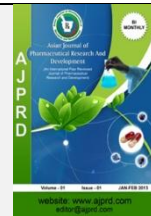


Available online on 15.04.2019 at <http://ajprd.com>

Asian Journal of Pharmaceutical Research and Development

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Review Article

An Overview of Pharmaceutical Co-Crystal

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ABSTRACT

Pharmaceutical co-crystals are nonionic supramolecular complexes and supramolecular chemistry. Pharmaceutical co-crystal consists of active pharmaceutical ingredients and coformers. Pharmaceutical co-crystals can be employed to improve vital physicochemical characteristics of a drug, including solubility, dissolution, bioavailability and stability of pharmaceutical compounds while maintaining its therapeutic activity. Co-crystals can be constructed through several types of interaction, including hydrogen bonding, pi-stacking, and vander Waals forces. Pharmaceutical co-crystals could play a major role in the future of API formulation. Pharmaceutical co-crystal can be improvement future aspect problems related physicochemical properties of API.

Key words: Pharmaceutical co-crystal, Co-crystallization, coformers, Hydrogen bonding.

ARTICLE INFO: Received 30 Jan 2019; Review Completed 15 March 2019; Accepted 2 April 2019; Available online 15 April 2019

Cite this article as:



Ancheria Rahul Kumar *, Jain Saloni, Kumar Deepak, Soni Sankar Lal, Sharma Mukesh., An Overview of Pharmaceutical Co-Crystal, Asian Journal of Pharmaceutical Research and Development. 2019; 7(2):39-46
DOI: <http://dx.doi.org/10.22270/ajprd.v7i2.483>

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INTRODUCTION

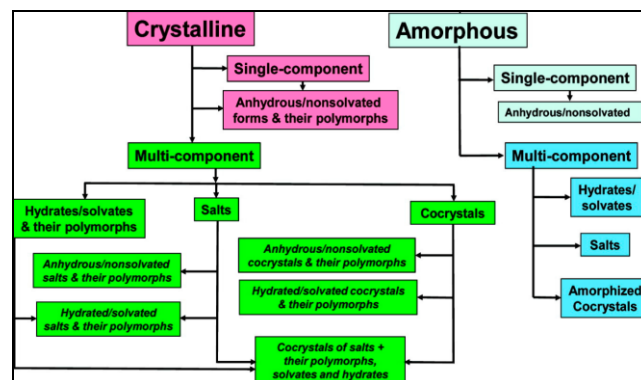
Many active pharmaceutical ingredients (APIs) have not been developed in formulations due to low aqueous solubility, which causes low bioavailability of drugs. Researchers have developed various approaches to enhance the solubility of drugs, which lead to improvement in the bioavailability¹ Size reduction, solid dispersion, complexation, salt formation, nanoparticles, self-emulsifying drug delivery system (SEDDS), addition of co-solvents, nano-suspension and emulsion and co-crystal formation³. 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 desired physical and chemical properties⁴.

CO-CRYSTALS

The term “co-crystal” and design rules of hydrogen bonding of an organic co-crystal were first reported by Etter^{5,6}. Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Co-crystals have regained attention as attractive alternate solid forms for drug development. Co-crystallization with pharmaceutically acceptable (GRAS) compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior. Co-crystallization is a result of competing molecular

associations between similar molecules, or homomers, and different molecules or heteromers^{7,8}. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single component crystals and their polymorphs) or with different molecular components (multiple component crystals or co-crystals) in the crystalline state⁸.

SOLID FORMS OF API



The components in a co-crystal exist in a definite stoichiometric ratio, and assemble via non-covalent interactions such as hydrogen bonds, ionic bonds, π - π or van der Waals interactions rather than by ion pairing.

PHARMACEUTICAL CO-CRYSTALS

The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences^{9,10}. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former¹¹. Co-crystal former may be an excipient or another drug. Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API^{15,16}. Scientists showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical co-crystal formation improved the performance of a drug known to have poor solubility. Pharmaceutical co-crystallization is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability, hygroscopicity, and compressibility without alternating their pharmacological behavior^{18,20}. The expanding scope of crystal form selection, emergence of crystal engineering in pharmaceutical science and pharmaceutical co-crystals were reviewed. Some common aspects of co-crystal formation, screening strategies and outline methodologies for co-crystal functionality were reported. The use of co-crystals in drug design and delivery and as functional materials with potential applications as pharmaceuticals has recently attracted considerable interest. Pharmaceutical co-crystals have been described for many drugs such as acetoaminophen, aspirin, ibuprofen, flurbiprofen etc. Co-crystals of antitubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool^{16,18}.

DIFFERENCE BETWEEN CO-CRYSTAL, SALT, SOLVATES AND HYDRATES

USFDA defined the co-crystal, salt and polymorphs in the draft guidance. The polymorphs are defined as the compounds which are present in different crystalline forms such as solvates or hydrates (also known as pseudopolymorphs) and amorphous forms¹⁴. Polymorphs have different lattice arrangement and also, they have different physicochemical properties due to their crystal lattice structures. Salts are the compounds which are formed by complete transfer of proton from one compound to another. Salts and co-crystal can be differentiated based by a proton transfer from an acid to base. A complete transfer of proton takes place between acid-base pairs, whereas, no proton transfer occurs during co-crystal formation. Two components are bound to each other by non-covalent interactions such as hydrogen bonding, π - π stacking, van der Waal forces. A prediction can be made by ΔpK_a value whether co-crystal are formed or not. It is generally accepted that a salt will be formed if the ΔpK_a value is greater than 3 and ΔpK_a value less than 0 will lead to the formation of co-crystal. This parameter is not accurate to predict the formation of co-crystal in solids between the ΔpK_a values 0 and 3 but the possibility of salt formation will increase when the ΔpK_a increases. Co-crystal and solvates can be differentiated based on their physical state of the components. The compounds which are liquid at room temperature are called as solvates whereas those compounds which are solid at room temperature are called as co-crystals. If the solvates contain water as a solvent in their crystal lattice then they are known as hydrates. Solvates/hydrates are commonly formed during the co-crystallization via solution or liquid assisted grinding^{18,19}.

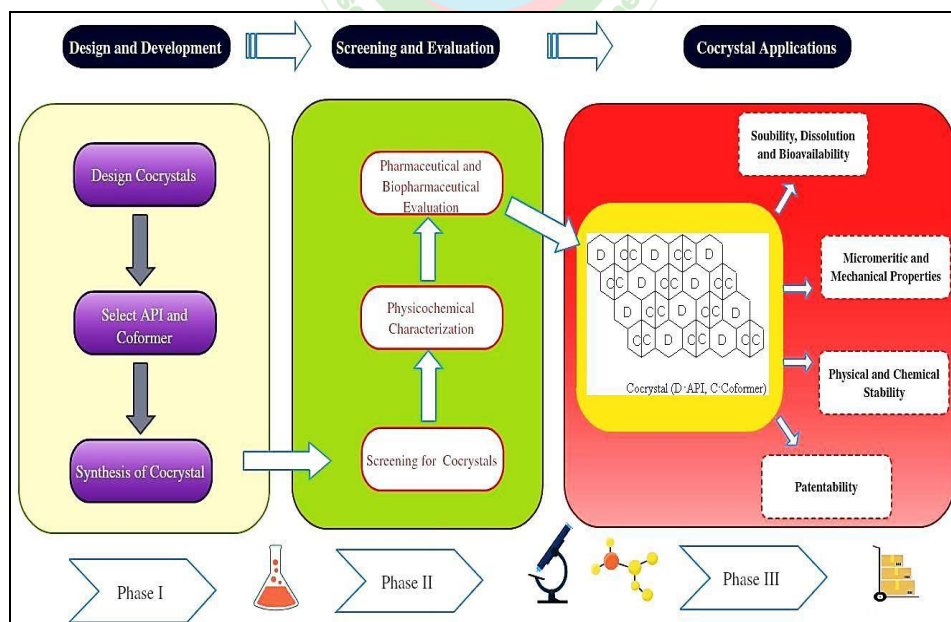


Figure 1: Process for co-crystal development, screening and applications

PHYSICOCHEMICAL PROPERTIES

Pharmaceutical co-crystal can enhance the physicochemical properties of drugs such as melting point, tableability, solubility, stability, bioavailability, permeability and these properties are highlighted here with suitable examples.

Melting Point:

Melting point is a fundamental physical property, and is defined as the temperature at which the solid phase is in equilibrium with the liquid phase, and it is a thermodynamic process in which the free transition energy is zero^{20,22}. Melting point is the physical property

of solids, which is used to determine the purity of the product with sharp melts and narrow ranges. High melting point demonstrates the thermodynamically stability of the new materials i.e. thermal stability of an API can be increased by selecting the coformer with higher melting point²⁴. Melting point of pharmaceutical co-crystal can be tailored by judicious selection of the conformers. Differential scanning calorimetry (DSC) or the Kofler method are considered to be the methods of choice for obtaining melting point data, due to their ability to detect additional thermal data. The determination of the melting point of a compound is the means by which it can be classified, and its purity identified³⁰.

It is standard practice to determine the melting point of a compound as a means of characterization or purity identification; however, within pharmaceutical sciences, the melting point is also very valuable due to its correlations to aqueous solubility and vapor pressure. The molecular arrangement within the crystal lattice, molecular symmetry, intermolecular interactions, and conformational degrees of freedom for a molecule, one clearly sees the difficulties in attempting to draw strict comparisons from molecular structure to crystalline lattice energy to melting point²⁸. The situation only becomes more complex when observing multicomponent systems because each component has its own characteristic properties and those can influence the environment (and intermolecular interactions) around its neighbors. In this section we will examine the thermal behavior of co-crystal in which one component is an API, although findings and trends should be translatable to all co-crystalline materials²⁹.

Solubility:

Solubility is an important parameter to investigate the formulations of poorly soluble drugs. Many approaches have been used to improve the solubility of drugs such as salt formation, solid dispersion, particle size reduction, and so on, amongst which co-crystallization has been used by several researchers²⁷. The first investigation on the behavior of co-crystal in solution as a function of co-crystal component concentration was based on the extensive knowledge of molecular complexes, solid-state complexes, and molecular compounds that existed before the introduction of the term of co-crystal, and is analogous to the effect of common ions on the solubility of sparingly soluble salts. The solubility of co-crystal has been reported in a number of cases and in a variety of media, including water, 0.1 N HCl, phosphate buffer, SGF, and SIF. Most studies report powder dissolution data with multiple time points. In some cases, particle size was controlled by sieving samples, in some there was no reported control, and in others different particle size ranges were used for comparison²⁵. This shows the wide range of experimental variables that can be used for solubility testing which can be tailored to obtain the desired information²². Three itraconazole co-crystal (succinic acid, L-malic acid, and L-tartaric acid) were compared with crystalline itraconazole (particles less than 10 μm) and commercial Sporanox beads (amorphous itraconazole). Solutions of 0.1 N HCl were used and sampled over 500 min. The co-crystal all exhibited higher solubility than the crystalline itraconazole. The L-malic and L-tartaric acid co-crystal exhibited solubilities similar to that obtained for the Sporanox beads (approximately 7

$\times 10^{-4}$ M) and the succinic acid was lower (approximately 2×10^{-4} M). The co-crystalline forms achieved and sustained from 4- to 20- fold solubility increases over the crystalline itraconazole.

Stability:

Stability study is extremely important during the development of new dosage formulation. During development of pharmaceutical co-crystal several stability studies should be performed such as relative humidity stress, chemical stability, thermal stability, solution stability and photostability study. In relative humidity stress, automated water sorption/desorption studies are performed to determine the effect of water on the formulation²⁵.

Relative Humidity (RH):

In solid forms, changes in RH must be considered when developing a co-crystal. Studies on automated humidity sorption/desorption are usually performed to determine the “problematic” conditions and give directions for more detailed studies, if necessary. Moisture uptake can be controlled through the exposure of the co-crystal to a particular RH using an appropriate humidity chamber and then analyzing the sample after reaching equilibrium⁸. A systematic study in which caffeine was co-crystallized with various carboxylic acids, namely oxalic, malonic, maleic and glutaric acid, showed that the co-crystal produced exhibited reduced hygroscopicity compared to the raw API. The samples were placed in four RH conditions and analyzed after 1, 3 and 7 weeks.

Thermal stress:

Stability (physical and chemical) of the solid API under high temperature conditions is always evaluated. A study examining the co-crystal of a monophosphate salt with phosphoric acid at 60 C showed no detectable degradation or transitions between forms²⁹.

Photostability:

Carbamazepine undergoes photodegradation, with the mechanism depending on the distances between the rings in the crystal lattice (it requires $< 4.1 \text{ \AA}$). The carbamazepine-saccharin and carbamazepine-nicotinamide co-crystal have longer ring distances, eliminating the mechanism of photodegradation. Thus, the co-crystal can be protected from unwanted processes, since co-crystallization may affect chemical stability through the rearrangement of the molecules in the crystal lattice.

Solution stability:

This is defined as the ability of the co-crystal components to remain in the solution and to not readily crystallize. This is an important parameter to evaluate during development, both for solutions and suspensions, as well as for solid dosage forms that will dissolve in the gastrointestinal tract. Since co-crystal dissociation may occur, the stability in solution is a key element in their development. A study on carbamazepine co-crystal with 18 coformers evaluated the formation of carbamazepine hydrate when the co-crystal were slurried in water for 24–48 h. Of the studied co-crystal, seven maintained their crystalline structures, and the rest were converted into carbamazepine hydrate. The aqueous solubility of the

coformer appeared to be an important parameter for the formation of the hydrate. It was noted that co-crystal containing coformers with relatively high solubility in water resulted in the hydrated form, while co-crystal with coformers of relatively low solubility remained stable in aqueous media^{15,16}.

Bioavailability

Bioavailability is defined as the rate and extent of pure drug that reaches into systemic circulation. Low oral bioavailability of APIs is a major challenge during the development of new formulations. Crystal engineering is mainly used to design and synthesize the pharmaceutical co-crystal with enhanced aqueous solubility and oral bioavailability. Oral bioavailability of baicalein was increased by formation of co-crystal with nicotinamide and showed that co-crystal had 2.49 times higher peak plasma concentration (C_{max}) and 2.80 times higher area under the curve (AUC) as compared to pure drug in rats. Meloxicam co-crystal with aspirin exhibited better oral bioavailability as compared to pure drug and showed 12 times faster onset of action than pure drug in rats¹⁸.

Permeability

Drug absorption and distribution of drugs mainly depends upon the permeability of drugs across the biological membrane. Permeability of drugs mainly depends upon the n-octanol/water partition coefficient by using log P and (C log P) for unchanged form of drug. Permeability of a BCS class-III drug, 5-fluorouracil, was enhanced by co-crystallization with different coformers such as 3-hydroxybenzoic acid, 4-aminobenzoic acid and cinnamic acid. Permeability study of hydrochlorothiazide and co-crystal with different coformers was studied by using Franz diffusion cells. The amount of drug flux in all co-crystal was higher as compared to pure drug except for succinamide co-crystal. Co-crystal permeability was improved due to formation of heterosynthons between drug and conformer²⁶.

METHODS OF CO-CRYSTAL PREPARATION

The process of co-crystal formation is not fully understood. It is not clear whether formation of intermediate states (e.g., amorphous phase) precedes co-crystallization. A recent study based on solid-state NMR suggests that co-crystallization is not mediated by the transient formation of an amorphous phase.

1. Solvent Evaporation Technique:

This is the most commonly used technique for generating co-crystal. The materials (API and coformer) are dissolved in a common solvent with a suitable stoichiometric ratio and completely evaporate. During evaporation, the solution of the molecules undergoes changes, with the creation of hydrogen bonds between different functional groups, thus producing a thermodynamically favored product. The selection of the solvent plays an important role in solubility. If the solubility of the two components is not similar, then the component with the lower solubility will precipitate. Preparation of co-crystal by solvent evaporation is a small-scale technique that does not require complex equipment, and results in co-crystal of high quality and purity. However, the use of large amounts of solvent and

its limited scalability are two disadvantages to this technique¹⁶.

2. Solid-State Grinding Technique Or Neat Grinding:

This is a co-crystallization method without a solvent. The solid materials that will result in the co-crystal are admixed in appropriate stoichiometric amounts, pressed and crushed together with a mortar, and pestle, or a ball mill or vibrator mill. The common grinding duration ranges from 30 to 60 min. With this method, numerous co-crystal can be prepared, and any failure is generally due to the use of inappropriate settings. Reducing the particle size increases the specific surface area of interaction between the materials for the development of intermolecular bonds. This offers the advantage of increased selectivity compared to co-crystallization through dissolution. It is simple, and allows quick preparation of the desired co-crystal. Experiments on mixing co-crystal with other components that can also form co-crystal with the API have been carried out. In the latter case, the coformer is replaced, and this can be used either to assess the stability of a co-crystal in the presence of other excipients or to disclose alternative modifications of the co-crystal. Modifications that don't necessarily take place in the process of dissolution, e.g., caffeine-trifluoroacetic acid co-crystal, were initially only obtained by grinding. That is to say that it has also been used as a method of clarifying hydrogen bond preference. Mechanochemistry (i.e., solid-state grinding) was used for the patent of the pterostilbene-caffeine co-crystal³⁰.

3. Liquid-Assisted Grinding, Or Solvent-Drop Grinding:

This is a modification of neat grinding by adding a small amount of solvent during the grinding process, and has been used to enhance supramolecular selectivity, both polymorphic and stoichiometric, in crystalline systems. It includes mixing the two components and adding a very small amount of solvent (~a few tenths of an equivalent of solvent per mole of the component). The effect of the solvent can be described as catalytic, as its small amount is not part of the final product. Its advantages lie in its increased performance, in the ability to control the production of polymorphs, and in the improved crystallinity of the product, while a large number of coformers are suitable for the co-crystallization. This method enhances the co-crystallization rate, as some co-crystal showed poor performance in co-crystal formation following neat grinding for a considerable amount of time. This method can be used to prepare high-purity co-crystal with a significant reduction in the preparation time. It also allows the synthesis of selective polymorphic forms of co-crystal. For instance, in caffeine-glutaric acid (1:1) co-crystal, neat grinding resulted mainly (not always) in form I, while liquid-assisted grinding to pure form I with less polar solvent (e.g., cyclohexane or hexane) and to pure form II with more polar solvent (e.g., water or acetonitrile). This allows interconversion between crystalline forms of polymorphic organic components, depending on the polarity of the solvent. Limitations of liquid-assisting grinding include the fact that it is a small-scale technique, requires high energy consumption, and has a low performance in terms of product purity. Liquid-assisted grinding was used for the patent of pterostilbene-carbamazepine co-crystal^{17,18}.

4. Slurring Technique:

This is a simple process, whereby crystallization solvent is added. The solid API dissolves in the solvent, forming a solution into which the coformer is added, after which the resulting suspension is stirred, filtered and dried. Slurring was used for the patent of celecoxib-venlafaxine co-crystal. This multi-drug co-crystal combines the therapeutic properties of celecoxib (which has anti-inflammatory properties for patients with chronic musculoskeletal inflammatory diseases) and venlafaxine (with an antidepressant effect)²³.

5. Antisolvent Co-Crystallization:

a solvent in which the compound is less soluble is often added to the solution, favoring the precipitation of the solids. The resulting suspension is filtered, and the collected solid can be characterized by XRPD. Disadvantages of this method are its lower performance compared to grinding that uses a solvent, as well as the large volume of solvent used²³. Antisolvent crystallization has been reported for the production of carbamazepine-saccharin and indomethacin-saccharin co-crystal. In both studies, the construction of phase solubility diagrams was an integral part of the methodology for identifying the optimal conditions (e.g., ratio of solvent to antisolvent) for the formation of co-crystal.

6. Use of Supercritical Fluids:

Supercritical fluid (SCF) is a very good solvent, and has the unique ability to diffuse through solids like a gas and dissolve materials like a liquid (gas flow properties and dissolving liquid properties); thus, it can replace organic solvents. CO₂ is the most frequently used supercritical fluid for co-crystallization as solvent, as anti-solvent and as atomized anti-solvent. A detailed review of the preparation of pharmaceutical co-crystal through sustainable process using supercritical carbon dioxide has been provided by Pando et al.

Co-crystallization with supercritical solvent (CSS): The active substance and the coformers are dissolved in the supercritical CO₂ (sc-CO₂) inside a stainless-steel vessel, and depressurization then leads to the loss of dissolving dominance of sc-CO₂, to supersaturation and eventually to the formation of co-crystal. The application of CSS requires sufficient (ideally equal) solubility of the pure components in sc-CO₂. Its main disadvantage is its low performance in pure products.

Supercritical antisolvent (SAS): If a substance is not soluble in sc-CO₂, the sc-CO₂ can be used as an anti-solvent for a solution of co-crystal components (coformer and API) in an organic solvent. Therefore, the active substance and the coformers dissolve into an organic solvent (primary solvent). This is followed by its dropwise mixing with the sc-CO₂ by passing the organic solution through a nozzle. The sc-CO₂ dissolves quickly in the droplets of the organic solution, reduces the dissolving power of the solvent and simultaneously extracts it, causing saturation and supersaturation, during which co-crystallization nuclei are formed and the precipitation of co-crystal by the anti-solvent effect of sc-CO₂ takes place. This technique requires complete miscibility of the organic solvent with the sc-CO₂ and lower solubility for the solute in the mixture. Then, the organic solvent is removed, and a product without solvent is obtained.

Itraconazole (antifungal drug of poor bioavailability) and succinic acid co-crystal preparation, with sc-CO₂ as an antisolvent, is an example of such, while the same method was used for the patent of the carbamazepine-aspirin co-crystal.

Atomized anti-solvent (AAS): In the AAS technique, the sc-CO₂ enhances the atomization of the organic solution, producing particles by two different mechanisms: antisolvent crystallization and spray-drying crystallization. The solution containing the API and coformer is pumped through a coaxial nozzle, where it mixes with the sc-CO₂ or N₂ in the mixing chamber prior to its depressurization into the precipitator vessel (for SAS technique, the precipitator is filled with CO₂ at high pressure, whereas in the AAS technique, it is at ambient pressure). Pure indomethacin-saccharin co-crystal have been produced by the AAS technique.

7. Sonocrystallization:

Ultrasound, apart from its wide application in various fields of medicine (e.g., as a diagnostic method) and cosmetology, offers promising prospects in the generation of nuclei during the process of crystallization of drugs. For example, it has been used for the formation of pharmaceutical microparticles sized 2–6 μm, primarily intended for inhalation. The generation of such particles through mechanical methods causes problems of physicochemical stability, performance, and product modification, attempts to improve all of which are being made through the use of the escalating power of ultrasound^{8,9}.

8. Spray Drying:

This method has been used recently for generating co-crystal. Solutions of disparately saturated systems lead to the formation of pure co-crystal, as opposed to the mixtures obtained after solvent evaporation. Thus, co-crystal formation can be monitored kinetically and/or mediated by the glassy state of the material⁶.

9. Resonant Acoustic Mixing® (Ram):

This is a non-contact mixing technology that relies upon the application of a low-frequency acoustic field to facilitate mixing. This new technology has shown several advantages for numerous complexes and multiphase systems, while it reduces both mixing time and cost. Carbamazepine-nicotinamide co-crystal have been formed with this method by adding a solvent (20 μL/100 mg of the co-crystal component) such as CH₃Cl, H₂O, DMF, DMSO, MeOH, and LabRAM was operated for two hours at 90% intensity with automatic tuning. This method can be used for co-crystal production at a large scale, and provides high-purity co-crystalline products^{20,21}.

10. Twin-Screw Extrusion (TSE):

Extrusion is the process of converting an unprocessed material or mixture of materials that have been ground or granulated into a product of uniform shape and density by pressing them through a die under controlled conditions. During TSE, the mixture of the active substance, the thermoplastic polymer carrier, excipients, and other auxiliary agents (e.g., plasticizers, antioxidants), is heated in the extruder. By the end of the process, a solid form (e.g., granules) is obtained from the output of the extruder. TSE was used for the patent of the L-malic acid and L-

tartaric acid co-crystallization. Medina et al. showed that the TSE technique can be used as an effective method for generating pharmaceutical co-crystal. Furthermore, the matrix-assisted co-crystallization (MAC) approach uses the TSE technique to produce co-crystal embedded in a formulation matrix. Equimolar amounts of API and coformer are mixed in solid form with a matrix material prior to the feeding in the extruder. The extruder is set at a temperature where only the matrix is liquid via either the formation of soft material or melt. Co-crystallization occurs during extrusion due to the mixing and grinding of the components in the pliable matrix. The co-crystal particles formed in this way are incorporated in the matrix, where they remain in a fluidized state until the exit from the extruder. In the MAC product, the material of the matrix plays a double role:

- During TSE it plays a role similar to that of a catalyst, for example, as a solvent. The use of a molten or pliable matrix promotes good mixing and reduces the excessive shear stress generated when solid materials are placed in the extruder. This reduction in the shear stress mitigates potential damage to the crystalline structure; and
- The matrix acts a functional component of the formulated product in the finished product. Thus, the selection of the matrix material is very important for offering additional functionality to the formulated co-crystal, such as improved flowability, compressibility and release kinetics of the drug. The MAC method provides simultaneous production and formulation of the pharmaceutical co-crystal, giving high-quality co-crystal²⁷.

MECHANICAL PROPERTIES:

Mechanical properties, such as tensile strength, forces to rupture, elastic properties, compressibility and tableting capacity may be altered through co-crystallization due to changes in the crystalline structure. For instance, paracetamol cocrystal with different conformers were found to exhibit enhanced mechanical properties. Specifically, paracetamol co-crystal with 5-nitroisophthalic acid were able to be successfully manufactured into tablets of the desired tensile strength without compromising the dissolution profile due to the presence of slip planes in the co-crystal. Other examples of co-crystal with improved mechanical properties include vanillin isomers and the co-crystal of carbamazepine with nicotinamide.

Co-Crystal Polymorphism:

During the development of co-crystals, efforts are made to identify and characterize the polymorphic forms of the compounds because they may have different physicochemical properties. It has been traditionally suggested that polymorphism is a phenomenon seen less frequently in co-crystals than in monocomponent crystals, and that co-crystallization can be used to prevent polymorphism. However, many recent examples of co-crystal polymorphism have been discovered and entered into the CSD. For example, Prohens et al. recently discovered nine new co-crystal of agomelatine, which is an atypical antidepressant. Two of the coformers produced polymorphic co-crystal during screening, indicating that, similarly to single-component crystals,

polymorphism in co-crystal should be studied, as it could expand the co-crystal landscape²⁹.

Selection of Coformers and Screening of Co-Crystal

A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former. Co-crystal former may be an excipient or another drug.

Hydrogen Bonding Propensity:

In co-crystal, API and coformers interact with each other by non-covalent bonding such as hydrogen bonding and van der Waal forces. Among all of these, hydrogen bonding between API and coformer plays an important role in the formation of co-crystals. Etter described a graph-set notation system which has been mostly used as motif for labelling of hydrogen bonding and suggested 3 rules for preferable hydrogen bond formation: every hydrogen molecule, which is acidic in nature will be present in bond formation, all hydrogen bond acceptors will be used when there are available hydrogen bond acceptors, and hydrogen bond will be formed when there will be best hydrogen bond donors and hydrogen bond acceptors. The quantitative measurement of hydrogen bond formation between donor and acceptor functional groups present in indomethacin and isonicotinamide was analysed by assigning a value between 0 to 1 and higher value indicates the formation of hydrogen bond²⁶.

Synthonic Engineering:

Desiraju described the "synthon approach" for the selection of coformers which formed a supermolecule by using specific molecular fragments within the co-crystal to establish "supramolecular synthons". According to this approach, the functional groups present in API and coformer will play a major role in the formation of co-crystal and coformer with suitable functional group will be used for a particular APIs. Synthons are present in the supermolecules as basic structural units which are associated with non-covalent bonding. Supramolecular synthon approaches are of two types: supramolecular homosynthons and supramolecular heterosynthons. Supramolecular homosynthons are composed by same functional groups present in API and coformer such as the amide-amide homosynthons, carboxylic acid-acid homosynthons whereas supramolecular heterosynthons are formed by different functional groups such as the carboxylic acid-amide heterosynthons, the acid-pyridine heterosynthons. Supramolecular heterosynthons are generally more favoured than homosynthons, e.g., the acid-amide and the acid-pyridine heterosynthons are commonly used as compared to carboxylic acid and amide homodimers¹².

CSD:

CSD is a validated tool to facilitate the statistical analysis of packing motifs and thereby provide information about common functional groups. CSD is used to provide the information about molecular association of drug and coformers based on functional group that engage into supramolecular synthons. A library of suitable coformers can be prepared by CSD for an API. This is a computer based approach used to find appropriate co-crystal forming pairs, and reduces the research time and experimental cost⁸.

PKa Rule:

Co-crystal or salts formation can be predicted by proton transfer between acid and base. The formation of salts or co-crystal can be predicted by determining the $\Delta pK_a = [pK_a(\text{base}) - pK_a(\text{acid})]$. It is generally accepted that proton transfer will occur from acid to base if the difference in the pK_a values is greater than 2 or 3. A smaller ΔpK_a value (less than 0) indicates the formation of co-crystal whereas higher value (more than 2 or 3) indicates the formation of salts. ΔpK_a rule was validated and quantified by studying 6465 co-crystal from CSD and explained a linear relationship between ΔpK_a value and possibility of proton transfer between acid-base pair. It was analysed that a non-ionized complex should be formed when the value of $\Delta pK_a < -1$; an ionized complex is formed when the value of $\Delta pK_a < 4$ and the possibility of formation of ionized complex increase by 17% by increase in ΔpK_a by one unit from 10% at $\Delta pK_a = -1$ to 95% at $\Delta pK_a = 4$. By determining the ΔpK_a value, the possibility of formation of co-crystal and salts can be determined. This is a simple and less time-consuming method for the preparation of co-crystal¹².

Fabian's Method:

Different sets of reliable co-crystal forming structures were extracted from the CSD and the molecular descriptors (single atom, bond and group counts, hydrogen bond donor and acceptor counts, size and shape, surface area and molecular electrostatic) were calculated for each molecule. On the basis of calculated molecular properties, the database described pairs of molecules that were able to form co-crystal. The strongest descriptor correlation was related to the shape and polarity of co-crystal formers¹⁶.

Hansen Solubility Parameter (HSP):

Mohammad MA, et al reported the use of Hansen solubility parameter (HSP) for prediction of co-crystal formation. The concept was originally proposed for predicting polymer solubility in paints by Hansen C.M. The basis of these so-called HSPs is that the total energy of vaporization of a liquid comprising of several individual component forces. These forces arise from (atomic) dispersion forces, (molecular) hydrogen bonding (electron exchange) and (molecular) permanent dipole-permanent dipole forces. The difference in total solubility parameters ($\Delta\delta t$) of the API and conformer is calculated for the purpose of prediction of co-crystal formation. $\Delta\delta t$ values less than 7 MP0.5 indicates likely co-crystal may be formed and values greater than 10 MP0.5 fewer chances of co-crystal formation. The result reported in the study indicates limited application of this approach in co-crystal prediction as only a few conformer formed co-crystal although $\Delta\delta t$ was less than 7MP.

Cosmo-RS:

For screening of suitable conformers for an API, COSMO-therm software based on COSMO-RS fluid-phase thermodynamic approach was used to describe the miscibility of conformers in super cooled liquid (melt) phase. The excess enthalpy, Hex (a major factor for H-bonding interactions) between API and conformer mixture as compared to pure components reflects the tendency of those two compounds to co-crystallize. This was demonstrated that COSMO-RS theory allowed reasonable

ranking of conformers for an API and the experiments should be focused on those conformers which an increased probability of co-crystallization, leading to the largest improvement of the API solubility. In a similar way as potential conformers were identified for co-crystallization, solvents with highest value of Hex with an API, were selected which had the least probability to form solid solvates. Different conformers for itraconazole and solvents for Axitinib (tyrosine kinase inhibitor) were selected by this method to avoid formation of hydrates and solvents.

Virtual Co-Crystal Screening:

Musumeci et al. predicted that all the possible intermolecular interaction sites present on the surface of molecules were responsible for the formation of co-crystal. The strength of hydrogen bond depends upon the H-bond donors and H-bond acceptors; best H-bond donor and best H-bond form the strongest H-bond, and next best H-bond acceptor interacted with the next H-bond donor, and so on, until all sites are satisfied. Calculated gas phase MEPS approach has been used for screening of co-crystal. This approach assumed that the energy difference, ΔE , between the two pure solids and co-crystal in different stoichiometries give an idea about the co-crystal formation. The results showed that the probability of co-crystal formation was 50% more, when ΔE difference of co-crystal and two pure solids should be more than 11 kJ/mol¹⁸. This approach was validated by using about 1000 compounds from literature for APIs (caffeine and carbamazepine) and ΔE parameter was found to be favourable and fast screening tool.

Cocktail Co-Crystal Method:

A new "co-crystal cocktail method" was developed for screening of co-crystal formation in which four conformers were ground simultaneously with API in ball mill, this method reduced the workload by 50% and hence it was convenient and less time consuming as compared to conventional single time-consuming methods. The chemical moieties present in conformers and drug interacted with each other and synthons were formed between drug and conformers i.e. homosynthons or heterosynthons. Co-crystal of itraconazole was prepared with succinic acid and serine by using this method and the results showed the highest in vitro solubility and dissolution rate as compared to all other formulation.

Thermal Analysis:

Thermal screening of co-crystal by DSC gave some ambiguous results. So, some researchers used DSC with other techniques for the screening of the co-crystal. Hot stage microscopy was also used for identification of co-crystal and found to increase the overall screening efficiency. This method offers identification of number of phases present in the system by direct visualization when two components were heated. High melting point component melted and recrystallized before another molten component came in contact with it, and zone of mixing was created. In this method, thermodynamic landscape was elucidated with the help of binary phase diagram and efficiency of co-crystal screening was increased. Nicotinamide was selected as conformer and hot stage microscopy was used for screening of co-crystal' formation with different APIs. Hot stage microscopy is also known as Kofler contact method²⁷.

Synthon Matching:

Synthon matching is the computational theory used to investigate the intermolecular interactions in the crystal structure and is an important tool for the co-crystal screening. The major limitation of this approach is that in vivo properties of co-crystal cannot be determined exactly. This synthon approach is used to estimate the possibility of hydrogen bond formation between API and cofomer. Over the past few years, various methods have been evolved to determine the intermolecular interactions in crystal structures qualitatively and quantitatively, such as the conformational similarity index for proteins, graph-set analysis for hydrogen bonds, Voronoi-Dirichlet polyhedral for crystal packing, continuous symmetry measures, and the Hirshfeld surface by using computer programs such as ESCET, COMPACT, TOPOS, Xpac²⁸.

APPLICATION:

Co-crystallization has an advantage to optimize the physicochemical properties of drugs without altering the molecular structure of drugs. The choice over whether co-crystal or salts will have the desired properties depends upon the API and specific project. Co-crystal with negative ΔpK_a value will give non-ionized drug when dissolved whereas salt will give ionized API, which is more soluble in water. Whenever dissolution rate of drug should be important rather than equilibrium solubility, co-crystal can be better than salt form of drug. Co-crystallization is an alternative way to enhance the solubility and bioavailability of poorly water soluble drugs, especially for those compounds which are neutral or weakly ionized in nature. Further, co-crystallization also offers possibility of altering improving the melting point, tabletability, solubility, stability, bioavailability and permeability. as discussed in previous sections.

CONCLUSION:

Pharmaceutical co-crystal a new aspect of pharmaceutical industry and better understanding this process. we are understanding this article high potential physicochemical and biopharmaceutical properties of pharmaceutical co-crystal. pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs. It will stimulate investigation of old APIs to see new benefits. Co-crystals – High Throughput gives vital information on relationship between formation and chemical structure of the API and co-former.

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