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PHARMACEUTICAL CO-CRYSTALLIZATION: AN AEON IN SOLUBILITY ENHANCEMENT

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ABSTRACT
Cocrystal concept of the supramolecular chemistry is gaining wide interest of researchers from pharmaceutical, chemical sciences, and regulatory agencies. Pharmaceutical cocrystal engineering has emerged as a new era in the field of medicine in developing a new moiety with improved solubility, dissolution, bioavailability, micrometric properties, and pharmacokinetic and pharmacodynamic properties of a drug. Different methods have been used for the synthesis of cocrystal such as grinding, slurry, antisolvent, hot melt extrusion, sonocrystallization, supercritical fluid, spray drying etc. The article highlights the co-crystallization, its methods and significance.

KEYWORDS: Pharmaceutical Co-crystals, Co-crystallization, solubility, stability, bioavailability, Grinding, Slurry conversion.

INTRODUCTION

Now a day's solubility is the major problem of many drugs. To enhance solubility of active pharmaceutical ingredient co-crystallization is mostly used approach. Poorly water soluble drugs pose significant hurdles for drug bioavailability. Among the biopharmaceutical properties, solubility remains a key issue with drugs often discarded during commercial production due to their low solubility.[1] Improving the solubility of drugs is currently one of the main challenges for the pharmaceutical industry. Many approaches have been adopted for improving the aqueous solubility of drugs including micronisation, salt formation, emulsification, solubilisations using cosolvents, and the use of polymer drug vehicles for delivery of poorly soluble drugs. Although these techniques have been shown to be effective at enhancing oral bioavailability, success of these approaches is dependent on the specific physicochemical nature of the molecules being studied.[2] Over the last decade, there has been growing interests in the design of pharmaceutical cocrystals, which emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility. The ability to deliver the drug to the patient in a safe, efficient and cost effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state.[3] This provides a significant driving force for inventing new approaches to designing pharmaceutical solid materials with specific physicochemical properties. The property of a solid material is depending not only on the identity of its constituents but also on their arrangement. Crystalline solids are the compounds in which the component atoms, molecules, or ions are arranged in a regularly ordered, repeating pattern in three dimensions. It is somewhat common for a single constituent to be able to exist in more than one crystalline arrangement.

Consequently, solids with significantly different physical properties may be constructed from a single atom, ionic compound, or molecule. This type of behavior in single-component organic crystals is called polymorphism. Crystals also may contain more than one type of atom, ionic compound, or molecule. Such Cocrystals will have different properties than do crystals made from each constituent alone.[4] A solid form can exist in the two forms. They are amorphous and crystalline forms. Solid dosage forms are the mostly chosen as oral drug delivery systems in crystalline form. A solid can exist in different forms like polymorphism, hydrate form, solvate form or co crystal forms. Chemists and engineers in the pharmaceutical industry prefer to deliver crystalline forms of their active compounds, mainly due to the characteristic stability of crystalline materials as well as the well-established impact of crystallization processes on purification and isolation of chemical substances.[5] 40% of the drugs in the present era have solubility problems. Progress in high throughput screening methods leads to greater amount of newly discovered drugs, but a lot of them have low aqueous solubility.[6]

Five major physicochemical properties like pKa, solubility, permeability, a higher risk of failure during discovery and development, since insufficient solubility may compromise with other property assays, mask additional undesirable properties, influence both pharmacokinetic as well as pharmacodynamic properties of the compound and finally may affect the developability of the compound. Low solubility in water finally results in poor bioavailability.[6] If there is no any way to improve the solubility of drug then it will not be able to be absorbed from the gastrointestinal tract into the bloodstream and reach at the site of action in body.[6] Therapeutic efficiency of the drug depends upon the bioavailability i.e. the amount of drug that reaches into the systemic circulation. Two main factors which influence the bioavailability of drug are Solubility and Permeability. There is also other factors which influence these bioavailability such as chemical stability of drug, poor dissolution rate, purity, compaction behavior of crystal, moisture absorption and crystal habit etc.[04, 07]

There are various approaches for solid state modifications which have been used to improve the bioavailability of drug without changing its pharmacological activity. These approaches are described such as polymorphs, solvates, hydrates, salts, Cocrystals, and amorphous solids which involves non covalent interactions within molecules. Generally developers and regulatory authorities prefer such types of crystal forms, because highly pure products that are superior with respect to reproducibility and scalability were afforded by crystallization method. The formation of Cocrystal (freely reversible multi component assemblies) may be potentially employed with all drugs, including acidic, basic and non ionisable molecules.[4] Currently, salt formation is one of the important solid-state approach used to modify the physical properties of APIs, and it is estimated that over half of the medicines in the market are administered as salts. But this approach contains one major limitation that the API should possess a suitable (basic or acidic) ionizable site within its structure. In comparison, cocrystals (multicomponent system held together by freely reversible, noncovalent interactions) offer a different mechanism of formation, where any API regardless of acidic, basic, or ionizable groups, could be potentially cocrystallized.[8] This aspect helps as complement for molecules that had limited pharmaceutical profiles based on their nonionizable functional groups by reintroducing it in existing method.[8] The number of potential nontoxic Cocrystal formers (or coformers) that can be incorporated into a Cocrystallization reaction is also numerous. It should be noted that no one particular strategy offers a solution for property enhancement of all APIs. Each API must be examined and evaluated before use on a case-by-case basis in terms of molecular structure and desired final properties. For this purpose, general guidelines for rational Cocrystal design through supramolecular synthesis will be given below. Crystal engineering, when applied to Cocrystal systems, generally it involves the design as well as study of new materials in order to enlarge the knowledge base of successful engineering strategies, and the application of that particular knowledge to provide Cocrystals with specific properties for a large number of applications. Pharmaceutical Cocrystals— Crystalline compound comprising an active pharmaceutical ingredient (API) and a Cocrystal former — have recently invented as an innovative strategy to improve the performance of medicines by altering their physical properties without changing any covalent bonds in either of the species. The Cocrystal former may be another API or, if it is not, then it should be ideally a generally recognized as safe (GRAS) substance.[9] As Cocrystals represent unique solid forms of the parent APIs with different physical as well as chemical properties, multi-API Cocrystals are also potential solid forms for the delivery of combination drugs that can be used to overcome problems associated with traditional combination drugs. Another very important benefit of a multi-API Cocrystal is the improvement in drug release as well as bioavailability and improvement of patient's long-term medication compliance in long-term drug therapy, since few pills need to be taken.[9]

PHARMACEUTICAL COCRYSTALS

Active pharmaceutical ingredients (APIs) are the most conveniently developed and delivered orally as solid dosage forms that contain a defined amount of crystalline form of an API. Cocrystals are an enabling technology which is used in new or existing drug delivery systems by majority of pharmaceutical industries informulation and drug development.[9] The term and the definition of Cocrystal is still a subject of topical debate. According to principle this is multi-component systems which have host and guest type chemistry; both components are solid in pure state and under ambient conditions. There are a lot of definitions of cocrystals; for example, Bhogala and Nangia defines Cocrystals as multi-component solid-state system oftwo or more compounds which are held together by any type or combination of intermolecular interactions.[6]

Childs and Hard castle define Cocrystals as a crystalline material which is made up of two or more components, usually in a stoichiometric ratio, each component being an atom, ionic compound, or molecule.[6] The simplest definition of Cocrystals was given by Bond: "Cocrystal is synonym for multi-component molecular crystal".[6] Cocrystals as defined by the FDA are, "Solids that are crystalline materials composed of two or more molecules in the same crystal lattice". Pharmaceutical cocrystals represent a subset of cocrystals.[10] The molecules are associated with each other by the help of hydrogen bonding. The designing of Cocrystals involve a fixed stoichiometric ratio of components in association with van der Waals force of attraction, π-π bonding, ionic bonding as well as hydrogen bonding in a crystal lattice.[11] As an alternative for the solid dosage forms, Cocrystals are emphasized prominently for the development of dosage forms. With the help of such kind

of modifications to the APIs, the physicochemical properties of the drug molecules can be improved significantly. However, the modification of drug molecules in Cocrystals form does not affect their pharmacological response, rather there will be an enhancement in physical properties of drug molecules such as compaction behaviour, hygroscopicity and aqueous solubility. In the process of Cocrystallization it has been observed that there is a competition for aggregation of nuclei for development of a three dimensional lattice design either between homomers (same components) or heteromers (different components).[11]

NEED OF OPTIMIZATION FOR COCRYSTALS

In the pharmaceutical industry the main problems are stability, solubility, dissolution, and stability melting point, bioavailability and mechanical properties of active pharmaceutical ingredients (API). Crystals have first priority in pharmaceutical industry because of their higher stability, reproducibility comparison to amorphous and other solid solutions such as partially crystalline forms.[12,13] Now days, there is issues like 'solubility of drugs' have one of the most challenging problem, in pharmaceutical industry and in order to increase the aqueous solubility of drugs, various methods have been proposed such as salt formation, microionization, emulsification, polymer drug vehicles. Nevertheless, achievement of these methods is depending on the physicochemical properties of the specific molecule being studied. Over the last decade, Cocrystals have taken the place in the pharmaceutical industry as a new class of compounds for research.[13] Cocrystallization is a new method of crystallization, which recently has attracted scientists' attention in the pharmaceutical field. Pharmaceutical Cocrystals have a great range of advantages and high prospects for the future as a new type of API solids and the crystal engineering design strategies have been studied much in order to simplify the formation of Cocrystals of API and Cocrystal formers. Cocrystals offers more opportunities in drug development process as well as in drug delivery and chiral resolution. A Cocrystal is a multi-component crystal in which all components are in solid state at room temperature in a stoichiometric ratio and it involves non-covalent interactions such as hydrogen bonds, van-der Waals bonds, ionic bonds in a crystal lattice.[13] The coformers for synthesis of pharmaceutical Cocrystals are literally selected from the Generally Recognized as Safe molecules so there is no issue like toxicity. In addition, the number of potentially active nontoxic Cocrystals formers (or coformers) that can be incorporated into a Cocrystallization reaction is numerous.[12]

Various solid state modifications have been done to improve the bioavailability of drug without changing its pharmacological activity.[4] Drug-drug Cocrystals fulfills the criteria for patent eligibility: novelty, utility, and non-obviousness for pharmaceutical development. There is a lot of potential to explore Cocrystal design of established APIs among each other to increase solubility as well as bioavailability of the product.[9] A Cocrystal former have recently emerged as an innovative strategy to enhance the performance of medicines by altering their physical properties without changing any covalent bonds within the species. Another obvious benefit of a multi-API Cocrystal is the improvement of patient's long-term medication compliance inlong-term drug therapy, since fewer pills need to be taken.[14] Cocrystals offers opportunities in drug development process, drug deliveryand chiral resolution of APIs. In addition to these, Cocrystallization could mostly be useful to enhance other properties such as melting point, crystallinity as well as physical and chemical stability of APIs.[13] Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical Cocrystals can increase otheressential properties of the APIs such as flow ability, compressibility and hygroscopicity.[15] It is also very much useful in green chemistry in the context of solid state synthesis. Thus it can be stated that different arrangement and conformational changes in the molecules of the crystal structure leads to differences in properties as follows.

A. Mechanical (hardness, compactness, etc.)
B. Surface (surface energy, interfacial tension, etc.)
1.Kinetic (dissolution values, stability, etc.)
2.Spectroscopic (electronic, vibrational state transition, etc.)
3.Thermodynamic (melting point, sublimation, enthalpy, entropy, etc.)
4.Packing properties (molar volume a density, hygroscopicity, etc.)

Synthon approach

Cocrystals consists two or more components which are joined together by supramolecular synthons. In order to obtain formation of Cocrystals, functional groups should be capable of forming supramolecular hetero or homo synthons as shown in Fig.3 which are present in the API and coformer. In supramolecular synthons approach, steps involved in developing Cocrystals are as follows.

1) Selection of the target molecule (API).
2) Finding the complementary functional groups which are capable of forming a hydrogen bond. (coformer selection)
3) Methods of Preparation.[15]

The supramolecular synthon approach uses crystal engineering to carefully analyze the relevant supramolecular arrangements that an API might exhibit by utilizing the Cambridge Structural Database and effectively prioritizes all possible guest molecules for crystal form screening of drugs and another parameter is hydrogen bonding.[15] The supramolecular synthon approach is a statistical analysis that utilizes the Cambridge Structural Database to effectively prioritize coformers for crystal form screening if an appropriate supramolecular heterosynthon can be identified. Supramolecular heterosynthons, typically involving

hydrogen bonds between different but complementary groups, are exemplified by carboxylic acid /amide and carboxylic acid/aromatic nitrogen supramolecular heterosynthons. Crystal engineering affords a platform for rapid development of pharmaceutical Cocrystals.[15] It can be defined as an application of the concepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are actual manifestations of self-assembly. Crystal engineering based on the basic principles of supramolecular chemistry, chemistry beyond the molecule in developing novel entities by manipulating the non-covalent intermolecular interactions.[15] Hydrogen bonding, metal co-ordination, van der Waals forces, hydrophobic forces, electrostatic effects and □-□ interactions are some of the interactions which are commonly encountered in this regard.[15] Crystal engineering is nothing but understanding the basic behind formation of synthons using non covalent interaction.[15] The term synthon was coined by Corey in the context of organic chemistry and it is defined as "structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions". A supramolecular synthon is a pattern which is composed of molecular and supramolecular elements. When crystal patterns repeat regularly, the pattern of such interactions can be called a supramolecular synthon.[15] Supramolecular synthons are further categorized into.

(a) Supramolecular homosynthon:These are composed of identical self-complementary functionalities.

(b) Supramolecular heterosynthons: These are composed of different but complementary functionalities.

Single-component or a compound which contains the functional groupscan be sustained by supramolecular homosynthons whereas; supramolecular heterosynthons can dominate in the presence of other competing functionalgroups.[15]

A) Supramolecular homosynthon [In this case synthon is between two carboxylic acid groups]

(B) Supramolecular heterosynthon [In this case synthon is between carboxylic acid and amide group]

Selection of an API and coformer for design of Cocrystals

Cocrystals are basically solid state forms that containing two or more crystals in the same crystal lattice. Choice of excipients and API is necessary for enhancement in characteristics of the drug, drug stability, bioavailability and patient compliance. At the some stage of development, there is an association between excipient and API. There is a difference between Cocrystals and solid state forms. A Cocrystal offers more advantages than a solid state form material and better than API in case of lack of ionsable functional group for salt formation. Pharmaceutical Cocrystals are significant in pharmaceutical industry unlike salt form components which are involved in crystal lattice forms are in an ionized state. API and excipients interact at the molecular level but there is an exception for Cocrystal molecular association that is occurred within lattice of crystal. API which treated with the Cocrystallized excipient to produce API excipient so Cocrystals may be treated as the drug intermediate. In case of pharmacological activity, API dissociates from excipient from reaching at the site of action.[13]

Cocrystal can simultaneously address multiple functional groups in a single reaction, including acidic as well as basic and nonionizable molecules. In the formation of salts transfer of hydrogen atom occurs and such a transfer does not occur in the formation of Cocrystals. Cocrystals contain two or more components in single molecule which are held together by supramolecular synthons. In order to obtain Cocrystals, functional groups are capable of forming supramolecular hetero or homosynthons should be present in the API and coformer. In supramolecular synthons approach, steps which are involved in developing Cocrystals are as follows.

1) Choosing the target molecule(API)

2) Finding the complementary functional groups which is capable of forming a hydrogen bond. (coformer selection) 3) Methods of Preparation.[15]

One of the important tasks in pharmaceutical Cocrystals development is the selection of coformers that are compatible with a particular API. A general approach for coformer selection is by "tactless" Cocrystals screening, whereby a predetermined library of pharmaceutically acceptable and approved compounds is used to attempt Cocrystallization. The lead Cocrystals compounds with superior physicochemical and pharmacological properties can then be developed into a dosage form.[15] The success of Cocrystals design by using hydrogen-bonded supramolecular synthons clearly shows the value of hydrogen bond in forming Cocrystals. After metal coordination bonds and ionic interactions (e.g. dipole-dipole) the strongest interactions in crystal engineering are hydrogen bonds.[15] Due to the strength as well as directionality, and ubiquitous presence of hydrogen bonds in the organic molecules, it is also known as the 'key- interaction' in crystal engineering.

Guidelines proposed to facilitate the design of hydrogen bonded solids.

(1) All good proton donor's s well as acceptors are useful in hydrogen bonding;

(2)If in six-membered ring intramolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen bonds.

(3) The best proton donors and acceptors remaining after intramolecular hydrogen-bond formation, then they will form intermolecular hydrogen bonds to one another.

SALT VERSUS CO-CRYSTAL FORMATION

Co-crystal and salts may sometimes be confused. The understanding of the fundamental difference between a salt formation and a co-crystal is very important for both pre-formulation activities and chemical or

pharmaceutical development aspects. Indeed, salts and co-crystals can be considered as opposite ends of multi-component structures. Salts are often chosen instead of the free acid or base as these can improve crystallnity, solubility and stability of a pharmaceutical compound. Co-crystals are used as an alternative to salts when these do not have the appropriate solid state properties or cannot be formed because of the absence of ionizable sites in the API. Salt formation involves acid–base reaction between the API and an acidic or basic substance. The widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs. Salt formation is a three component system having an acid (A), a base (B) and one or more solvents. A salt is formed by transfer of a proton (H+) from an acid (A) to base (B).

A-H + B → (A-) (B+- H)

Proton transfer is thought to mainly depend on the pKa values of the components. When there is no such transfer and the components are instead present in the crystal as neutral entities, the product is generally defined as a co-crystal. In other words, a co-crystal is an A-B composite in which no proton transfer occurred. Salt formation includes acid–base reaction between the API and an acidic or basic substance. Salt formation generally requires a difference of about 2.7 pKa units between the conjugate base and the conjugate acid (A) i.e. [pKa (base) - pKa (acid) ≥ 2.7]. For example, succinic acid having pKa 4.2form co-crystal with urea base (pKa0.1) while succinic acid form salt with L- lysine base having pKa9.5. Generally base pKa values are not sufficiently high to allow proton transfer when co-crystal is formed. Certain drug may give different output of solubility, dissolution & Bioavailability by changing co-former of same drug.[2]

METHODS OF COCRYSTALLIZATION

A. Grinding

1. Solid state neat grinding or mechanical milling technique
2. Solvent assisted grinding.

B. Solution Cocrystallization

1. Solvent evaporation technique
2. Cooling crystallization.
3. Antisolvent addition/Precipitation
4. Slurring technique

5. Other methods

1. Supercritical fluid atomization process
2. Hot melt extrusion
3. By using intermediate phase
4. Sonocrystallization Method
5. Reaction Cocrystallization
6. Sublimation.

A. Grinding

1. Solid state grinding

Solid state grinding is method in which the materials are mixed, pressed and crushed in a mortar and pestle. We can also crush it in mill. This technique provides particle size reduction but in case of co-crystallization these have proved to be a viable method for solid-state grinding along with liquid state grinding. Many co-crystal materials can be prepared from both solid state grinding and solution growth. Failure to form product of co-crystals by grinding may be due to an inability to generate suitable co-crystal arrangements rather than due to the stability of the initial phases. Although co-crystal formation by solid-state grinding has been established for some time and in late 19 th century report solid state grinding is often cited as reference to such a procedure. Now a day the recent technique of adding small amounts of solvent during the grinding process has been shown to enhance the kinetics and facilitate co-crystal formation and as lead to increased solid-state grinding as a method for co-crystal preparation. However in some cases the solid state grinding has proved its effectiveness more intensely in comparison to the different synthetic methods. The simplicity in developing Cocrystals with solid state grinding makes it the most important as well as convenient technique for screening of the same.[2]

2. Solvent assisted grinding

This technique is considered to be a very good alternative to solid state grinding in the development of pharmaceutical Cocrystals. The technique includes the grinding of two different materials as that of solid state grinding along with a little quantity of solvent which is acting as a catalyst for the development of Pharmaceutical Cocrystals. The technique was first demonstrated through Cocrystallization of nitrogenous bases with cyclohexane tricarboxylic acid derivatives.[11]

B. Solution Cocrystallization

The two components must have similar solubility characteristic for solution Co crystallization; otherwise the component which has low solubility will precipitate out completely. On the other hand similar solubility of two components alone willnot give chance of success. It has been recommended that it possibly useful tobelieve polymorphic compounds, which exist in more than one crystalline form ascrystallizing components. If a molecular compound exists in numerous polymorphicforms, then it has showed a structural flexibility and it does not locked into a singletype of crystalline lattice or packing mode.[5]

1. Solvent evaporation technique

Solvent evaporation is the most conventional method in case of crystallization. In this technique the all material is mixed with the common solvent serially andevaporated completely. During evaporation stage the solution of molecules areexpected to undergo various hydrogen bonding reactions. But in case of co-crystallization which consists of coformer and active

ingredient, solubility of both inthe selected solvent plays a great role. If the solubility of both is not similar, then theone with low solubility than the other will precipitate out. Molecule has ability toparticipate in the intermolecular interaction to form a co-crystal. The majordisadvantage of this method is that it requires large amount of solvent. Example-Patent on Co-crystallization of Fluoxetine HCl and Benzoic Acid.[2]

2. Cooling crystallization

This is another method called cooling crystallization which involves variationin the temperature of the crystallisation system, which has recently attracted moreattention for its potential of large scale Cocrystals production. First, large amounts of reactants and solvent are mixed in a reactor, a typicallyjacketed vessel, and then the system is heated to a high temperature to make sure thatall solutes are totally dissolved in the solvent and is followed by a cooling down step. Cocrystals will be precipitate out when solution becomes supersaturated with respectto Cocrystals as the temperature drops down.[11]

3. Antisolvent addition/Precipitation

This is one of the mostly used methods for precipitation or recrystalization of the co-crystal former and active pharmaceutical ingredient. Solvents include buffers (pH) and organic solvents. For example, preparation of co-crystals of Aceclofenac using chitosan, here coformer solution i.e. chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. The prepared dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.[5]

4. Slurring technique

Slurry crystallization is simple process which includes the addition of crystallization solvent in the API along with its acceptable coformer. The selection of this process is mainly depends upon the physical stability of the crystallization solution to co crystals and its solid former or a solid compound dissolved in solvent to form a solution. A solid coformer is added to the solution, the suspension is stirred until the formation of cocrystal is complete. In some cases, aliquots of Antisolvent may subsequently be added to the solution. Solid formed in the solution re filtered and dried. The solid is cocrystal of compound and coformer. While preparation of cocrystals for Trimethoprim and sulfamethoxazole through slurry technique simple distilled water is used as solvent. The major disadvantage of this method is that the yield obtained from this was not sufficient as compared with solvent drop grindingmethod.[2]

C. Other methods

1. Supercritical fluid atomization process

Supercritical fluids use offers additional advantages compared to the other co- crystal production methods. Co-crystallization by supercritical solvent (CSS) is a method where an API and a co-crystal former are mixed together by magnetic stirring after being pressurized by supercritical CO2 in a high-pressure vessel. The Supercritical Anti-Solvent (SAS) technique explores the anti-solvent effect of supercritical CO2 to precipitate particles (cocrystals) from solutions. Pure co-crystals of itraconazole: malic acid was produced using either supercritical CO2 or a traditional liquid solvent, such as n-heptane and were confirmed by both XRD and DSC. Phase transformation during processing affect the mechanism of conversion of crystalline drugs to co-crystal.[2]

2. Hot melt extrusion

Extrusion is very useful method for synthesis of cocrystals, it involves highly efficient mixing and improved surface contacts. In this method Cocrystals are prepared without use of solvent. The selection of this method primarily depends on thermodynamic stability of compound. This method was studied with the use of four models for cocrystal formation. Solvent drop extrusion technique used to optimize and make the process more flexible. Solvent drop extrusion technique gives an advantage to carry out process at lower temperature. Hot melt extrusion method was used in synthesis of Carbamazepine-nicotinamide cocrystals with polymer as former. Continuous co-crystallization, API and coformer poured in the twin extruder. As a result of continuous addition of mixture the barrel temperature also increases.[2]

3. Sonocrystallization Method

The development of sonochemical method for preparation of organic cocrystals of very finite size has been done. This method was primarily developed for preparation of nanocrystals. Caffeine- maleic acid cocrystal preparation commenced with use of ultrasound method. The comparative study of method of preparation of caffeine and theophylline as API and L tartaric acid as coformer by Solvent drop grinding method and sonochemical method has been commenced. The results of methods were consistent hence sonocrystallization proves to be a significant approach.[2]

Example - Patent on Co-crystal of fluoxetine HCL & benzoic acid in acetonitrile by sonication.

4. By using intermediate phase

Using intermediate phases to synthesize these solid-state compounds are also employed. By use of a hydrate or an amorphous phase as an intermediate during synthesis in a solid-state route has proven to be successful in formation of a cocrystal. We can also employ a metastable polymorphic form of one cocrystal former. In this method, the metastable form acts as an unstable intermediate on the nucleation pathway to a cocrystal. As always, a clear connection between pair wise components of the cocrystal is needed in addition to the thermodynamic requirements in order to form these compounds. The most common formation methods are

based on solution and grindingmethod. Among two, first one is most important due to formation of crystal by such method shows single X-ray diffraction testing (SXRD). Solution method includes reaction crystallisation method, evaporation of a heterometric solution method & cooling crystallisation. Grinding method includes neat grinding & solvent drop grinding. Apart from solution method and grinding methods, there are also other newly emerging methods, such as co-crystallisation using supercritical fluid, hot stage microscopy, and ultrasound assisted co-crystallisation.[2]

5. Reaction Cocrystallization

A reaction Cocrystallization experiment is performed by addition of reactant B to a saturated or closely to saturated solution of reactant A, and then this solution becomes supersaturated with respect to Cocrystals AB. This method is most effective with non-equivalent solution concentrations and when solutions are saturated with respect to reactants. In one study reaction Cocrystallization experiments wereperformed by adding Carbamazepine to saturated or nearly saturated solutions of 18coformers separately and several pure Carbamazepine Cocrystals were obtained.[11]

6. Sublimation

If a compound is sufficiently volatile at accessible vacuum pressure it can be crystallized. This technique is often used in the purification of crude mixtures. Crystals may form from a fusion, or by sublimation; but crystallization almost always takes place from solution.[5]

CHARACTERIZATION OF COCRYSTALS

Characterization of Cocrystals involves both structures (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction) as well as physical properties like melting point apparatus, differential scanning calorimetry, and thermo gravimetric analysis. Other methods like studying the morphology of crystals by microscopic methods, observing changes in crystal forms with temperature, interpreting molecular motion, phase transition by thermal methods, and chemical environment by the use of vibrational spectroscopy and solid state NMR are used. Single crystals of the 1:1 Cocrystal of piracetam and gentisic acid obtained via slow evaporation from acetonitrile solvent. Cocrystals prepared via grinding or slurrying in water was characterized by IR, melting point, DSC, Powder XRD and single crystal XRD. The basic physicochemical properties of cocrystals usually characterized by analytical Techniques like powder X-ray diffraction (PXRD), infrared spectroscopy (IR), Raman spectroscopy, single crystal X-ray diffraction (SXRD), solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and terahertz spectroscopy.[5]

1. Fourier Transform Infrared (FT-IR) Studies
2. Raman Spectroscopy
3. Crystallographic Method
4. Thermal analysis
5. Nuclear magnetic resonance
6. Scanning electron microscopy

1. Fourier Transform Infrared (FT-IR) Studies

Photons in NIR region have the highest energy and therefore it can excite molecules vibrationally into even higher excited vibrational states than the first level, i.e. the second, the third and others. These transitions are called overtones. Absorption of radiation in the NIR region is usually based on higher energy transitions between vibrational levels of molecules, namely combination transitions and overtones and not fundamental transitions, which are dominant in mid infrared region (MIR).[6]

2. Raman Spectroscopy

Raman spectroscopy is a spectroscopic method used to study vibrational, rotational, as well as other low frequency modes in a system, which has been demonstrated to be a powerful tool for distinguishing isostructural phase. There are various applications using Raman spectroscopy like identify characteristic peaks of co crystal products.[5]

3. Crystallographic Method

Crystallographic methods include both single crystal X-ray diffraction as well as powder X ray diffraction. The single crystal X-ray diffraction study can provide unambiguous atomic positions and complete structural information, but obtaining a single crystal suitable for this study becomes restricted access. In such cases, powder X-ray diffraction studies using microcrystalline samples become a key tool. When an X-ray beam is directed at a crystalline sample, the atomic structure of the lattice causes the X-rays to be scattered in a defined manner creates a diffraction pattern. The electron density in the crystal may be deduced from this diffraction pattern, giving an accurate molecular structure. To understand this theory further and more precisely determine crystal structures it is useful to have a general knowledge of crystal structures and their interaction with X-rays.[5]

4. Thermal analysis

This is one of the important method, which is widely used in pharmaceutical industries for characterization of polymorphism, purity, salvation, degradation and drug compatibility, which includes Thermogravimetry, Differential Thermal Analysis (DTA).[2] It measure physical and chemical properties of a substance, a mixture of substances or also of a reaction mixture as a function of temperature or time during a controlled temperature program. For analysis of Cocrystal mainly differential scanning calorimetry (DSC) and its modifications, differential thermal analysis (DTA) and thermogravimetry analysis (TGA), are of great importance. In DSC, the sample is subjected for linear (or modulated) heating, and the heat flow rate in the sample is proportional to the actual specific heat and is

continuously measured. There is some very interesting and useful modifications of DSC like hyper DSC, micro DSC and modulated DSC.[6]

5. Nuclear magnetic resonance

Nowadays solid state NMR is also used for characterization. NMR studies give the chemical environment of the nuclei which is different in polymorphs because of magnetic non-equivalence. NMR peaks for the magnetically non- equivalent nuclei will differ in different polymorphs and can yield very useful information.[2] Solid-state NMR has ability of providing detailed structural information about organic and pharmaceutical Cocrystals and complexes. This method gives idea about molecular association and possibility to observe structural features (like hydrogen bonding) are great advantages of this method. These advantages can be utilized in the analysis of pharmaceutical Cocrystals, which are produced using techniques like solvent drop grinding that do not lend themselves to single-crystal growth for X-ray diffraction studies.[6]

6. Scanning electron microscopy

Scanning electron microscopy (SEM) was conducted to characterize the surface morphology of the particles with excellent ease and efficiency. SEM differs from other electron microscope wherein the image is duly obtained right from the electrons that are strategically emitted by surface of an object in comparison to the transmitted electrons.[2] SEM is a type of electron microscope that images a sample by scanning it with a high energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals which gives information about the sample's surface topography. It is applied to determine the co crystal micrograph and particle size.[16, 17]

APPLICATIONS OF COCRYSTALS

1. Cocrystal engineering the most widely studied and used application is in drug development and more specifically, the formation, design, and implementation of active pharmaceutical ingredients, or API's. Changing the structure & composition of the API can greatly influence the bioavailability of the drug.[18]
2. The principal idea is to develop superior physico-chemical properties of the API while holding the properties of the drug molecule itself constant.
3. The objective for pharmaceutical cocrystals is to have properties that differ from that expected of the pure API's without making and/or breaking covalent bonds
4. In addition to these, Cocrystallization could mostly be useful to enhance other properties such as melting point, crystallinity, physical dissolution rate and chemical stability, compressibility, flow ability.[13]
5. Cocrystals will provide additional options for IP, regulatory, and lifecycle management for new and old drugs.[12]

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