Review Article

An Overview on Novel Particle Engineering Design: Co-crystallization Techniques

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ABSTRACT

Pharmaceutical co-crystals use principles of crystal engineering for the design of crystalline forms of drugs that have been created enormous scrutiny due to their potential on improving the physicochemical problems of active pharmaceutical ingredient, such as Poor aqueous solubility which can reduce the drug performance. Present review furnishes abundant information about co-crystals, screening techniques for prediction of co-crystals generations without wasting time and money, methods of preparation, mechanism by which these novel particle engineering designs were obtained and finally their applications in pharmaceutical medicines. Co-crystallization is an emerging strategy to design materials in a new path with desirable properties like solubility, dissolution, bioavailability, stability, hygroscopicity modulation, pH-dependent solubility properties, thermolability, photosensitivity and micromeritic properties.

Keywords: screening methods, hydrogen bonding, methods of preparation and mechanism.

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INTRODUCTION

The word "crystal engineering" was first introduced by R Pepinsky in 1955 and Schmidt with his splendid work carried out engineering in the contest of topochemical reactions in 1980's crystal engineering designs were continued to gain high rise of interest from various different aspects like solid-state chemistry, crystallography, inorganic chemistry, theoretical chemistry.[1-5] In 1989 Desiraju clarified by giving a statement about crystal engineering as "the understanding of intermolecular interactions in the circumstances of the crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties" his definition laid a foundation for many modern concepts of crystals preparation supramolecular synthesis of compounds with desired structures at molecular levels. This crystal engineering concept helped in many ways to design predicted co-crystals with desired physicochemical properties.[6] Moreover first co-crystal was prepared in very early decades at 1844 by Wohler of co-crystal complex, between benzoquinone and hydroquinone named quinhydrone.[7] Another author namely Ling A.R stated that was first prepared co-crystal in 1893 by grinding method of 1:1 molar quantities of P-Benzoquinone and hydroquinone.[8] From antiquity, crystallization has been known for the purification process. If a solution contains a mixture of several compounds to separate and yield high level of purity for a single compound, in general the crystallization technique was employed to meet the aim. A supersaturating or super cooling, condition of a solution obeying kinetically controlled processes to form a nucleation of a single component solid phase is called a crystal.[9] In the purification process crystallization automatically yields crystals of two or more type of molecular entities, unless and until there may be specific reaction or chemical conditions, to produce one crystalline molecular entity with high purity levels. Within this type category or category of compound, one may inserts the another type of molecule or solvent molecules or gas molecules or salt molecules in the integral part of crystal structure having periodicity arrangement and structured regularly, to configure a binary crystal or multi-component molecular crystals.[10]

The binary crystals were named as solid solutions, molecular compounds, addition compounds, co-crystal and molecular complexes.[11, 12] The term co-crystal refers to a crystal in which two different molecular components were linked with hydrogen bonds. Consider A and B as two molecules which were having hydrogen bonding capacity, stronger in A---B type arrangement than A---A or B---B type arrangement. This is the driving force for the formation of co-crystals, if the acidic nature of donor molecule and basic nature of the acceptor molecules are very high, then the proton transfer takes place across the hydrogen bond and results in formation of salt.[13] It is very difficult to judge whether a co-crystal which contains neutral molecules or a salt which contains ions. In addition to this there are some other multicomponent molecular crystals which

were mediated by π---π stacking interactions between hydrocarbon residues.

Co-crystals were defined by many paragons in different ways as followed below

1. According to Bond A " *it is a synonym for multi component molecular crystal*."[10]
2. According to Aakeroy C B " *it is a compound constructed from discrete neutral molecular species all solids containing ions, including complex transition-metal ions are excluded*." It was prepared by the compounds that are solids at ambient conditions, structurally homogeneous crystalline material consists two or more neutral molecules that are present in definite stoichiometric ratios.[13]
3. According to Stahly G.P "*co-crystal is a molecular complex that contains two or more different molecules' in the same crystal lattice*".[14]
4. According to Nangia A "*Co-crystal is a multi-component solid –state assemblies of two or more compounds held together by any type or combination of intermolecular interactions* ".[15]
5. According to Childs .S.L "*it is a crystalline substance composed of two or more compounds present in a stoichiometric ratio, each component being an atom or ionic compound or molecule* ".[16]
6. According to Jones W "*it is a crystalline complex of two or more neutral molecular constituents bond together in the crystal lattice through noncovalent interactions often including hydrogen bonding*".[17]
7. According to Zaworotko M.J "*they are formed between a molecular or ionic API and a co-crystal former that is a solid under ambient conditions*".[18]

Different types of definitions with various parameters had been applied to define co-crystals till to date by great people under the vast academic literature reviews. However, the common parameters that is agreed to be co-crystals are crystalline substances composed of at least two varient components (multi component crystal) were held together by non-covalent freely reversible interactions. The different components like solid, liquid, gas or neutral or ionic species that are in solid state under ambient conditions. The addition of the new small neutral polymer or molecule or drug or organic entity into the crystal lattice of multi component system is known as co-former. A conformer may be pharmaceutically acceptable molecule (GRAS), don't affects the intrinsic activity and without any structural modifications of API but improve the physicochemical properties and technical properties like solubility, bioavailability hygroscopicity, compaction behaviour, membrane permeation, chemical stability micromeritic properties by changing the lipophilic behaviour. These changes in the different pharmaceutical properties depend on the nature of the co-former component. GRAS was a list of compounds prepared by food and drug administration (FDA) which consists of about 3000 substances like food additives, preservatives, excipients vitamins, minerals, amino acids, bio-molecules and APIs. Overall co-crystallization is a sequel of competing molecular associations between similar molecules (homomers) and different molecules (heteromers).[19-24]

What are co-crystals?

Co-crystals are most dynamically homogenous structural crystalline multi component adduct, generated by a perfect definite selection of compounds in a stoichiometric ratios, with the establishment of reversible chemical interactions like hydrogen bonding, π-π, ionic bond or vandeer waals forces. Co-crystals had been defined in many different ways by named as addition compounds, organic molecular compounds, complexes, hetero molecular crystals.[25]

The physiochemical and technical properties enhancement of pharmaceutical drug products had direct effect on the drug delivery, processing and efficacy of drug. The crystal structure of API directly affects the imperative factors of the substances. One scrutiny revealds that nearly 40% out of 90% of the new chemical entities (NCE) have limitation in solubility they cannot reach the action site in the body by normal conventional techniques. Nearly 80% of the drugs in solid dosage formed were observed via passive diffusion from gastrointestinal that are listed in worlds health organisation (WHO) were investigated to be insoluble and poorly water soluble as per the bio-pharmaceuticals classification system.[24-28]

One best approach of attaining the enhanced bioavailability of API was to prepare in salt forms although of ionisable groups which are responsible for the formation of respective salts. From all the facts it was necessary to generate a new solid-state formulation. A blaze of spark *Crystal Engineering* concept had shown a way to flash out all these drawbacks by the wide range of possibilities to design various crystalline solid-state formulations like, polymorphs and co-crystals etc. Goutam Desiraju is the first person to explore the crystal engineering concept, he is the father of the field crystal engineering defined 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 or new chemical entities with desired physical and chemical properties. These are all alternatives to provide success in procuring desired alterations in the properties of APIs. Among them co-crystals is relatively modern crystal engineering technique to modulate the bio pharmaceutical properties which is having no limitations as compared to other techniques.

Different solid forms

The alterations in the physical and chemical properties of the active constituents was attained by the changes in the solid-state properties, it was bagged off by changing the API into different forms like polymorphs, hydrates, salts etc. Chemists explained the solid state of substances as –

A solid matter basically exists in two forms based on their structural arrangement, one is crystalline forms and another is amorphous forms, these two are different in their properties. Again, crystalline substances are divided into two types, single crystal component and multi component crystalline substance. These multicomponent crystalline substances have more than one molecule assembled in different patterns resulting into variety of solid forms namely Hydrates, salts, solvates, polymorphs and co-crystals.[23, 29, 30, 31]

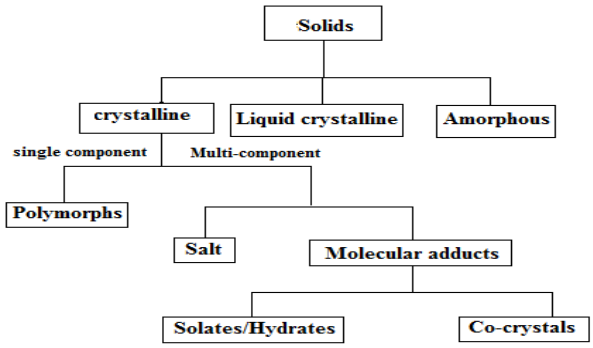


Figure 1: Classification of solid forms of active pharmaceutical ingredients

How to distinguish co-crystal from salt?

- Co-crystal has API and co former in solid state and their intermolecular interactions are non-ionic in nature, cannot formed in lack of ionisable sites in API[31-33]
- A salt is formed by the transfer of a proton (H^+) from an acid (A) to base (B)

$$AH + B \rightarrow (A^-) + (B^+H)$$

- A co-crystal (A-B) molecule is non proton transformation, having neutral entities
- A salt has proton transfer, mainly depends on the pKa values of the components according to the rules of Etter hydrogen bonding of molecules.
- A salt formation can be predicted by the value difference between conjugate base (B) and conjugate (A) i.e., pKa (base) – pKa (acid) ≥ 2.7 units.[23, 31]

As per Cruz-Cabeza acid-base crystalline complexes, improvement of the method pKa rule permits ΔpKa ≥ 3.75 units predicts the salt formation.[24, 34]

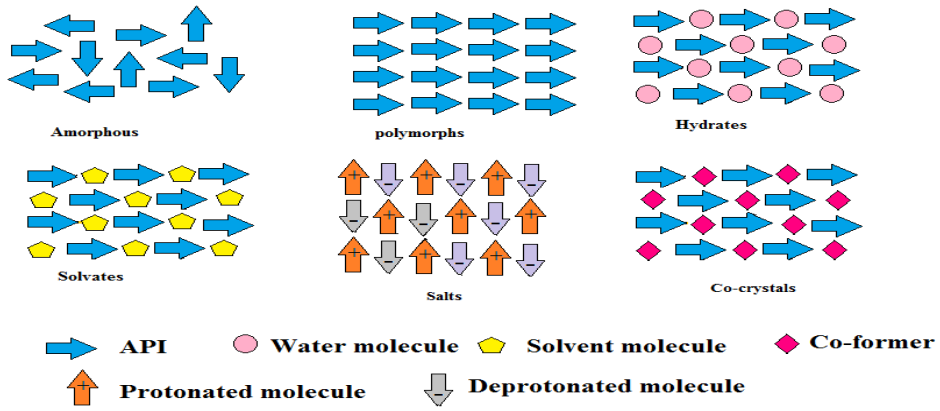


Figure 2: Schematic representations of different types of solid forms

Table 1: Summary of Pharmaceutical Co-crystal products with current status[24]

S.no	Pharmaceutical Co-crystal	Components	Indication	Approved date or source
1.	Entresto	Valsartan and Sacubitrill	Used in chronic heart failure	FDA on 7/7/2015
2.	Lexapro	Escitalopram and oxalic acid	Depression	FDA on 2002
3.	Beta-Chlor	Chloral hydrate and betaine	Sedation	FDA on 1963
4.	Depakote	Valproic acid and valproate sodium	Epilepsy	FDA on1983
5.	Cafcit	Caffeine and citric acid	Infantile apnoea	FDA on 1999
6.	Suglat	Ipragliflozin and L-proline	Diabetics	FDA on 2014
7.	Odomzo	Sonidegib monophosphate and phosphoric acid	Basal cell carcinoma	FDA on 2015
8.	Steglatro	Ertugliflozin and L-pyroglutamic acid	Diabetes	FDA on 2017
9.	Dimenhydrinate	Diphenydramine and 8-chlorotheophylline	Motion sickness	FDA on 1977

10.	Dichloralphenazone	Antipyrine and chloral hydrate	Migraine	PubChem CID 10188
11.	Iron sorbitex	Iron, sorbital and sodium citrate	Iron deficiency anaemia	PubChem CID 20715017
12.	Nicotinamide-ascorbic acid	Nicotinamide and ascorbic acid	Vitamin complex	PubChem CID 54710212
13.	Tetracycline phosphate	Tetracycline and phosphoric acid	Antibiotic	PubChem CID 54713149
14.	Caffeine-sodium benzoate	Caffeine and sodium benzoate	Headache	British Pharmaceutical Codex 1907
15.	Caffeine-sodium salicylates	Caffeine and sodium salicylates	Headache	British Pharmaceutical Codex 1907
16.	Acridine-sulfonamide	Acridine and sulfonamide	Antiseptic	PubChem CID 54710212
17.	TAK-020	TAK-020 and gentisic acid	Bruton tyrosin kinase inhibitor	Under phase-I clinical trial Identifier- NCT02723201
18.	E-58425	Tramadol hydrochloride and celecoxib	NSAID	Under phase-III clinical trial Identifier- NCT03108482
19	CC-31244	Non-nucleoside polymerase inhibitor	Non-nucleoside polymerase inhibitor	Under phase-IIa clinical trial Identifier- NCT0276075
20.	T121E01F/T121E02F	Zoledronic acid Co-crystals	Anti-cancer	Under phase-I clinical trial Identifier- NCT01721993

Screening of Co-Crystals

Co-former selection is one of the main challenges in co-crystal development. Designing and preparation of pharmaceutical co crystals is a complex and multi stage process. As per the definition of co-crystal, it is composed of minimum of two compounds one must be API and another must be a co-former, which may be an excipient or API or any other compound in the GRAS list, as discussed earlier.

Selection of coformer will be done by knowledge-based methods or experimental based method. Trial and error was a traditional proposal was mainly followed by all types of coformers for an API, and then the structure of co-crystal was elucidated by suitable characterized techniques. This type of approach is expensive and time-consuming process. Hence research implemented some other knowledge-based approaches were designed and applied to select the appropriate co-former for an API following are the screening methods.[35]

1) Hydrogen bonding propensity
2) Synthonic engineering
3) Supramolecular compatibility by CSD
4) pKa based models
5) Fabian's method
6) Lattice energy calculations
7) Conductor like screening model for real solvents (COSMO-RS)
8) Hansen solubility parameter
9) Virtual co-crystal screening (Based on Molecular Electrostatic Potential Surfaces MEPS)
10) Thermal analysis
11) Measuring saturation temperatures
12) Kofler contact method
13) Cocktail co-crystal method

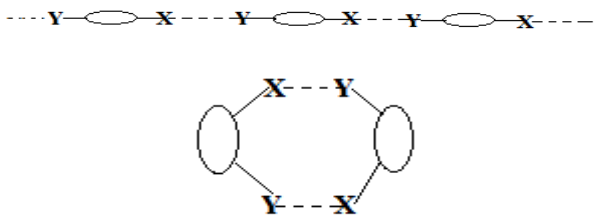
Hydrogen bonding propensity (HBP)

Hydrogen bonding propensity was recently developed tool in CSD software package (Mercury) was used to predict the crystal forms as well as the probability of forming intermolecular or intra molecular bonding between the APIs and co-formers an interactions with in the APIs if possible. This HBP provides information about the active constituents like number of donor groups, number of acceptor groups, they also give the propensities values of each Hydrogen bonding possibilities between the APIs and coformers, thus the values of propensities were lies between 0 to 1, greater or nearer to the value 1, the more confirmation and stronger of bond forming.

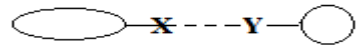
Indomethacin-Nicotinamide(1:1) co-crystal were considered to predict all possible combinations of donors and acceptors of Indomethacin and Nicotinamide co-former, there by the crystal structure determination had been reported straight forwardly. Mridul Majumdar et al calculated the Hydrogen bond propensities of Indomethacin-Nicotinamide co-crystals, using program mercury 3.1. Propensity for a donor-acceptor pair can be taken a value between 0 and 1, where 0 predicts no

likelihood of Hydrogen bond formation, 1 predicts the good likelihood and always able to form Hydrogen bond.

As co-crystals must and should compose of hydrogen bonding between components. Earlier in 1990 Margaret .C. Etter explained about the Hydrogen bond rules and graph- set notation system[32]. Hydrogen bonds were used as a tool for intermolecular synthesis, these synthesis results in molecular clusters established by the connectivity models emerged by hydrogen bonds. These molecular clusters can result in solutions, at interfaces or in solid states. This aggregates formation composed of two species usually a Host and a guest molecules, where their association or binding constants are very high as 10^4 M^{-1}. Ideal adduct systems having a set of neutral molecules with sterically accessible hydrogen binding groups with intermolecular interactions were taken place by minimal competing steric or ionic hinderance



The above both representations showing –X--Y– as intermolecular interaction in the same molecule showing homosynthons



i

ii

(i) and (ii) represents the co-crystal patterns. In the (ii) pattern Z had better hydrogen bond acceptor than Y, thus they exhibits competitive hydrogen-bonding.

Hydrogen-bond sequence recognition in molecular clusters was made simplicity with the help of topological decoding scheme. It will facilitate the comparison of hydrogen bond sequences by aid of decomposing networks into graph sets which are based on the number of proton donors (subscripts) and acceptors (superscripts). According to M.C. Etter, Graph sets notation was written as $G^a_d(n)$ where G denotes one of the possible patterns

G=S, indicates intramolecular Hydrogen-bonding,

G=C (chain) or R (Ring) or D (Discrete) referred to inter molecular Hydrogen-bonding.

a= number of acceptor groups

d= number of donor groups. a and d can be neglected when a=d=1

n = total number of atoms present in the Hydrogen bond, also known as degree of pattern.

The graph set notation provides a way to evaluate, the molecular aggregates patterns of even more complexity of compounds, leads to describe in a simplest manner and also explicitly the combinatorial possibilities of hydrogen bonds formed between two or more compounds. This graph set also explains the comparison of Hydrogen – bond patterns of polymorphs.

Hydrogen Bond rules

Victory of co-crystal innovation lies in the hydrogen bonded supra molecular synthons. It clearly supports that the bonding was the strongest interactions in crystal engineering than metal coordination bonds and ionic – ionic interactions (dipole – dipole). In crystal engineering, the hydrogen bonds were termed as “key-interaction” on account of their strength, directionality and predominant presence in organic molecules. Hydrogen bond rules reflects the relationships of graph set analyzing bond patterns of one or more than one functional groups and provide useful information like preferred connectivity patterns, Hydrogen-bond selectivity and stereo electronic properties of hydrogen bonds.

Etters Hydrogen bond rules

General rules

1) All good donors and acceptors were used.
2) If six membered ring intramolecular hydrogen bonds were formed, they will usually occur in preference to intermolecular hydrogen bonds.
3) The best proton donor and acceptor remaining after intramolecular hydrogen bond formation, they will form intermolecular hydrogen bonds to one another molecule. Strong bonds were N–H---O, O–H---O, N–H---N and O–H---N, while weak bonds include C–H----O—N and C–H----O=C

Hydrogen bonding selectively will depend on the functional group competitions of compounds in a homomeric crystal or hetromeric crystals. The simple technique involves, analyzing the donors which are capable to form hydrogen bonding with limited number of acceptor or vice versa during co-crystallization. The most commonly found hydrogen bond acceptors are carbonyl oxygen and aromatic nitrogen, while the hydrogen bond donors were ranked in order of decreasing activity in the following order COOH> NH>> R–OH.[36]

Synthonic engineering

At first Corey defined synthons as “Structural units within which molecules can be formed and or assembled by known or conceivable synthetic operations” in 1967.The word synthon used to denote structural units in the final molecules. It is naturally a small unit and less complex than the final molecule and till contains most of the important (vital) bond connectivities and stereo chemical information required to synthesize the largest structure. The analysis of a complex target molecule was broken into simpler synthons through a series of rational bond disconnections

this being termed as "Retrosynthesis". This synthon approach is advantageous by providing a simplification in understanding of crystal structures. The relationship between a molecule, a functional group and a supra molecular synthon and its necessity in building up of the entire crystal structure was explained under below figure 3.

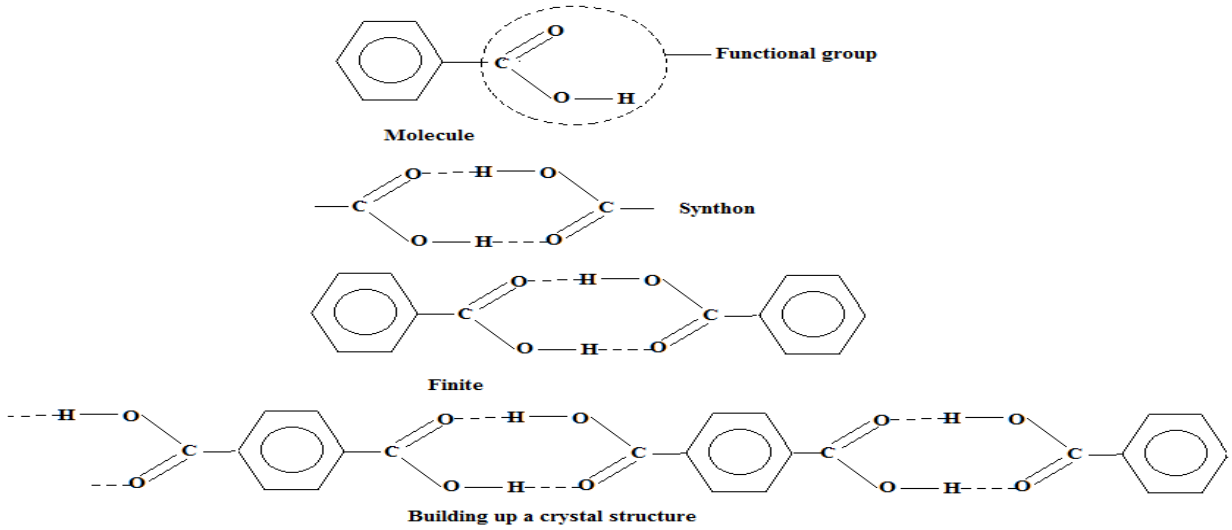


Figure 3: Self assemblies from molecule to crystal via supramolecular synthons

A supra molecular synthon is a sequence of molecule and supramolecular elements. When crystal sequence repeated regularly, the pattern of interactions may be called as supramolecular synthon. It was categorized into two types, they are 1) Supramolecular Homosynthons: Composed of identical self-complimentary functionalities. Homo synthons generally formed between carboxylic acid dimer, amide dimer, alcoholic dimer, amino dimer and halogen dimer. 2) Supra molecular Heterosynthons: These composed of different but complementary functionalities.

Heterosynthons generally formed between carboxylic acid group and pyridine, alcohol and ether group, alcohol and amine, amide and pyridine, amide and N-oxide, inter halogen bonds etc.[30]

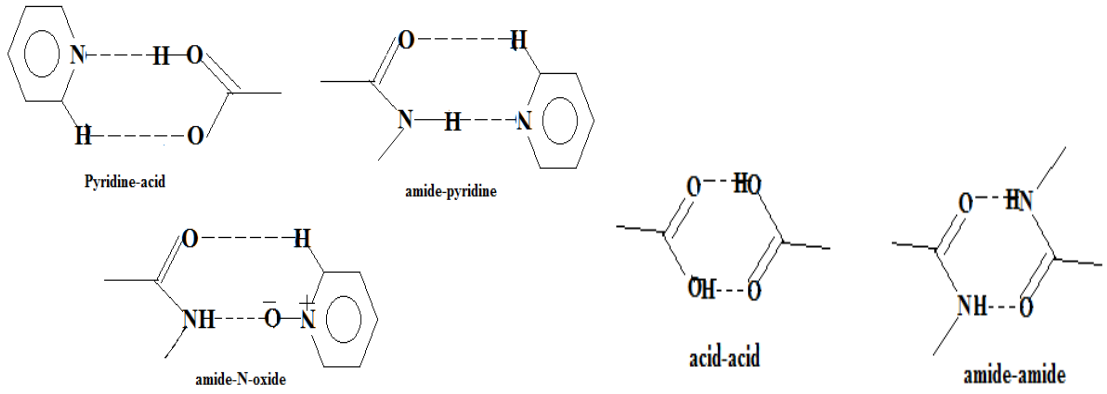


Figure 4: Examples of heterosynthons and homosynthons

Bis et al had conducted many research work on synthons and concluded that supramolecular heterosynthons are strongly preferred than homosynthons.[37] There are different types of bond synthons they are Single bond synthons, Double bond synthons, Triple bond synthons, Quadruple bond synthons, Cyclic synthons and π - synthons.

This supramolecular Synthonic engineering has been more efficiently used to screening of co-crystals, and to predict the acceptor-donors bonding and as well as the structure of the resultant crystals. Hathwar et al had worked on multi-polar parameters of many organic compounds and supra molecular synthons, that provides novel information about the combined atomic charges, of the compounds. The charge densities of the supra molecular synthons were proven to be transferable to a series of Hydrogen bonded co-crystal systems, by the analysis of charges and topology of the electron density in the co-crystal systems.[38]

Dunitz and Gavezzotti worked on the comparison study of absolute and relative strengths/stability of several supramolecular synthons with an emphasis (Significance) on hydrogen bonding. In addition to that they included aromatic stacking, and other several types of C-H---O interactions. They included the carboxylic acids, amides, alcohols, N-H---N hydrogen bonds, Cl---Cl synthons were compared with C—H---Cl synthons. A concept based on

Desiraju's supramolecular synthon, they calculated cohesive energies and thermal stabilities of proposed synthons by employing PIXEL, which provides accurate mapping of intermolecular surfaces. The most important stability comparisons were judged by calculating Binding energies and streching vibrational amplitudes at room temperature.[39]

Most cases of co-crystals formations include Hydrogen bonding, but in some cases, they are locking of hydrogen bonds in their structures had identified. Those non hydrogen bonded co-crystals were based on exclusively π---π stacking between two components, which are mostly having flat aromatic hydrocarbons. The main structural patterns in these types of co-crystals had been identified as the "alternate ladder and slanted column". Another approach to characterize and quantification of relative strengths/stability for various hydrogen interactions by using "Charge density analysis".[40]

Supramolecular compatibility by Cambridge structural database (CSD)

It is established in 1965, to provide essential search, visualization and analysis features of the organic compounds. This CSD has supreme functionality like 2D/3D search, extensive geometry analysis tool, intermolecular interaction analysis, highly impact graphics etc. CSD is a depository for molecule crystal structures; it provides complete information about the particular compound to the scientists. They use the information stored in CSD to compare the new crystal grown in laboratories. The information can also be used to visualize the structure in a variety of software such as atoms, powder cell etc. CSD plays a vital role in the prediction and identification of an unknown new chemical entity without undergoing any other crystal growth. In other words, it will help in new drug designing without any experimental procedures. It will save time, cost. CSD is a very powerful tool to systematic analysis of large, complex structures with output results that cannot be made by any other method. It is based predominantly on shape and polarity of co-crystal formers.

To design a perfect co-crystal by using CDS, they need to have sound knowledge of Hydrogen bond propensities. Firstly, we need to create the co-crystal data base. It means the molecule of co-former must contain at least one atom in the following list C, H, N, O, S, P, F, Cl, Br, I. These atoms have good charge density for the formation of synthons with drug molecules. Secondly, molecular descriptors like bond nature, group counts, hydrogen bond acceptors, and donor counts, size, shape descriptors, surface area descriptors and molecular electrostatic descriptors, should be calculated. Thirdly statistical analysis was to be done for the molecular descriptors of molecules. Molecules descriptor present in the co-crystal may have chances to combine each other same molecules descriptor to form a pairs of descriptors. If such type of descriptor pairs exhibits a molecular properties, which will influence co-crystal formation and misguide or misleads the favorable and unfavorable combination values of guest and host molecules. To eliminate and evaluate such type correlations, correlation coefficients should be calculated for all possible pairs of descriptors. Distribution of descriptor values were summarized by median, lower quartile and upper quartile values rather than by mean and standard deviation. Median is the value that "splits" the data set into two halves 50% of lower values and 50% of higher values. Quartiles are defined proportions of values that are divided into four ratio portions. In addition to the most common Pearson's correlation coefficient 'r' (r= based on mean and standard deviation) Spearman's non parametric correlation coefficient 'F' (F= based on ranking values) can be calculated for each molecular descriptor pair.

Quarterly the Molecular polarity plays a major role in CSD screening of co-crystals. Molecular polarity determines the strength and type of intermolecular forces of attraction at work in a sample of the substances. It is the strongest correlation found to the polarity of the molecule. The positive sign of the correlation coefficients recommends the formation of co-crystals with partners of similar polarity. The greater the value of polarity for a particular molecule, greater it's solubility in polar solvents and expected to be higher in B.P. and M.P. of the co-crystals.

The highest correlation relates the fractional polar volume (FPV) of co-crystallized molecule. FPV is defined as the fraction of the molecular volume that belongs to polar atoms like N, O, S, H, and F. A simpler alternative way to determine 'FPV' by descriptor FNO, which is obtained by dividing the total number of N and O atoms by the number of heavy atoms in the descriptor molecule. Shape correlations means "that molecules of a flat shape having more tendency to form co-crystals with other flat molecules, or partners of similar shape.

Globularity is a shape descriptor that relates the surface area of a molecule to its volume. Globularity value was small for the smooth surface, greater value for the bumps and hollows surface molecular shapes. Shape relationship appears to be stronger for smooth molecules.[30]

pKa based models

The pKa value is one of the methods to indicate the strength of an acid. pKa is a negative logarithm of the acid dissociation constant (Ka) of a solution. A very simple and best method to identify, whether they obtained product is co-crystal or salt by ΔpKa determination. Cruz-Cabeza et al had done modifications to the ΔpKa rule to use as a measuring / prediction tool of co-crystal formation.[29]

$$\Delta pKa = [pKa\ (base) - pKa\ (acid)]$$

If ΔpKa lies between -1 to 4 values indicates the co-crystal formation. If ΔpKa more than 4 value it confirms the salt formation.[41] By the PhD work entitled structural and thermal analysis of organic solids by B Sarma, 2009, University of Hyderabad, India worked on pKa thumb rule of co-crystals and elucidated that ΔpKa<0 were conferred

as neutral synthon; 0<ΔpKa<3.75 were considered as mixed ionization state i.e. they contains both co-crystals and salts; ΔpKa>3.75 were considered as completely salt forms.[24] Jones et al carried out Pyrimethamine co-crystals with different GRAs compounds. The ΔpKa rule was used and predicted the formation of salt/co-crystal with respective GRAS compounds. Pyrimethamine: Carbamazepine: Methanol in the ratio 1:1:2 formed solvated co-crystal which is having ΔpKa – 8.43 values. Pyrimethamine: Theophylline (1:1) ratio formed co-crystals, which is having ΔpKa – 1.66 Pyrimethamine: α – ketoglutaric acid (1:1) formed salt, which is having ΔpKa-4.47.[42] Succinic acid formed co-crystals with urea base having ΔpKa – 3.2 value. P-amino benzoic acid (PABA) with Sulfamethazine having ΔpKa of 2.59 formed a co-crystal. Meloxicam with aspirin having ΔpKa – 0.7 formed a co-crystal. Co-crystal of Isoniazid with 4-aminosalicylic acid having ΔpKa 0.1 value. Bicalutamide with Salicylamide formed co-crystals having ΔpKa-3.58 value.

Fabian's Method

Different sets of reliable co-crystal forming structures were extracted from the CSD and the molecular descriptors like single atom, bond and group counts, size and shape, surface area, molecular electrostatics were calculated for each molecule. On the basis of calculated molecular properties, the data base described pairs of molecules that were able to form co-crystals. The strongest descriptor correlation was related to the shape and polarity of co-formers.[35]

Lattice energy calculations

Lattice energy was released from the substances when ions were combined to form a new compound. It is a measure of the cohesive forces that binds ions. The lattice energy value of two component system (co-crystal) musts found to be lower or equal to the sum of the absolute sublimation enthalpies of the pure components. At least 50% of the lattice energy comes from the hetero synthon and a fewer relatively from strong Hydrogen bonds between hetero dimers and the adjacent molecules. [43]

$$\Delta H = (H_{API} + H_{co\text{-}former}) - H_{cc}$$

$$\Delta H = (H_A + H_B) - H_{AB}$$

Where A = API; B = co former; AB = Co-crystal and ΔH = Difference in lattice energy.

A work done by A.N. Manin et al on Salicylamide co-crystals experimentally proven that lattice energy of the co-crystals was found to be 143 ± 4KJ/mol which is less than the sum of two individual lattice energies of pure compounds i.e.,156 KJ/mol. ΔG values should be as lower as much will indicates the probability of co-crystal formation. If lattice energy is negative i.e., exothermic reactions, it will definitely form the co-crystals, If the lattice energy was positive (endothermic), it will not form co-crystals.[44, 45]

COSMO-RS (Short For conductor like screening model for real solvents)

This method was first published in 1995 by A.Klamt COSMO-RS is a novel approach to predict the fluid phase thermodynamic properties like activity coefficients, solubility, partition coefficients, vapour pressure and free energy salvation. It is based on quantum chemical calculations for the individual molecules, followed by a statistical thermodynamics of interacting surfaces, which uses the quantum chemical information to quantify the molecular surface interactions. This is one of the novel methods to screen the co formers for a particular API based on miscibility of co-formers in super cooled liquid (melt) phases.[46]

The excess enthalpy (H_{ex}) was a major factor for Hydrogen bonding interactions between API and co-former mixture was calculated and compared to the pure individual compounds that reflect the tendency to co-crystallize. This method was used to avoid formation of hydrates and solvates during the co-crystal designing with the assistance of any solvents. It is a most reliable thermodynamic method of chemical engineering design and development process of a co-crystal, due to efficiency, safety, costs, Feasibility based on quantitative process models.[35]

Hansen Solubility Parameter (HSP)

The concept of solubility parameters was introduced by Hildebrand and Scott, proposed the miscibility with similar values. The total cohesive energy of a molecule was divided into three individual components like

(i) Dispersion

(ii) Polar (Dipole-dipole forces)

(iii) Hydrogen Bonding.

The cohesive energy parameters can be used to determine the physicochemical properties like solubility, melting point of a material. The cohesive energy is the sum of the forces like Vander Waals forces, covalent bonds, hydrogen bonds and ionic bonds that all will hold the material intact. The cohesive energy per unit volume is termed as the Cohesive Energy Density (CED). CED is used to calculate the solubility parameters (δ)

$$\delta = [CED]^{0.5} = [\Delta E_V/V_M]^{0.5} \quad \text{-------- (1)}$$

Where E_V = energy of vaporization, V_M = molar volume. δ was measured in $[J/cm^3]^{0.5}$ or $[cal/cm^3]^{0.5}$. Total solubility parameter (δ_t) can also known as three-dimensional solubility parameters, can be calculated by

$$\delta_t = (\delta_d^2+\delta_p^2+\delta_h^2)^{0.5} \quad \text{----------(2)}$$

δ_d = dispersion parameter, δ_p = polar/dipole-dipole parameter, δ_h = hydrogen bonding parameter.

Different methods were used to estimate the HSPs of a material such as various theoretical and practical methods based on solubility, Calorimetry, sublimation, vaporization, inverse gas chromatography and group contribution

methods. The above group contribution method requires normal and common theoretical knowledge of the compounds chemical structure to calculate the HSPs. Krevlen others recommended that the beneficial solubility will be achieved if $\Delta\delta_t \leq 5MP^{0.5}$for both components. But recently Greenhalgh et al proposed the $\Delta\delta_t$ of drug and carrier as a tool to predict the miscibility having the values less than or equal to $7MP^{0.5}$ which will predicts the co-crystal formation[35, 47, 48, 49]

Virtual Co-crystal Screening

Virtual screening is a computational technique used to drug discovery. "An Automatically evaluating very large libraries of compounds" using computer programs. Professor Christopher Hunter and his co-workers have developed software to carry out the virtual screening. This software was capable to predict at what combinations of APIs and co-formers are likely to form co-crystals. Virtual screening of co-crystals was based on the principle hierarchical organization of functional group's interactions determines the structure of a crystalline solid. It means that the strongest Hydrogen bond is formed between the first best donor and acceptor, the next best H–bond is formed between next best donor and acceptor and so on, until all the interaction sites (i, j) were satisfied. In this approach Hunter's hydrogen bond parameters like α and β were used to predict the intermolecular interactions.

$E = -\sum_{ij}\alpha_i\beta_j$, where E indicates energy of solid forms

Hunters approach assumes that co-crystals only have attractive electrostatic interactions and thus the difference between the interaction site pairing energies of the co-crystal (E_{CC}) and the two pure compounds E_1 and E_2 provides information of probability of co crystal formation.

$$\Delta E = E_{CC} - nE_1 - mE_2$$

Where n and m represents the co-crystal stoichiometric ratio, ΔE = Molecular Electrostatic Potential surfaces (MEPS)

The ΔE of any pair and two individual components shows more than 11 KJ/mol, having the probability of formation of co-crystal by 50% and more.[50, 35]

Thermal Analysis

Differential Scanning Calorimetry (DSC)

This DSC was used to construct the binary phase diagrams in the screening of co-crystal formation. A binary phase diagram shows the formation and the stability of the generated co-crystal. The ability of co-crystal formation can be determined by heating the physical mixture (1:1) in DSC. A thesis/postulation proposed that there endothermic and two exothermic curves stand for the co-crystal formation with stoichiometric diversity, two endothermic and one exothermic curve stands for the formation of co-crystal with certain molar ratio and if only one endothermic curve states no co-crystals formed. A vast work done by Yamashita H et al on 20 physical mixtures of drug-conformer systems were thermally analysed by DSC on the binary phase diagram bases, they found an exothermic peak always associated with formation of a co-crystal.[51]

The co-crystal melting points will differ from the pure individual compounds melting points. In other words that sharp endothermic peaks appear at a lower temperature in comparison to the sharp endothermic peaks at higher temperatures of the individual compounds. If the compound has existed with impurities, a second peak can be created as a continuation of the main melting peak. DSC has been used for screening of co-crystals as well as compatibility study of API with co-formers/excipients. This method is very rapid screening tool to detect the probability of co-crystal designing with the aid of a small quantity of sample and no assistance of any solvent system. Hence this method is known as "Green technique". One limitation is present by this technique, the compounds which are thermally unstable and volatile in nature cannot be screened by this method.

P. Saganowska and M. Wesolowski selected 5 types of benzodiazepines like Clonazepam, diazepam, lorazepam, oxazepam and temazepam with eight types of co-formers to produce co-crystals and these 15 types of physical mixture were studies by rapid thermal method-DSC to evaluate. DSC was a green technique and rapid screening tool for the detection of co-crystallization under heating. One of group of mixtures consists of 48 samples were studied and they illustrated with the aid of DSC scans, that no co-crystals were formed by one or two only endothermic peaks. But in case of sparse mixtures, an additional exothermic peak was observed at higher temperatures due to decomposition of sample. In this case if the peak temperature of mixture was lower than both pure components that single endothermic effect is the evidence of possibilities of detaining co-crystals. In another mixture, there was a short exothermic peak after first endothermic peak; this exothermic peak appears will reveals the possibility of the co-crystal formation of this compound.[52]

Saturation temperature method

By determining the saturation temperature of a co-crystal and their individual components, will help to screen the conformers effectively. This is another novel innovative for screening of co-formers to produce co-crystals of API. Firstly, a saturation solubility of API and co-formers has to be determined individually at a particular temperature. This temperature was termed as "Reference temperature". Secondly determination of saturation temperature of both API and co-former can be measured by increasing the temperature more than 10 degree from the reference temperature by heating at a rate of 0.3°C/ min. At these elevated temperatures they have possibilities for the formation of co-crystals.[35]

Kofler Contact Method

Kofler hot stage microscope or Kofler bench was developed by the Austrian pharmacognosist Ludwig Kofler

and his wife Adelheid Kofler. It is a metal strip with a temperature gradient up to 300 degree centigrade. This apparatus was used to reveal its thermal behaviour at any temperature point of wish. Kofler contact method was often used in Optical Thermal Microscopy to examine binary phase transitions. Kofler contact method is also known as Hot-stage Microscopy method (HSM). It is a combination of both microscopy and thermal analysis to study the physical characteristics of a material in solid form as a function of temperature and time. It was the best method used for identification of co-crystals and found to offers identification of number of phases present in the system by direct visualization when two components were heated. HSM creates the controlled heating of the sample by the transfer of heat from a particular metal by the aid of electricity. By the change of temperature, the sample gets heated, thus produces thermal changes such as melting point, crystal growth, crystalline transformations, stability, phase changes etc. were clearly visualized through optical microscope which was arranged to it. By this HSM the screening of co-crystal components were done efficiently, accurately and quickly.[35, 37, 53]

Cocktail co-crystal method

A new simple "cocktail grinding method" was implemented by Katsuhiko Yamamoto for rational screening of co-crystals formation. Grinding method is most effective for co-crystal synthesis than any other crystallization form solution-based test. In this method API was allowed to ground with mixture of coformers at a time. They choose much number of coformers with same functional groups and tried grinding method. That means four coformers were grounded simultaneously with API in a Ball mill which were having the same functional group. No false negatives/positives were observed in co-crystal grinding. When Carbamazepine was used as model compound false negatives were observed for only one compound form among three model compounds, indicating that cocktail co-crystal grinding (CCG) facilitates efficient co-crystal detection and that it had higher through put than does the conventional method. However, this is very tedious process and most convenient method. This type preparation reduces work load by50%. The moieties present in the coformers will interact with API moieties and leads to the formation of synthons i.e. homosynthons or heterosynthons, finally results in a product either positive co-crystal or with some other forms.

Co-crystals of itraconazole had prepared with Succinic acid and Serine by using cocktail grinding method and produced results with highest in-vitro solubility and dissolution rate as compared to all other formulations.[35, 54, 55]

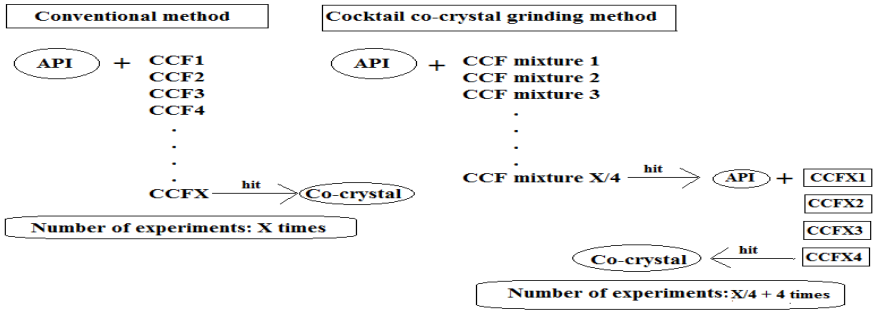


Figure 5: Pictorial representation of cocktail method

Methods of Co-Crystal Preparation

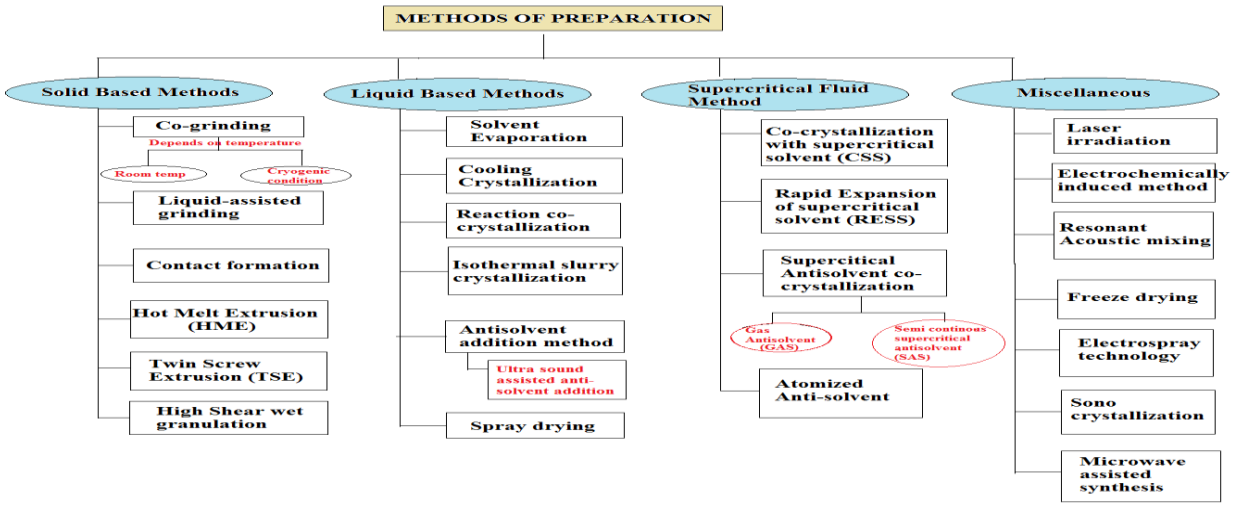


Figure 6: Schematic representations of different types of co-crystal preparation methods

Mechanism of Co-Crystal Formation

Mechanisms involved in the generation of co-crystals were affected by many variables, which are mostly affected by nature of solvent and reactants. For example, Functional groups of reactants in the particular solvents in addition to this many experimental conditions like stoichiometric ratio of the reactants, temperature, time of rotation or stirring, pH, grinding time and type of equipments used. On the other hand, the screening tools like graph set notations, Hydrogen bond propensity, Synthonic engineering, Cambridge structural data base, Hansen's solubility parameters (HSP), Virtual screening, Lattice energy calculations, Thermal analysis, Kofler contact method, cocktail co-crystal method, Fabians method, COSMO-RS, ΔpK_a values were supportive in designing co-crystal system. The co-crystal preparation was a multistage experimental process. Preparation methods were classified into two types depending upon their technology of preparation.

1) Traditional methods

2) Advanced methods

Mechano-chemical type of techniques present in both traditional models and advanced models were optimistic in productivity of co-crystals in an affordable synthetic pathway. Co-Crystallization is not a single step process, composed of series of some mechanical and chemical conversions which encompasses molecular diffusion, eutectic formation, amorphous stage and conversion into co-crystal nucleation and co-crystallization finally precipitation. Most commonly observed mechanism in the formation of co-crystals between two different compounds was the presence of an intermediate bulk phase like gas, liquid or amorphous solid. This intermediate bulk phase enhances the mobility and increases the energy of reactant molecules when compared to the initial starting crystalline forms of compounds.[56]

Depending upon the reactants nature and method of preparation, the mechanism involved in the formation of co-crystals were varies. The frequently occurred some of the predicted mechanisms in the evolution of co-crystals were likely to be molecular diffusion, Eutectic formation, Amorphous intermediates, Deliquescent conditions, Thermodynamic parameters, and solubilities of compounds.

One of the most commonly occurring basic mechanisms in co-crystal by tradition method grinding/kneading was "molecular diffusion". The transfer or movement of individual molecules through a fluid means may be liquid state or gases state. Both reactants have high vapour pressures in the solid state this molecular diffusion occurs during grinding process results in adduct formation. During grinding process, the molecular arrangement of each compound was disturbed and set to a free state to move in any directions with the aid of their attraction or magnetic forces. This disturbed situation creates more availability of fresh surfaces, which will enhance the molecular diffusion between two reactant molecules in a random walk process. In addition to this high vapor pressure molecular diffusion, the mechanical grinding forces break downs the intermolecular bonds of the crystals of the reactant molecules. This cleavage and splitting of molecules leads to rearrangement in a co-crystal patterns with the aid of Hydrogen bonding propensities according to the Synthonic engineering and Cambridge structural data base (CSD). [57]

In liquid assisted co-crystallization methods, the generation of co-crystals was developed by Eutectic Formation mechanism when one of the reactant was liquid at room temperature, the co-crystals was formed by an intermediate liquid phase. For example, diphenylamine and benzophenone was selected as reactants for co-crystal production, the interface of two colorless substances was revealed by microscopical observation, there by the contact surfaces of two substances was converted into liquid form. Incorporating grinding with eutectic mediated co-crystallization enhances the process through two mechanisms, firstly the fresh reactant surfaces was increased for eutectic formation. Secondly, improving the co-crystal nucleation in the eutectic phase form.[56] If there is no mass transfer pathway like liquid or gas phase, then the co-crystallization can be taking place through the formation of amorphous intermediates. In liquid assisted grinding technique, the liquid just plays the role of lubrication by providing a medium to facilitate the molecular diffusion between the two reactants. Hence the co-crystals formed by neat and liquid assisted grinding were typically thermodynamically stable. This type of mechanism was also observed in the slurry co-crystallization technique, where solvent for slurry preparation acts as just a lubricant to smoothens and accelerate the molecular diffusion between the two reactants to generate co-crystal nucleation by Hydrogen bonding thumb rules.

Deliquescent and moisture sorption reactants undergo the co-crystallization during storage and co-grinding process. The basic mechanisms present in this type of reactants, was moisture uptake to create the solubility of both reactants in the moisture, then molecular diffusion was attained due to the solvent lubrication according to the screening tools related to the particular reactants. For example, Carbamazepine-Saccharin, Saccharin was a deliquescent compound which will absorbs the moisture from the atmosphere and produces the co-crystals upon storage. Co-former plays a vital role in controlling the formation of co-crystals. The appropriate stoichiometric ratio of both reactants produces the perfect co-crystal with high stability. 1:1 and 1:2 ratios of Carbamazepine - 4-amino benzoic acid co-crystals having more stable than equimolar ratio co-crystal.[23]

Another major parameters can also be involved in the mechanism of co-crystal formation, they are thermodynamic variables like solubility products (K_{sp}),

complexation constants(K_{11}) and Gibb's free energy (ΔG^o) of the reactant compounds. The solubility product (K_{sp}) is the equilibrium constant for a solid substance dissolving in a particular aqueous solution. It indicates the level of solute dissolves in solution, the more soluble the solute substance, there by higher the (K_{sp}) value. Mutually miscible the two compounds in a solvent with higher (K_{sp}) leads to co-crystal formation. Complexation constant (K_{11}) is also known as stability constant It is an equilibrium constant for the formation of a complex in the solution. It is a measure of the strength of the interaction between the two reactants, that forms adduct or complex. Up on changing the temperature of the system, the complexation constant varies. This complexation constant value states the supramolecular complex held by hydrogen bonding, Vander Waal forces, π-π interactions and electrostatic effects.[29]

Production of high-quality purity co-crystal by considering the binary or ternary phase diagrams for the equilibrium of the solvent with two components, of the co-crystal system. Binary phase diagram shows the eutectic points between each phase and hence implies the existence and number of co-crystal phases. The ternary phase diagram was highly influenced by the relative solubilities of the two components. If the solubilities of two components in a given solvent were similar, they are represented as the figure 7 (a), while the (b) schematically shows the more complicated phase diagram that represents the compounds having different solubilities in a particular solvent.[20, 37]

By these diagrams, the slow evaporation of a 1:1 ratio concentrated solution of two ingredients may lead either a co-crystal formation or a mixture of co-crystal and the individual compounds. The resultant depends on whether the crystallization path passes through the mixed-phase region or the single – phase region.[58]

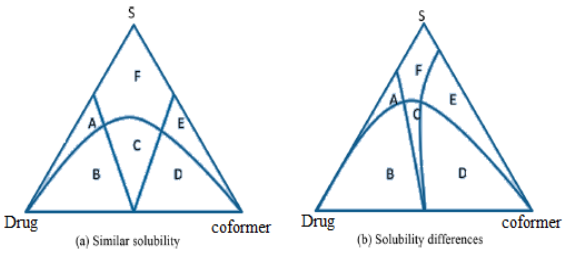


Figure 7: Schematic representations of Isothermal Ternary phase diagrams with (a) Similar solubility b) Different solubilities. Region A- drug and solvent; B- drug and co-crystal; Region C- co-crystal; Region D-Co-former + co-crystal; Region E- coformer + solvent; Region F – solution

Application of Co-Crystals

Table 2: Examples of co-crystals with enhancement in physicochemical properties and combination therapy

S.no	Drug + Conformer	Observation	Ref
1	Resveratrol + 4-amino benzamide and +Isoniazid	Enhanced solubility when compared to pure.	59
2	Febuxostat +arginine	Increased solubility from 7.5 mg/L to 571mg/L	60
3	AMG 517+Cinnamic acid +Benzoic acid +Cinnamamide +Benzamide	Showed faster intrinsic and powder dissolution rates. P.k showed a 2.4-7.1 folds increases in AUC rats.	61
4	Danazol + Vanillin +TPGS (solubilizers) + precipitation Inhibitor	Improved solubility and Bio availability over 10 times than pure Danazol	62
5	Resveratrol + 4-amino benzamide + Isoniazid	Showed enhanced tabletability	59
6	Paracetamol + Theophylline + oxalic acid + Naphthalene + Phenazine	Compression properties were improved	63
7	Hydrochlorothiazide + Sucralose	Benefits of enhanced rate of dissolution and taste masking of drug.	64
8	Rosuvastatin Hemi calcium + vanillin	Enhanced light stability	65
9	Nilotinib+ Fumeric acid	Reduction in Hygroscopicity	65
10	Theophylline + oxalic acid +maleic acid +Malonic acid + Glutaric acid	Improved in physical properties and relative humidity stability	66
11	Meloxicam +Aspirin	Enhanced Bio availability by 4-folds, 12 times reduction in time to reach the therapeutic concentration	67

12	Pyrazinamide+ Diflunisal	Side effects of Pyrazinamide was reduced and solubility of Diflunisal was increased	68
13	Isoniazid + 4-amino salicylic acid and Pyrazinamide + 4- amino salicylic acid	Enhanced therapeutic activity	69

REFERENCES

1. Penisky R. Crystal Engineering: New concepts in crystallography. Physical Review.1955; 100: 971-971.
2. Schmidt G M. Photodimerization in the solid state. Journal of pure applied chemistry. 1971; 27: pp. 647-678.
3. Thomas J M. Diffusion less reactions and crystal engineering. Nature 1981; 289: pp 633-634.
4. Addadi L, Lahav M. Towards the planning and execution of an "absolute" asymmetric synthesis of chiral dimers and polymers with quantitative enantiomeric yield. Journal of pure applied chemistry. 1979; 5: pp. 1269-1284.
5. Wegner G. Topochemische Reaktionen von Monomeren mit Konjugierten Dreifachbinungen I. Mitt: Polymerisation von Derivaten des 2.4 – Hexadiin – 1.6 diols im kristallinen zustand. Z. Naturforsch . B 1969; 24: pp. 824-832.
6. Desiraju G R. Crystal engineering. The design of organic solids. Elsevier, Amsteram 1989.
7. F Wohler. Untersuchungen uber des chinons. Annalen chem. Pharm. 1844; 51: 145-163.
8. Ling A R, Baker J L XCVI. – Halogen derivatives of quinine. Part III. Derivatives of quinpydrone. Journal of the chemical society, transactions. 1893; 63: 1314-1327.
9. Gautam R. Desiraju. Crystal Engineering: A brief overview. Journal of chemical sciences, Sep 2010; 122(5): 667-675.
10. Andrew D Bond. What is a co-crystal? Crystal. Crystal Engineering communications. 2007; Issue 9: 833-834.
11. Gautam R Desiraju. Crystal and co-crystal. Crystal Engineering communications. 2003; 5: 466-467.
12. Jack D Dunitz. Crystal and co- crystal: A second opinion. Crystal engineering communications. 2003; 5: 506-506.
13. Aakeroy C B, Fasulo M E, and Desper J. Co-crystal or salt: Does it really matter? Molecular Pharmaceutics. 2007; 4(3): 317-322.
14. Stahly G P. Diversity in single and multiple-component crystals. The search for and prevalence of polymorphs and co-crystals. Crystal growth & Design. 2007; 7(6): 1007-1026.
15. Nangia A. Supramolecular chemistry and crystal engineering. Journal of chemical sciences. May 2010; 122(3): 295-310.
16. S L Childs and K I Hardcastle. Cocrystals of piroxicam with carboxlic acids. Crystal growth and Design 2007; 7(7): 1291-1304.
17. Jones W, Motherwell WD, Trask AV. Methods for stereoselective synthesis of bicyclic compounds. MRS Bull 2006; 341: 875-879.
18. Vishweshwar P, Mc Mahon J A, Bis J A, Zaworotko M J. Pharmaceutical co-crystals. Journal of pharmaceutical sciences. 2006; 95(3): 499-516.
19. S Mirza, I Miroshnyk, J Heinamaki, J Yliruusi-Dosis. Co-crystals: An emerging approach for enhancing properties of pharmaceutical solids. 2008; 24(2).
20. Steed J W. The role co-crystals in Pharmaceutical design. Trends in pharmacological sciences. 2013; 34(3): 185-193.
21. Jayasankar A, Somwangthanaroj A, Zezhi J S and Hornedo N R. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. Pharmaceutical Research. Oct 2006; 23(10).
22. Desale P K. A novel method: Co-crystallization. International Journal of pharmaceutical invention. March 2013; 3(1).
23. Sekhon B S. Pharmaceutical co-crystals a review. ARS pharmaceutica. 2009; 50(3): 99-117.
24. Ranjit T and Bipul S. Drug-Drug and Drug-Nutraceutical cocrystal/salt as alternative medicine for combination therapy: A crystal engineering approach. Crystals. 2018; 8(2): 101.
25. Mukherjee S. Crystal Engineering of pharmaceutical co-crystals. Graduate school theses and dissertation. University of South Florida 2011; 1-24.
26. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta pharmaceutical sinica B 2015; 5(5): 442-453.
27. Takagi T, Ramachandra C, Bermejo M, yamashita S, yu L X, Amidon G L. A provisional Biopharmaceutical classification of the top 200 oral drug products in the United states, Great Britain, Spain and Japan. Molecular Pharmaceutics 2006; 3: 631-643.
28. Available online: http://apps. Who.int/iris/bitstream/10665/43443/1/WHO-TRS-937-eng.pdf.
29. B S Sekhon. Pharmaceutical co-crystals- An update. International Bulletin of drug Research. 1(2): 24-39.
30. Sulbha R Fukte, Milind P Wagh and Shilpi R. Coformer selection: An important tool in cocrystal formation. International Journal of pharmacy and pharmaceutical sciences. 2014; 6(7).
31. M Akshay Vithalrao, F Neeraj Kumar, B Kailash Radheshyam. Co-crystallisation: An alternative approach for solid modifications. Journal of Drug Delivery and therapeutics, 2013; 3(4): 166-172.
32. Margaret C Etter. Hydrogen bonds as Design elements in organic chemistry. Journal of physical chemistry. 1991; 95: 4601-4610.
33. Childs S L, Stahly G P, Park A. Salts and co-crystals of theophylline. Molecular pharmaceutics 2007; 4: 323-338.
34. Cruz-Cabeza A J. Acid – base crystalline complexes and the pK_a rule. Crystal Engineering communications. 2012; 14: 6362-6365.
35. S Kumar and A Nanda. Pharmaceutical co crystals: An overview. Indian Journal of pharmaceutical sciences. 2017; 79(6): 858-871.
36. Anna Karagianni, Maria Malamatari and Kyriakos Kachrimanis. Pharmaceutical Cocrystals: New solid phase modification approaches for the formulation of APIs. Pharmaceutics 2018; 10(18).
37. Bis J A, Vishweshwar P, Weyna D, Zaworotko M J. Hierarchy of supramolecular synthons: Persistent Hydroxyl Pyridine Hydrogen bonds in cocrystals that contain a cyano acceptor. Molecular pharmaceutics.2007; 4: 401-416.
38. Hathwar V R, Thankur T S, Guru Row T N, Desiraju G R. Transferability of multiple charge density parameters for supramolecular synthesis: A new tool for quantitative crystal engineering. Crystal Growth Design 2011; 11: 616-623.
39. Dunitz J D, Gavezzotti A. A supramolecular synthon: Validation and Ranking of Intermolecular Interaction Energies. Crystal Growth Design. 2012; 12: 5873-5877.
40. Krawczuk A, Macchi P. Charge density analysis for crystal engineering. Chem. Cent. J. 2014; 8: 1-15.
41. Abida Rehman, Amit Delori, David S Hughes and William Jones. Structural studies of crystalline forms of triamterene with carboxylic acid, GRAS and API molecules. IUCrJ, 2018; 5: 309-324.

42. Whitesider G M, Wong A P. The intersection of biology and materials science. MRS Bull 2006; 31: 19-27.

43. Mikhail V Vener, Elena O Levina, O A Koloskov, A A Rykounov, A P Voronin and V G Tsirelson. Evaluation of the lattice energy of the two- component molecular crystals using solid-state Density Functional Theory. Crystal Growth Design. 2014; 14(10): 4997-5003.

44. L N Kuleshovo and R Boese. Lattice energy calculation. A quick tool for screening of cocrystals and estimation of relative solubility. Case of Flavonoids. Chemical Physics letters. March 2013; 564(28): 26-32.

45. A N Manin, A P Varoain, N G Manin et al. Salicylamide cocrystals: Screening, crystal structure, sublimation thermodynamics, Dissolution and solid-state DFT calculations. The Journal of physical chemistry B. 2014; 118(24): 6803-6814.

46. Abramov Y A, Loschen C, Klamt A. Rational co former or solvent selection for pharmaceutical co-crystallization or desolvation. Journal of pharmaceutical sciences. 2012; 101(10): 3687-97.

47. Venkata Deepthi V, Srinivas L. Insight into concept and progress on pharmaceutical co-crystals: An overview. Indian Journal of pharmaceutical Education and Research. Oct-Dec 2019; 53(4).

48. Mohammad Amin Mohammad, Amjad Alhalaweh, Sitaram P V. Hansen solubility parameter as a tool to predict co crystal formation. International journal of pharmaceutics. 2011; 407: 63-71.

49. Van Krevelen D W, Hoftyzer P. Properties of polymer their estimation and correlation with chemical structure. 2 nd ed Amsterdam: Elsevier science 1976.

50. Musumeci D, Hunter A C, Prohens R, Scuderi S, Mc Cabe F J. Virtual Cocrystal screening. Chem.sci. 2011; 2: 883-890.

51. Yamashita H, Hirakura Y, Yuda M, Terada K. Coformer screening using Thermal analysis based on binary phase diagram. Pharmaceutical Research 2014; 31: 1946-57.

52. P Saganowska, M Wesolowski. DSC as a screening tool for rapid co-crystal detection in binary mixtures of benzodiazepines with co-formers. Journal of Thermal analysis and Calorimetry. 2018; 133: 785-795.

53. Berry D J, Seaton C C, Clegg W, Harrington R W, Coles S J, Horton P N et al. Applying hot-stage microscopy to co-crystal screening: A study of nicotinamide with seven active pharmaceutical ingredients. Crystal growth design. 2008; 8(5): 1697-712.

54. Shete A, Murthy S, Korpale S, Yadav A, Sajane S et al. Co crystal of itraconazole with amino acids: Screening, synthesis, solid state characterization. Invitro release and antifungal activity. Journal of Drug Delivery Sciences of Technology. 2015; 28: 46-55.

55. Yamamoto K, Tsutsumi S, Ikeda Y. Establishment of cocrystal cocktail grinding method for rational screening of pharmaceutical co-crystals. International Journal of Pharmaceutics 2012; 437: 162-71.

56. Friscic T, Jones W. Recent advances in understanding the mechanism of Cocrystal formation via grinding. Crystal Growth Design.2009; 9(3): 1621-1637.

57. Kuroda R, Higashiguchi K, Hasebe S, Imai Y. Crystal to crystal transformation in the solid state. Crystal Engineering Communications.2004; 6: 463-468.

58. David John Good. Pharmaceutical cocrystal Eutectic Analysis: Study of thermodynamic stability, solubility and phase behaviour. Deep blue. 2010

59. Zhou Z, Li W, Sun WJ, Lu T, Tong HHV, Sun CC et al. Resveratrol co-crystals with enhanced solubility and tabletability. International Journal of pharmaceutics 2016; 509: 391-9.

60. Kang Y, Gu J, Hu X. Synthesis, structure characterization and dissolution of two novel cocrystals of Febuxostat. Journal of Molecular structures. 2017; 1130: 480-486.

61. Stanton M K, Kelly R C, Colletti A, Kiang Y H, Langley M, Wells M et al. Improved Pharmaceutics of AMG 517 through co-crystallization part 1: Comparison of two acids with corresponding amide co-crystals. Journal of pharmaceutical sciences. 2010; 99(9): 3769-3778.

62. Childs S L, Kandi P, Lingireddy S R. Formulation of a Danazol cocrystal with controlled supersaturation plays an essential role in improving bioavailability. Molecular Pharmaceutics 2013; 10(8): 3112-3127.

63. Karki S, Friscic T, Fabian L, Laity P R, Day G M, Jones W. Improving mechanical properties of crystalline solids by co-crystal formation: New compressible forms of paracetamol. Adv Master. 2009; 21(38-39): 3905-3909.

64. Arafa M F, El- Gizawy S A, Osman M A, El-Maghraby G M. Sucralose as co-crystal co-former for hydrochlorothiazide: Development of oral disintegrating tablets. Drug Development and Industrial Pharmacy. 2016; 42(8): 1225-1233.

65. Martin V, Andreas H. Co- crystals and their advantages for APIs with challenging properties. Chimica oggi- chemistry Today. Sep/Oct 2015; 33(5).

66. Colombo V, Pesti L L, Gavezzotti A. Two – component organic crystals without hydrogen bonding: Structure and inter molecular interaction in bimolecular stacking. Crystal Engineering Communications. 2017; 19: 2413-2423.

67. M L Cheney, D R Weyna, N Shan, M Hanna, L Wojtas, M J Zaworoka. Coformer selection in pharmaceutical cocrystal development: A case study of a Meloxicam Aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics. Journal of pharmaceutical sciences. 2011; 100: 2172-2181.

68. A O L Evora, R A E Castro, T M R Maria, M T S Rosado, M R Silva, A M Beja et al. Pyrazinamide-Diflunisal: A new Dual drug co-crystal. Crystal Growth Design. 2011; 11: 4780-4788.

69. Grobelny P, Mukherjee A, Desiraju G R. Drug-Drug co-crystals: temperature-dependent proton mobility in the molecular complex of Isoniazid with 4-aminosalicylic acid. Cryst Eng comm. 2011; 13: 4358-4364.

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