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Pharmaceutical Cocrystals: Design, Development and Characterization

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ABSTRACT

The poor aqueous solubility and dissolution rate of API is one of the main challenge in pharmaceutical development. The improvement of solubility and dissolution profiles of these lipophilic drug molecules without altering the molecular structure is a particular challenge for the successful development of pharmaceutical products. Pharmaceutical cocrystals are molecular complexes of an API and one or more cocrystal formers, which are solids at room temperature, interacting through hydrogen bonding, π-stacking or van der Waals forces. A crystalline form of the API is strongly preferred because of their relative ease of isolation, and the physico-chemical stability that the crystalline solid state affords. The vast majority of APIs occur as solids; these include, salts, polymorphs, cocrystals and hydrates/solvates. Cocrystallization as a method of obtaining new forms of Active Pharmaceutical Ingredients (APIs) with improved physicochemical properties like solubility, stability, and melting point has gained much attention in recent years and is a promising alternative to so far employed preparation of salts, hydrates, solvates and other forms. Cocrystallization improves physicochemical properties of drug without affecting their pharmacological properties. There are various methods for preparation of cocrystals like solvent evaporation, solution crystallization, antisolvent addition, kneading etc. The characterization methods includes FTIR, DSC, PXRD, NMR, Raman spectroscopy etc.

Keywords: Co-crystals, solubility, dissolution, stability, characterization etc.

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INTRODUCTION

The poor aqueous solubility and dissolution rate of API is one of the main challenge in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase. The lead molecules discovered utilizing these screens are increasingly larger and more lipophilic. The improvement of solubility and dissolution profiles of these lipophilic drug molecules without altering the molecular structure is a particular challenge for the successful development of pharmaceutical products [1]. According to the Biopharmaceutics Classification System (BCS), a drug compound is poorly soluble if the highest dose strength is not soluble in 250 ml aqueous media over the pH ranges at 370C. These compounds mostly belong to Class II, which are poorly soluble and highly permeable according to the pH of the gastrointestinal fluid and tend to present dissolution-limited absorption[2]. Despite their high permeability, these drugs often have low oral bioavailability because of their slow and limited release of drug in gastrointestinal fluid. Therefore, one of the major challenges of the pharmaceutical industry is to apply strategies that improve the dissolution and/or apparent solubility of poorly soluble drugs to develop such problematic compounds into orally bioavailable and therapeutic effective drugs[1]. Cocrystals have been discussed in the literature since 1844 when Wöhler first described quinhydrone and Ling further investigated halogen derivatives of quinhydrone in 1893. Terminology used to describe cocrystals has been diverse including phrases such as “molecular complexes”, “addition compounds” or “solid-state complexes”. The definition of cocrystals is pharmaceutical cocrystals are molecular complexes of an API and one or more cocrystal formers, which are solids at room temperature, interacting through hydrogen bonding, π-stacking or van der Waals forces. Cocrystallization as a method of obtaining new forms of Active Pharmaceutical Ingredients (APIs) with improved physicochemical properties (e.g., solubility, stability, and melting point) has gained much attention in recent years and is a promising alternative to so far employed preparation of salts, hydrates, solvates and other forms. Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients. Frequently, however, the Active Pharmaceutical Ingredients crystallize into one or more crystal forms that possess undesirable physical properties and hence there is a need for the development of crystalline form of APIs with desired physicochemical properties. Various options are available including single component and multiple-component modifications of an API,

including polymorphs, salts, solvates, and hydrates. In addition to these established crystalline API modifications, pharmaceutical co-crystals, or crystalline molecular complexes involving an API, have recently attracted interest as an alternative approach. Cocrystallization improves physicochemical properties of drug without affecting their pharmacological properties.

Role of Crystal Engineering in Pharmaceutical Science

Crystal engineering strategies have been used in understanding and predicting hydrogen-bonding interactions in active pharmaceutical ingredients (API). Pharmaceuticals are generally comprised of an API, a formulation containing inactive ingredients as a carrier system, and a package for market performance and appeal. A crystalline form of the API is strongly preferred because of their relative ease of isolation, and the physico-chemical stability that the crystalline solid state affords. The vast majority of API‟s occur as solids; these include, salts, polymorphs, cocrystals and hydrates/solvates, as shown in Figure given below. Nevertheless the use of crystalline materials can result in problems such as poor solubility properties or the existence of more than one crystalline form of an API. However, crystal engineering affords a paradigm for rapid development of a pharmaceutical cocrystals.

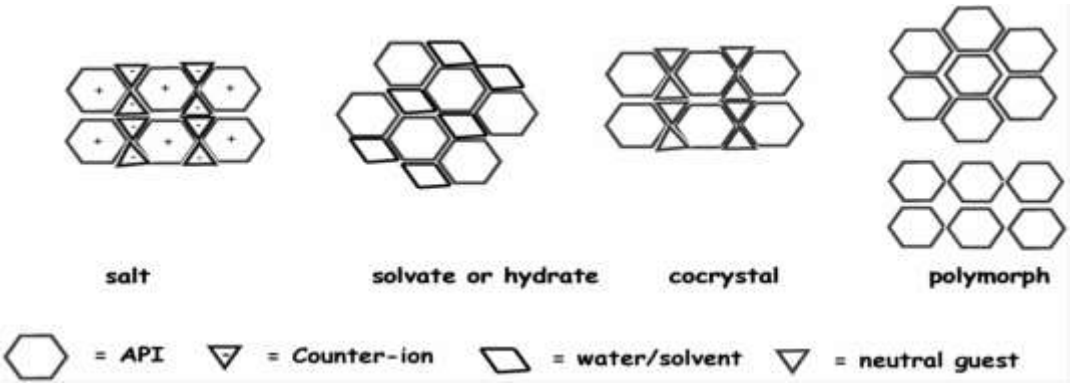

Figure 1: Pictures displaying the more common solid-state strategies and their respective components

he form “pharmaceutical cocrystal” is common place and usually applies when an API is one of the molecules in the multicomponent crystal. Two examples of pharmaceutical cocrystals are shown in Figure.

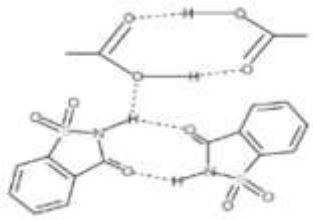

Figure 2: IND–SAC cocrystal structure[3]

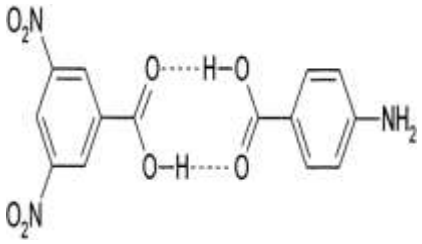

Figure 3: Cocrystal of 4-aminobenzoic acid and 3, 5-dinitrobenzoic acid

Problems encountered during the development of API

During the development and formulation of any API, several stringent performance parameters (e.g. solubility, dissolution rate, thermal stability, etc.) need to be carefully considered. It is thus not surprising that poor biopharmaceutical properties are the main reason that less than1% of active compounds eventually make it into the marketplace.

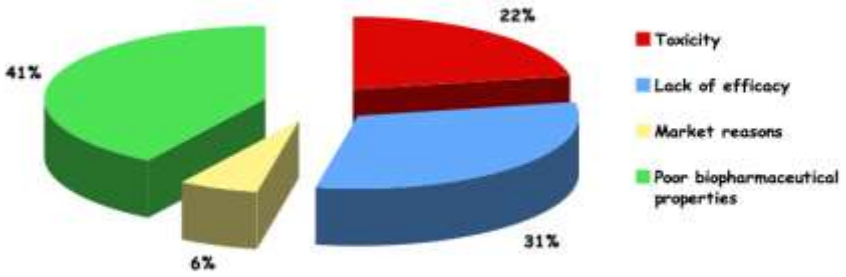

Figure 4: Reasons why compounds fail and slow down in development

Improvement in physicochemical properties by pharmaceutical cocrystal formation

It has been well established that issues ranging from poor solubility and inadequate dissolution properties to lack of crystallinity and attendant instability has been faced by the pharmaceutical industry. Recent studies, have shown that an opportunity exists to use co-crystallization to replace the solid forms of API that are being used, by taking advantage of supramolecular synthons.

Improvement in melting point behavior via co-crystallization

The thermal stability (i.e. melting point) is a fundamental physical property. There have been several literature reports where co-crystallization was used as a tool in improvement of melting point behavior of an API. These results showed that the API melting point can typically be fine-tuned according to which coformer is chosen; therefore if a higher melting cocrystal is desired then a higher melting coformer should be selected and vice versa.

Modulating solubility via co-crystallization

The aqueous solubility of a drug substance is one of the fundamental properties evaluated early in discovery. Majority of APIs fall into Biopharmaceutical Classification System (BCS) classification II i.e low solubility and high permeability, furthermore aqueous solubility is a major indicator of the solubility in the intestinal fluids. To generally describe solubility the Pharmacopoeia (USP) uses seven different solubility expressions as shown in Table 1.

Table 1: Solubility Definitions

Descriptive term (Solubility definition)	Parts of solvent required for one part of solute	Solubility required (mg/ml)	Solubility assigned (mg/ml)
Very soluble	<1	>1000	1000
Freely soluble	From 1-10	100-1000	100
Soluble	From 10-30	33-100	33
Sparingly soluble	From 30-1000	10-33	10
Slightly soluble	From 100-1000	1-10	1
Very Slightly soluble	From 1000-10000	0.1-1	0.1
Practically insoluble	>10000	<0.1	0.01

Pharmaceutical cocrystals have been demonstrated to profoundly modify the solubility of the parent API, and at least 90 APIs have been studied in the context of co-crystallization. Often APIs that are targeted for pharmaceutical co-crystallization display undesirable solubility and possess multiple hydrogen bonding sites. In fact, Bak and co-workers highlighted the ability of a series of pharmaceutical cocrystals for improving the solubility of the parent API. It was found that oral administration of the cocrystal showed a maximum plasma concentration 8 times greater compared to the oral administration of the pure API. Similarly, Childs *et al* highlighted a cocrystal that exhibited approximately 4-fold increase in plasma concentration over the pure API after a single oral dose.

Hydrogen Bond in Crystal Engineering

Hydrogen bonding, the master key for molecular recognition, is the most reliable directional interaction in supramolecular construction, and is highly significant in crystal engineering; the latter has been 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 with desirable physical and chemical properties*." The field of crystal engineering is greatly indebted to the pioneering work of Etter and co-workers who began to focus attention on the ability of hydrogen bonds to help control molecular crystallizations. Moreover, this early work revealed that reliable hydrogen-bonding motifs are formed by many elementary functional groups frequently encountered in simple molecules. Together, these observations along with the hydrogen bond rules provide useful information about preferred connectivity patterns, hydrogen bond selectivity, and

stereoelectronic properties. The hydrogen-bond rules proposed by Etter are very useful and can be applied to organic hydrogen-bonded structures. The general rules state:

1. All acidic hydrogens available in a molecule will be used in hydrogen bonding in the crystal structure of that compound.

2. All good acceptors will be used in hydrogen bonding when there are available hydrogen-bond donors.

3. The best hydrogen-bond donor and the best hydrogen-bond acceptor will preferentially form hydrogen bonds to one another.

These guidelines have set the stage for important advances in crystal engineering where structures are built from more sophisticated molecules, specifically designed to incorporate multiple sites of hydrogen bonding and oriented in arrays favoring the assembly of networks with predictable architectures, Figure 5.

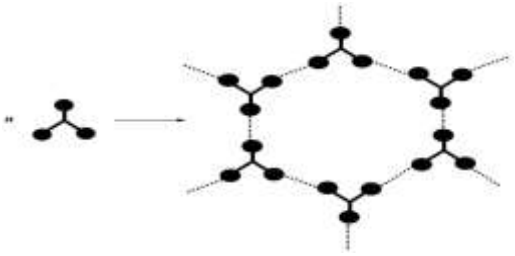

Figure 5: Formation of a hexagonal network, broken lines represents directional intermolecular interactions

Hydrogen bonds are usually written as D-H…A and normally involve an electronegative atom such as O or N as the acceptor (A) and an atom, as the donor (D) where D is more electronegative than A. Normal hydrogen bonds typically range in strength from approximately 4-60 kJ mol-1, although certain highly acidic compounds such as HF have hydrogen bond energies of up to 120 kJ mol-1. Whereas, the typical hydrogen bond distances are 2.50-2.80 Å (H…A), interactions in excess of 3.0 Å may also be significant. The design step of crystal engineering utilizes the knowledge of non-covalent forces that mediate the formation of supramolecular synthons, which are *"structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions."*

Hydrogen-bonded supramolecular synthons are commonly used in crystal engineering, and an improved understanding of their geometries, and their frequency of occurrence in the presence of other hydrogen-bonding groups, will allow us to design and synthesize novel cocrystals. Supramolecular synthons are divided into two categories; homosynthons, which are composed of self-complementary functional groups, as exemplified by the carboxylic acid dimer **1** and the

amide-amide dimer **2**, and heterosynthons, which are composed of different but complementary functional groups **3-6**, Figure 6.[2]

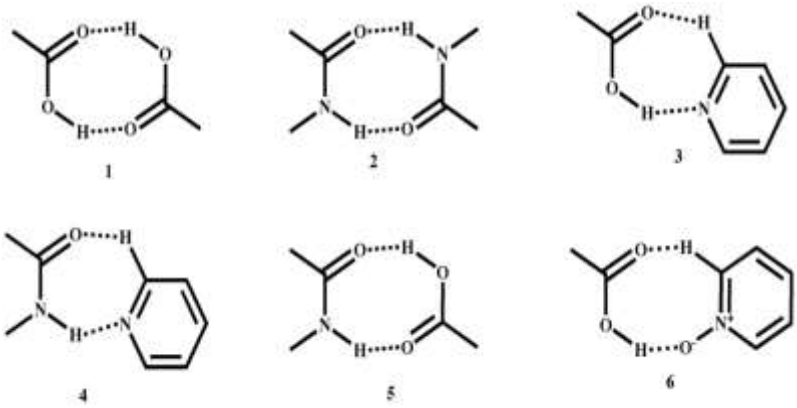

Figure 6: Few examples of supramolecular synthons selected from the recent literature: homosynthons (1-2) and heterosynthons (3-6).

Cocrystal as a Mean of Controlling Material Properties[2-4]

The value of cocrystals with pharmaceutical components lies in the ability to tailor the functionality of materials. Pharmaceutical scientists often consider alternative solid state forms to a free drug compound, such as polymorphs or salts, to improve pharmaceutical properties. In contrast to polymorphs, cocrystals implying that greater changes in materials properties and could be introduced compared with polymorphs. Some compounds do not possess cocrystals can alter pharmaceutical properties, they could become viable alternatives for drug product formulations. Properties that relate to pharmaceutical performance and that can be controlled by cocrystal formation include melting point, hygroscopicity, chemical stability, dissolution, solubility, mechanical properties, and bioavailability. Over the past few years, numerous examples have been published in which pharmaceutical properties of cocrystals have been presented and a selection is highlighted below.

Hydrate Formation

APIs can be cocrystallized with coformers such that the API will not form a hydrate or a solvate. Since cocrystals are supramolecular assemblies and are designed based on functional groups and hydrogen bond complementarity, solvate formation that relies on this complementarity will be inhibited by the formation of cocrystals, given that the intermolecular interactions between the API and coformer are stronger than between the API and solvent molecule. An example of this is the stability of carbamazepine cocrystals (nicotinamide or saccharin) when exposed to high relative humidities. Even though the pure carbamazepine anhydrous crystal transforms to carbamazepine dihydrate when exposed to high relative humidities, the cocrystals do not.

Chemical Stability

Cocrystal formation can also improve the chemical stability of an API when chemical reactivity requires that reactant molecules be in suitable positions in the solid state. For example, the single component CBZ polymorphs degrade by solid-state photochemical reaction, where a cyclobutyl dimer is one of the main decomposition products. Formation of the cyclobutyl dimer requires alignment and a distance between azepine rings of less than or equal to 4.1 Å. CBZ cocrystal formation with saccharin and nicotinamide inhibits photodegradation of CBZ by altering the molecular arrangements in the solid state such that the distance between the azepine rings is more than 4.1 Å, thereby preventing photodegradation.

Dissolution Rate

The authors found that in general, the co-crystals behaved in a similar manner to the amorphous form compared with the crystalline drug in achieving and sustaining from 4- to 20-fold higher concentrations on dissolution testing. The practical implications of this finding are important, as the ability to form and sustain a supersaturated solution can have a dramatic impact on drug absorption and bioavailability. Itraconazole (ITZ), an antifungal agent, is an API with very low water solubility so it is marketed as the amorphous form to increase oral bioavailability. Remenar et al. synthesized four cocrystals with a stoichiometry of 2:1 (drug: ligand) where the ligand was fumaric acid, succinic acid, malic acid, and tartaric acid. The powder dissolution rate in 0.1N HCl at 25°C of these four cocrystals was compared to the crystalline and amorphous forms of itraconazole. The cocrystals have 4- to 20-fold higher dissolution profiles than pure crystal itraconazole, and the L-tartaric acid and L-malic acid cocrystals have dissolution profiles similar to the amorphous itraconazole.

Cocrystal Solubility

Solubility is a crucial physiochemical property in drug discovery and development. Crystal engineering is claimed to be one of the essential strategies of improving drug solubility. Fluoxetine HCl was cocrystallized with benzoic acid (1:1), succinic acid (2:1), and fumaric acid (2:1) via traditional evaporation techniques. The fluoxetine HCl: benzoic acid cocrystal was found to have a decrease in aqueous solubility by 50%, and the fluoxetine HCl: fumaric acid cocrystal had only a slight increase in aqueous solubility. However, the fluoxetine HCl: succinic acid cocrystal exhibited an approximately two fold increase in aqueous solubility after only 5 min.

Bioavailability

If cocrystals are going to be a viable alternative for solid state forms of a drug, bioavailability studies need to be performed. Two manuscripts have been recently published that report the first

bioavailability studies using cocrystals. McNamara et al reported a 1:1 cocrystal of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide with glutaric acid that had a dissolution rate 18 times higher than the pure API. Bioavailability studies revealed the cocrystal attained approximately three times higher plasma concentrations for the same dose in dogs.

Mechanism of Solubility Enhancement

Solubility is determined by strength, crystal lattice and salvation of cocrystal components. Solubility can be increased by lowering lattice energy or increasing solvent affinity. This is maintained by cocrystal formation. On other hand salvation plays a decisive role as hydrophobic drugs exhibits limitations due to solvent solute interactions which reduce the observed solubility below that determine by lattice energy. Salvation lowers the observed solubility by as much as an order of magnitude in organic solvents and by as much as three orders of magnitude in water. Melting point often stands a parameter to judge aqueous solubility of cocrystal indicate that solubility is frequently limited by Salvation, and not by lattice energy. In organic solvents the melting point and cocrystal solubility are inversely proportional to magnitude of solvent- solute interaction is proportional to magnitude of lattice strength. Consequently melting point will be a poor indicator of aqueous solubility of cocrystals. Cocrystal solubility also been correlated with conformer solubility, as conformers generates or modifies the physicochemical properties of API,,s and this is because of a decrease in salvation barrier for a cocrystal to an extent proportional to that of the pure components[5]. Examples of some pharmaceutical cocrystals with improved solubility of API are summarized in table 2.

Table 2: Examples of some API with improved solubility via co-crystallization

Drug	Coformer	Method of preparation	Solubility	
			Drug	Cocrystal
Itraconazole[6]	Succinic acid	Grinding	5 µg/ml	18 µg/ml
Indomethacin[5]	Saccharin	Supercritical fluid technology	2.5-4 µg/ml	3.7 mg/ml
Tadalafil[7]	Salicylic acid	Neat Cogrinding	0.41 mg/ml	1.4 mg/ml
Norfloxacin[5]	Isonicotinamide	Solvent evaporation	0.21 mg/ml	0.59 mg/ml
Meloxicam[5]	Aspirin	-	0.005 mg/ml	0.22 mg/ml
Mefloquine HCL[8]	Citric acid	Solution crystallisation	11 µg/ml	55 µg/ml
	Benzoic acid			60 µg/ml
	Oxalic acid			70 µg/ml
Ezetimibe[9]	Benzoic acid	Solution crystallisation	0.012 mg/ml	2.66 mg/ml
Miconazole[10]	Succinic acid	Solvent evaporation	200 µg/ml	600 µg/ml

Advantages of Cocrystals

- Cocrystals are stable crystalline forms as compared to amorphous solids[6].

- Avoids formation or breaking of covalent bonds[11].
- Theoretical capability of all types of API molecules (weakly ionizable /non-ionizable) to form co-crystals[12].
- The existence of numerous potential counter-molecules (food additives, preservatives, pharmaceutical excipients, and other APIs).
- The only solid form that is designable via crystal engineering.
- Can be produced using solid-state synthesis green technologies; high yield, no solvent or by-products[13].
- co-crystal formation may offer for the pharmaceutical industry, opportunity of intellectual property (IP) protection and the possibility of extending the life cycles of old APIs[14].
- Co-crystals are less prone to suffer polymorphic transformations, thus avoiding undesirable downstream processing surprises.
- Co-crystals do not involve structural modification of the parent molecules; therefore, in the case of designing co-crystals of marketed drugs, their development programs (including clinical trials) shall be significantly shorter and less risky than those of New Chemical Entities (NCEs).

Methods of Preparation of Cocrystals

Antisolvent addition method

This is one of the 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, in which chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug[15].

Advantages

- An advantage of the antisolvent crystallization is that the process can be carried out at temperatures near the ambient temperature.
- It is quite convenient for heat-sensitive substances.
- Also, the process would demand less energy than a solvent evaporation process.
- The solvent-antisolvent mixture must be separated in order to recover and recycle one or both solvents.
- Another advantage of antisolvent crystallization is that the change in solvent composition may

favor one crystalline structure in those cases where the solute may crystallize in two or more crystalline phases i.e. polymorphism, and only one of them is desired for product application. Because of these characteristics, antisolvent crystallization has been widely used to crystallize pharmaceutical products, which are generally sensitive to degradation by heating and frequently have polymorphism occurrence.

Mechanism of solubility enhancement by antisolvent addition method

The cocrystals prepared by antisolvent addition method shows higher solubility because addition of an antisolvent which reduces the solute solubility in the resultant system, or changing the solute by chemical reaction producing another substance with much lower solubility[16].

Kneading method

Kneading or liquid-assisted grinding method is employed to produce cocrystal, using a mortar and pestle, using a ball mill, or using a vibratory mill. In liquid-assisted grinding, or kneading, a small or sub stoichiometric amount of liquid (solvent) is added to the grinding mixture. This method was developed in order to increase the rate of cocrystal formation.

Advantages

It has advantages over neat grinding such as increased yield, ability to control polymorph production, better product crystallinity, and applies to a significantly larger scope of cocrystal formers and nucleation through seeding[17].

Solution crystallization method

In this method drug and conformer are dissolved in similar solvent and keep it for evaporation at room temperature. During evaporation the crystals are grown in the solution.

Advantages

- It is useful for polymorphic compounds which exist in more than one crystalline form as co-crystallizing component.
- If a molecular compound exists in several polymorphic forms it has demonstrated a structural flexibility and is not locked into a single type of crystalline lattice.

Drawbacks

For solution crystallization, the two components must have similar solubility; otherwise the least soluble component will precipitate out exclusively[15].

Solvent drop grinding method

It is also called as solvent assisted cogrinding. It involves the use of addition of small amounts of solvent (typically a few tenths of one equivalent of solvent per mole of starting material or 20 µl of solvent per 100 mg of powder). During the cogrinding process it has been shown to enhance the

kinetics and facilitate co-crystal formation and has led to increased interest of solid-state cogrinding as a method of co-crystal preparation. The added solvent acts in what may be described as a catalytic role, in that the quantities employed are small and the solvent is not a component of the final cocrystal product. Shan et al. Further explained solvent drop cogrinding on the basis of additional degrees of freedom, enhancement of molecular collisions and formation of cocrystal seeds. Solvent drop grinding avoids excessive use of crystallizing solvent and hence it can be regarded as a "green" process. Solvent-drop grinding could also prove useful for polymorph control and selective polymorph transformation[18].

Advantages

With solvent drop grinding cocrystals can be made faster than with the dry cogrinding method, and new co-crystals which can be made only with this technique.

Drawbacks

Hydrates or solvates may develop during Solvent drop grinding.

Cogrinding method

Grinding can be considered as a green route for the production of co-crystals, as it does not involve inclusion of any solvent &alternatively there no issue of complete removal of solvent residue and can be recognized as green chemistry[19].

Advantage

- Cogrinding does not involve solubility limit in the system, the CCF can be added to the system until the activity of the drug is sufficient for interaction with the CCF and formation of CCs with the API.
- Interaction between the solvent and the drug or coformer does not disturb the interaction between the drug and the coformer.

Drawback

- It is difficult to control the reaction conditions like grinding time, temperature and pressure.
- The temperature can become high during cogrinding processes that it is even possible that the crystals melt and co-crystallization takes place in a liquid phase.
- Cogrinding is a time consuming and tedious because each of the CCFs being used needs to be ground with the drug individually.

Dry cogrinding is also called neat cogrinding and is mixing two solid state components with a mortar and pestle or a mechanical ball mill. The time needed for the completion of the co-crystal formation is different and it depends on the nature of drug and coformer. For each set of

conformers cogrinding time may vary from 5 min and up to 48 hours[20].

Mechanism for co-crystal formation by dry cogrinding

1. Molecular diffusion 2. Eutectic formation 3. Co-crystallization mediated by an amorphous phase.

Supercritical fluid technology

In SFCC, the generation of a new cocrystal phase is to be monitored. The objective of this work is to PAT enable SFCC technology. Challenges include a large number of process variables such as extruder screw rotation speed, screw geometry, processing temperature and feed rate, all of which can significantly influence the product quality and conditions encountered during extrusion. Therefore it is essential to carefully select the mode of process analytics in order to understand the effect of such variables[21].

Characterization of Molecular Complexes

FTIR Spectroscopy

IR is a very common spectroscopic technique in determining the chemical conformation of compounds. It can be a very powerful tool in distinguishing cocrystals from salts when a carboxylic acid is involved in hydrogen bond formation. A neutral carboxylic group (–COOH) has a strong carbonyl (C O)stretching peak around 1700 cm-1and a weak C–O stretch around 1200 cm-1; however, if deprotonation has occurred, a carboxylate anion (–COO-) has only a single C–O stretch in the fingerprint region of 1000–1400 cm-1[4].

Raman spectroscopy

In order to gain a better understanding about the solid structure, the integration of more advanced methods of solid state analysis is necessary. Raman spectroscopy is a spectroscopic technique used to study vibrational, rotational, and other low frequency modes in a system, which has been demonstrated to be a powerful tool for distinguishing isostructural phase. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products.

DSC

DSC is the most widely used technique for the thermal property testing of cocrystals. DSC is the preferred technique for obtaining comprehensive melting point data and additional thermal data, such as the enthalpy of melting, can also be obtained simultaneously. In addition to being a characterization technique, DSC has recently been used as a screening tool for rapid cocrystal screening.

Powder X-Ray diffraction

PXRD gives a unique “fingerprint” diffraction pattern characteristic of a particular solid form and

of course does not require the growth of high-quality single crystals to obtain the data. For this reason PXRD is ubiquitous in the pharmaceutical industry.

Single crystal XRD

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

Solid state NMR

SSNMR is another complementary technique to XRD, which is often used to characterize solid phases that cannot be studied by SXRD. Recently, high-resolution SSNMR has shown to be a versatile and powerful tool for characterization of pharmaceutical cocrystals. Notably, NMR not only allows for non-invasive, element-specific observation of different nuclei, but also facilitates the identification of chemically distinct sites based on NMR chemical shifts. Additional structural insights may be obtained from double-quantum1H MAS NMR. The application of different kinds of NMR methods in pharmaceutical cocrystal characterization were introduced by Khan et al. (2010), including1H or2H MAS NMR,13C or 15N CPMAS NMR, and two dimensional 1H–1Hor1H–13C,1H–15N,NMR[4].

Scanning electron microscopy

SEM is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is applied to determine the cocrystal micrograph and particle size in many examples.

Applications of Cocrystals

Cocrystal engineering is relevant to production of energetic materials, pharmaceuticals, and other compounds. Of these, the most widely studied and used application is in drug development and more specifically, the formation, design, and implementation of active pharmaceutical ingredients, or APIs. Changing the structure and composition of the API can greatly influence the bioavailability of a drug. The engineering of cocrystals takes advantage of the specific properties of each component to make the most favorable conditions for solubility that could ultimately enhance the bioavailability of the drug. The principal idea is to develop superior physico-chemical properties of the API while holding the properties of the drug molecule itself constant. Cocrystal engineering has become of such great importance in the field of pharmaceuticals that a particular subdivision of multicomponent cocrystals has been given the term pharmaceutical cocrystals to

refer to a solid cocrystal former component and a molecular or ionic API.

- Among the earliest pharmaceutical cocrystals reported are of sulfonamides. The area of pharmaceutical cocrystals has thus increased on the basis of interactions between API‟s and cocrystal formers. Most commonly, API‟s have hydrogen-bonding capability at their exterior which makes them more susceptible to polymorphism, especially in the case of cocrystal solvates which can be known to have different polymorphic forms. Such a case is in the drug sulfathiazole, a common oral and topical antimicrobial, which has over a hundred different solvates. It is thus important in the field of pharmaceuticals to screen for every polymorphic form of a cocrystal before it is considered as a realistic improvement to the existing API.
- Pharmaceutical cocrystal formation can also be driven by multiple functional groups on the API, which introduces the possibility of binary, ternary, and higher ordered cocrystal forms.
- The cocrystal former is used to optimize the properties of the API but can also be used solely in the isolation and/or purification of the API, such as a separating enantiomers from each other, as well and removed preceding the production of the drug.
- Chiral resolution: whether a molecule is ionizable or not, selective diastereomeric co-crystallization can be attainable using an enantiomerically pure conformer[35].
- Separation and purification: co crystals can be a good option, especially with non-ionizable products, to purify some intermediates, consequently avoiding expensive chromatographic techniques.
- Crystallization of non-solid products: liquids, pastes and oily products can become a solid form by means of co-crystallization, leading to more robust and efficient manufacturing processes.
- Improvement of solid state properties (of APIs and other organic substances): several important characteristics of pharmaceutical substances like solubility, bioavailability, stability, hygroscopicity, morphology, filtration and flowability can be modified by means of co-crystal formation[36].
- Number of pharmaceutically acceptable co-crystal formers is larger than the number of counter ions for salt formation[37].
- To enhance the solubility and bioavailability of the target flavonoid, herbal and vitamin molecules are incorporated in cocrystals.
- This novel concept is now successfully exploited in the synthesis of porous solids, clay like material and ion exchange material for separation and catalysis[38].

REFERENCES

1. Stanton M. Cocrystallization to improve the dissolution and Pharmacokinetics of a poorly soluble drug; 2010.
2. Forbes S. Hydrogen-bond driven supramolecular chemistry for modulating physical properties of pharmaceutical compounds. A dissertation; 2004.
3. Padrela L, Rodriguesa M, Velaga S, Matosa H. Formation of indomethacin–saccharin cocrystals using supercritical fluid Technology. Eur J Pharma Sci 2009; 38:9–17.
4. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G.et.al. Pharmaceutical cocrystals: An overview. Int J Pharm.2011; 419:1-11.
5. Thakuria R, Delori A, Jones W, Lipert MP, Roy L, Hornedo NR.et.al. Pharmaceutical cocrystals and poorly soluble drugs. Int J Pharm, 2013.
6. Shevchenko A, Bimbo LM, Miroshnyk I, Haarala J, Jelinkova K, Syrjanen K.et.al. A new cocrystal and salts of itraconazole: Comparison of solid-state properties, stability and dissolution behavior."Int J Pharm.2012; 436:403– 09.
7. Vinesha V ,Sevukrajan M et.al .Enhancement of solubility of tadalafil by cocrystal approach. Int Res J Pharm 2013;4:218-223.
8. Yadav AV, Dabke AP, Shete AS. Crystal engineering to improve physicochemical properties of Mefloquine hydrochloride. Drug Deve. And Indu. Pharmacy 2010; 36(9): 1036–45.
9. Mulye S, Jamadar S, Karekar P, Pore YV, Dhawale S. Improvement in physicochemical properties of ezetimibe using a crystal engineering technique. Powder Tech 2012; 222: 131–38.
10. Tsutsumi S, Iida M, Tada N, Kojima T, Ikeda Y, Moriwaki T, Higashi K.et.al. Characterization and evaluation of Miconazole salts and cocrystals for improved physicochemical properties. Int J Pharm 2011; 421:230-36.
11. Yadav AV, Shete AS, Dabke AP, Kulkarni PV, Sakhare SS. Co-Crystals: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients. Indian J Pharm Sci 2009; 71(4): 359–70.
12. Lu J, Li YP, Wang J, Li Z, Rohani S, ching CB. Pharmaceutical cocrystals: a comparison of sulfamerazine with sulfamethazine. J Crystal Growth 2011; 335:110–14.
13. Mariette de Groen. Chiral co-crystallization for enantiomer separation; 2010.
14. Yadav AV, Shete AS, Dabke AP, Kulkarni PV, Sakhare SS. Co-Crystals: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients. Indian J Pharm Sci. 2009; 71(4): 359–70.
15. Yadav AV, Shete AS, Dabke AP, Kulkarni PV, and Sakhare SS. Co-Crystals: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients. Indian

J Pharm Sci 2009; 71: 359–370.

16. Giulietti M, Bernardo A. Crystallization by Antisolvent Addition and Cooling. Crystallization – Science and Technology. 379-396.
17. Friscic T, Jones, W. Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. Crystal Growth & Design 2009; 9 (3): 1621.
18. Jones W, Motherwell WD, Trask AV. Pharmaceutical Cocrystals: An Emerging Approach to Physical Property Enhancement. MRS Bulletin 2006;(31): 875-79.
19. Karki S, Friscic T, Jones W, Motherwell WDS. Screening for Pharmaceutical Cocrystal Hydrates via Neat and Liquid-Assisted Grinding. American Chemical Society.2007; 4(3) 347-54.
20. Cheney, Miranda L. "The Role of Cocrystals in Solid-State Synthesis of Imides and the Development of Novel Crystalline Forms of Active Pharmaceutical Ingredients" 2009. Graduate School Theses and Dissertations. Paper 3693.
21. R. S. Dhumal, A. L. Kelly, P. York, P. D. Coates, A. Paradkar. Cocrystallization and Simultaneous Agglomeration Using Hot Melt Extrusion. Springer Science + Business Media, LLC 2010.
22. Qiang Zhang ,Xuan Zhang et. al .A novel nanomatrix system consisted of colloidal silica and pH-sensitive polymethylacrylate improves the oral bioavailability of fenofibrate. Eur J Pharm Biopharm 2011;79:126-134.
23. Wei Wu et.al.Enhanced bioavailability of the poorly water-soluble drug fenofibrate by using liposomes containing a bile salt. Int J Pharm 2009;376: 153–160.
24. Zhonggui He et.al. Preparation and in vitro/in vivo evaluation of fenofibrate nanocrystals. Int J Pharm 2013;455:267-275.
25. Ige P, Baria R, Gattani S. Fabrication of fenofibrate nanocrystals by probe sonication method For enhancement of dissolution rate and oral bioavailability. Colloids and Surfaces B: Biointerfaces 2013;108:366-373.
26. Vogt M, Kunath K, Dressman J. Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: Comparison with commercial preparations. Eur J Pharm Biopharm 2008;68: 283–288.
27. Zhang H, Dong Y, Wu C, Williams R. Formulation and delivery of improved amorphous fenofibrate solid dispersions prepared by thin film freezing. Eur J Pharm Biopharm 2012; 82:534-544.
28. Yadav VB, Yadav AV. Enhancement of solubility and dissolution rate of Fenofibrate by melt

granulation technique. Int J PharmTech Res 2009; 2:256-263.

29. Ajmera A, Deshpande S, Kharadi S, Rathod K, Patel K. Dissolution Rate Enhancement Of Atorvastatin, Fenofibrate And Ezetimibe By Inclusion Complex With ß-Cyclodextrin . Asian J Pharma Clinical Res 2012; 5:73-76.
30. Bhise S. Effect of Hydroxypropyl ß- Cyclodextrin Inclusion Complexation on Solubility of Fenofibrate . Int J Res Pharm Biomed Sci 2011; 2:596-604.
31. Indira TK, Lakshmi PK, Balasubramaniam J, Rajesh YV. Enhancement of Bioavailability of Fenofibrate with Alpha Tocopherol and Phospholipids as Solubilizers. J Bioequiv Availab 2012;14:1-8.
32. Ziyaur Rahman, Cyrus Agarabi, Ahmed S. Zidan,et al. Physico-mechanical and Stability Evaluation of Carbamazepine Cocrystal with Nicotinamide. AAPS Pharm Sci Tech 2011; 12:693-704.
33. Qiao N, Wang K, Schlindwein W, Davies A, Li M. In situ monitoring of carbamazepine–nicotinamide cocrystal intrinsic dissolution behavior. Eur J Pharm Biopharm 2013; 83:415-426.
34. Ando S, Kikuchi J,Fujimura Y, Ida Y,Higashi K. Physicochemical Characterization and Structural Evaluation of a Specific 2:1 Cocrystal of Naproxen–Nicotinamide. J Pharm Sci 2012;101:3214-3221.
35. TengOng T. Crystal Engineering of Molecular and Ionic Cocrystals. University of South Florida, Graduate School Theses and Dissertations. Paper no.7270.
36. Kelly AL, Gough T, Dhumal RS, Halsey SA, Paradkar A. Monitoring ibuprofen–nicotinamide cocrystal formation during solvent free continuous co-crystallization (SFCC) using near infrared spectroscopy as a PAT tool. Int J Pharm.2012; 426:15– 20.
37. Hornedo NR, Nehm SJ, Jayasankar S. Process Analytical Technologies to Analyze and Control Cocrystallization. American Pharmaceutical Review.1-7.
38. Dunitz JD. Cryst Eng Comm 2003; 5:506.