including ultrasound sound is used which is generally on the order of one second or less, about 1-5 seconds, about 5-10 seconds, or about 10 seconds or more. Sonication applied to a sample by conventional techniques such as by immersing a receptacle containing the sample in an ultrasonic bath, or by replacing the tip of an ultrasonic probe directly in to the sample or in well plate (such as 96- well microplate). The active agents are combined with one or more guests (CCFs) In the solid state. A sufficient amount of suitable liquid is added to form a solid paste and the resulting solid paste is sonicated to provide a sonicated paste. The suitable liquid of the solid paste provides a medium by which a sonic energy is transmitted throughout the entire solid paste. By virtue of being solid paste, the solid particles of active agent and guest have more efficient contact for the transmission of sonic energy than if they were simply physically mixed together.

Solvent medicated phase transformations (SMPT)

SMPT has been widely used in pharmaceutical sciences, being the most recently applied to the screening of more stable polymorphs and solvates. It is explained as-adding a solvent to equimolar binary mixture of powder of API and CCF. Upon exposure of the solid API and CCF to solvent, API and CCF will dissolve separately, approaching their respective apparently solubility values. In solution, the two may or may not associate to form complex. Upon nucleation of co-crystal, crystal growth of co-crystal ill result in decrease in the concentration of both API and CCF in solution. The solution will be under saturation with respect to API and CCF, therefore, resulting in the further dissolution of API and CCF. Over time, the solid mixture of API and CCF will convert to CC using the solution as a medium. The API/CCF dissolution and CC crystallization process will continue until activity of one of the components, either API or CCFs decrease to its critical value.

Different Methods of Characterisation of Co-Crystals[3]

Crystallography, microscopy, thermal analysis, spectroscopy and other physical techniques are widely used, alone or in combination with one another, to examine the form and function of co-crystals in solid state. In this contribution, many of the most commonly used techniques, along with few of the emerging ones, for characterizing the co-crystals are explored. Brief description of the methods themselves are provided and specific applications to screening, structural characterization and assessment of properties are presented.

Microscopy

Polarizing light microscopy is particularly useful for studying the optical properties of crystals. Microscopy was used to observe changes in the crystal morphology on co-crystallization. The drug sample before co-crystallization and after co-crystallization was placed on a glass slide and the changes were noted down.

X-Ray Differaction

X-ray diffraction is by far the most popular method used to characterize crystalline materials PXRD allows conventional fingerprinting to identify new co-crystal form(s) from a physical mixture of API and co-former.

Raman Specroscopy

Both Raman and IR spectroscopy give fundamental information about the molecular structure of materials. Although in most molecules all the bonds will give rise to both infrared and Raman bands, it is the asymmetric, dipolar bonds such as carbonyl and hydroxyl groups that tend to give rise to the strongest infrared absorption bands. The strongest Raman signals, however, come from the more symmetric structures such as aromatic rings or C=C, S-S bonds. Raman spectroscopy has the practical advantage that little or no sample preparation is needed, which is probably the biggest reason for preferring Raman spectroscopy to alternatives. The grinding and pressure that may be needed to obtain suitable material for measuring an IR spectrum can cause changes in crystal structure, although this is relatively uncommon.

IR Spectroscopy

IR spectroscopy gives fundamental information about the molecular structure of materials. The asymmetric, dipolar bonds such as carbonyl and hydroxyl groups that tends to give rise the strongest infrared absorption bands.

Simultaneous Dsc–Ftir Microspectroscopy

Combined DSC–FTIR TECHNIQUE is an easy and fast analytical method which not only can simulate the accelerated drug stability testing but also at the same time enable to explore phase trans- formation as well as degradation due to thermal-related reactions. This technique offers quick and proper interpretations.

Criteria for Selection of Co-Formers

Crystal Engineering[11]

The term crystal engineering was introduced as part of organic solid state chemistry in 1955 by R. Pepinsky and was implemented in the next context of organic solid state photochemical reactions by G.M.J. Schmidt. In the 1960's through the topochemical reactions on cinnamic acid. Today solid state synthesis continues to represent an active area of research in the context of crystal engineering. Though Schmidt and his contemporaries worked on this newly formed field to discover structures with reference to assembly of molecules and thereby stability in structures with the help of X-ray Crystallography. This field gain prominence from the 1900's with the advent of metal organics, organometallics and organic solids and since then field of crystal engineering has advanced resulting in greater understanding of how to design visible crystalline forms.

Gautam Desiraju, a pioneer in the field, defined in crystal engineering as 'the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with the desired physical and chemical properties'.

Crystal Engineering can also be defined as 'the application of the concepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are de-facto manifestations of self-assembly'. Consequently, crystal structure can be regarded as result of series of weak but directional molecular recognition events.

Intermolecular forces play a vital role in crystal engineering and the most important being non covalent interactions which includes hydrogen bonding, Van-der Wall's forces, hydrophobic forces, electrostatic forces, and π-π interactions, which further helps in crystal packing and self assembly. Favorable intermolecular interactions and geometries during self assembly are responsible for the generation of supramolecular networks that may lead to crystalline phases. These solid state supramolecules are assembled from non covalent interactions between molecules including hydrogen bonding, Van-der Wall's forces, hydrophobic forces, electrostatic forces, and π-π interactions. Supramolecules are the structural units that connect molecule to one another via these interactions. For Example the carboxy dimer O-H....O synthone in carboxylic acid and the carboxamide synthone N-H...O synthones in amides are important in pharmaceutical and biological systems. Thus intermolecular interactions can be used as a key molecular recognition elements in the design of crystalline multicomponent systems. Multicomponent crystalline systems can be divided into solvates, hydrates, salt, co-crystals.

Hence the field of crystal engineering has been focused on understanding the intermolecular interactions and connectivities that lead to the construction of supermolecules or extended architectures. Because of its strength and directionality, hydrogen bond is most important interaction in co-crystal formation. Crystal engineering allows for the new compositions of matter using existing pharmaceuticals which allows for a much larger range of pharmaceutical compositions than present method such as ion pairing. It has been suggested than pharmaceutical co-crystals could play a significant part in the future of API formulation.

Crystal engineering is also based on the principle of understanding motifs present in a molecule, leading to the formation of synthons using non-covalent interactions. The term 'synthon' as defined by Corey are 'Structural units between two molecules which can be formed and/or assembled by known or conceivable synthetic operations'. Desiraju further utilized this concept to define 'supramolecular synthons' which are defined as 'structural units within supramolecules which can be formed and/or assembled by known or conceivable synthetic operations'. In the context of set of compounds known as 'co-crystals'.

Synthon Approach

A supramolecular synthon is a well defined and reliable liner connection between molecular building blocks. Synthons are formed by the assembly of two molecules through molecular functionalities that interact with each other in a predictable fashion. Self complimentary functional groups, such as carboxylic acids, amides, and alcohols contain both a hydrogen bond donor and acceptor and are therefore are capable of forming supramolecular homosynthons. Other functionalities, which contain only hydrogen bond donor or acceptors, do not have these capabilities. However all functionalities are capable of forming supramolecular heterosynthons with other complementary functional groups. Groups that are capable of forming supramolecular synthons include, but are not limited to; acids (carboxylic, sulphonic, phosphonic, boronic), primary and secondary amides, alcohol, amino-pyridine, ketone, aldehyde, ether, ester, primary and secondary amine, aromatic nitrogen, cyano, imine, nitro, sulponyl, sulphoxide, water and ions such as Cl^- and Br^-.

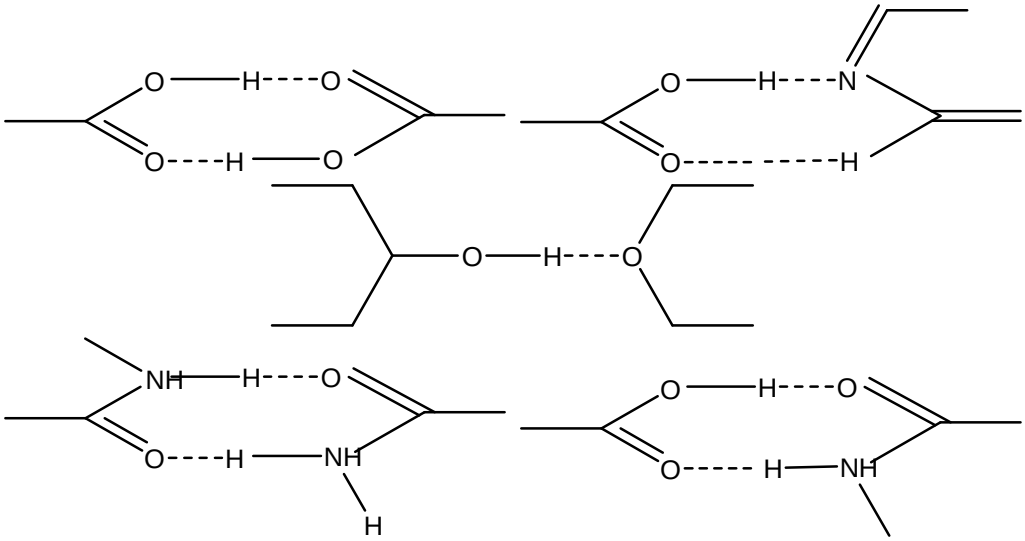

Fig. Most common supramolecular synthons in crystal engineering.

Supramolecular synthon further classified into-
(a) supramolecular homosynthon: composed of identical self- complementary functionalities.
(b) supramolecular heterosynthons: composed of different but complementary functionalities.

Single-component or compounds containing the functional groups can be sustained by supramolecular homosynthons whereas; supramolecular heterosynthonscan dominate in the presence of other competing functional groups. During the last years the principles of Co crystal design has been discussed. Intermolecular interactions depending on synthon approach that direct molecular assembly are regarded as a key point for Co crystal design. In synthon approach, one of the most useful interactions will be the hydrogen bonds, due to their inherently robust and directional nature. All good hydrogen bond acceptor and donors can be used to form hydrogen bonds. The tendency of the system to maximize electrostatic interaction on result in that the best hydrogen donor ends to interact with best hydrogen bond acceptor in given Co crystal structure. This phenomenon is concludes as „Hydrogen bond rules", which can be used for guideline for Co crystal design.

PKa Approach

Some report mentioned a simple design principle that the relatively solution-based pKa value or calculated molecular electrostatic potential surface could possibly used to select or specify parent molecule for Co crystal. This idea also got some support from the results of some experiments.

Cambridge Structural Database[4,6]

Cambridge structural database (CSD) as mentioned above is an essential tool in the field of crystal engineering. Data collected from this software helps in understanding the supramolecular synthons that could be formed between functional groups. With those statistics it is easier it is easier to understand what complementary functional groups would be promising for the functional group in a target molecule and thus the Co crystal formers can be selected. The CSD was developed in 1965 in Cambridge University by Kennard. It contains results of X-ray and neutron diffraction studies of organics, organometallics and complexes of metals. The database stores bibliographic information, crystallographic data and chemical connectivity information for each entry which is named as Refcode. The CSD consists of four components. i) Conquest: allows searching information and retrieving it. ii) Mercury: helps in visually looking at a structure. iii) Vista: provides numerical analysis and iv) Prequest: helps in database creation. The CSD had grown over time with huge number of structures being deposited every year and as of 2011, the total number of structures in the system has gone up to 562,000. And thus this has become a versatile tool and prerequisite before any crystal engineering experiments.

Hansen Solubility Parameter Approach[7]

One of the widely 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. The miscibility of compound has been estimated using various approaches, all of which are based on the general principle of „like dissolves likes". Compounds with similar δ values are likely to be miscible. Thus the difference in total solubility parameter between the drug and carriers ($\Delta\delta_t$) is a tool to predict miscibility i.e. a general trend indicating that materials with $\Delta\delta_t < 7$ MPA0.5a are miscible. Thus this miscibility can be used as Co crystal formation ability between the two i.e. APIs & CCFs.

The concept of solubility parameter was introduced by Hildebrand and Scott, who proposed that materials with similar value would be miscible. 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. In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions. Further, it has been suggested that HSPs could predict the compatibility of pharmaceutical materials, and their use is recommended as a tool in the pre-formulation and formulation development of tablets. HSPs have been widely used to predict liquid–liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surface.

The solubility parameters (i.e. cohesion energy parameters) can be used to predict the physicochemical properties such as solubility, melting point, etc. of a material. 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.[1] 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:

$\delta = (CED)0.5 = (Ev/Vm)0.5$ (1)

Where EV is the energy of vaporization, and V_m is the molar volume. δ is measured in units of $(J/cm^3)^{0.5}$, or $(cal/cm^3)^{0.5}$.

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 follows:

$\delta_t = (\delta^2_d+\delta^2_p+\delta^2_h)^{0.5}$ (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.[1,48] The partial solubility parameters can be calculated using the combined group contribution methods of Van Krevelen-Hoftyzer and fedors as follows:

$\delta_d = \sum_i F_{di} / \sum_i V_I$ (3)

$\delta_p = (\sum_i F^2_{pi})^{0.5} / \sum_i V_I$ (4)

$\delta_h = (\sum_i E_{hi} / \sum_i V_i)^{0.5}$ (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, and Vi is the group contribution to the molar volume.

CONCLUSION

Pharmaceutical co-crystals are becoming increasingly important alternative way to improve bioavailability of poorly water soluble drugs and to modulate the properties of solid state materials. Co-former selection is one of the major challenge in co-crystal development. Primary approach is screening of co-formers from library which is of GRAS status. Another approaches are CSD, HSP. The HSP can predict miscibility and co-crystal formation by using group contribution method, but all co-former predicted may or may not be miscible so, is only theoretical approach which would be useful for shortlisting of co-formers.

Needless to say, in the coming year's research in this area would be more focus on scaling up process. Meanwhile there is an need for better understanding of mechanism of co-crystallization process and theory for how pharmaceutical co-crystal improve the bioavailability of API's.

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