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COCRYSTAL: A REVIEW ON PHARMACEUTICAL CORYSTALS DESIGN AND PREPARATION

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ABSTRACT

Poor dissolution rate, solubility, bioavailability, chemical stability and moisture uptake are problems associated with most of the active pharmaceutical ingredients. Various approaches have been used for enhancement of solubility of poorly aqueous soluble drugs, Pharmaceutical cocrystal is a reliable method to modify above physicochemical properties without alternating their pharmacological behavior, but success of these approaches depends on physical and chemical nature of molecules being developed. Cocrystallization of drug substances offers a great opportunity for the development of new drug products with superior physicochemical properties such as melting point, tabletability, solubility, stability, bioavailability and permeability, while preserving the pharmacological properties of the active pharmaceutical ingredient. Cocrystal is a stoichiometric homogeneous multicomponent system connected by non-covalent interactions where all the components present are solid under ambient condition. This review article presents a systematic overview of pharmaceutical cocrystals. Differences between cocrystals with salts, solvates and hydrates are summarized along with the advantages of cocrystals. The theoretical parameters consider during selection of coformers and screening of cocrystals have been summarized and different methods of cocrystal formation and evaluation have been explained.

KEYWORDS: Cocrystals, coformer, electrospray.

INTRODUCTION

Most of the new chemical entity discovered are lipophilic in nature and faces the problem of poor biopharmaceutical properties, among these properties solubility remains a key issue.[1] Improving the aqueous solubility of drug is one of the main challenge to pharmaceutical industry.[2] Various approaches are used for improving solubility of drugs like salt formation,

emulsification, co-solvency, use of polymer, micronisation, solid dispersion, inclusion complex etc. Cocrystal synthesis may offer opportunity to pharmaceutical industry to address intellectual property issue by extending the life cycle of old APIs.

Over the last decade, there has been growing interest in the design of pharmaceutical cocrystals for enhancing the bioavailability of drug having low aqueous solubility. Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical Cocrystal can enhance other essential properties of the APIs such as flowability, chemical stability, compressibility and hygroscopicity.[2] Cocrystal is defined as, "a stoichiometric homogeneous multicomponent system connected by non-covalent interactions where all the components present are solid under ambient condition".[1] Based on this definition, pharmaceutical Cocrystal composed of one of the Cocrystal component as an active pharmaceutical ingredient (API) and other component is called as conformer. Conformer is selected from the Generally Regarded as Safe (GRAS) list or component approved by FDA.[2] Cocrystal can be constructed through several types of non-covalent interaction including hydrogen bonding, p stacking and vander waals forces.

Difference between cocrystals, salt, solvates and hydrates

USFDA defined the cocrystal, 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 forms. 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.[5] Salts and cocrystals 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 cocrystal formation. Two components are bound to each other by noncovalent interactions such as hydrogen bonding, π-π stacking, van der Waal forces. A prediction can be made by Δp*K*a value whether cocrystals are formed or not. It is generally accepted that a salt will be formed if the Δp*K*a value is greater than 3 and Δp*K*a value less than 0 will lead to the formation of cocrystals. This parameter is not accurate to predict the formation of cocrystals in solids between the Δp*K*a values 0 and 3 but the possibility of salt formation will increase when the Δp*K*a increases.[15,42] Cocrystals 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 cocrystals. If the solvates contain water as a solvent in their crystal lattice then they are known as hydrates.[43] Solvates/hydrates are commonly formed during the cocrystallization via solution or liquid assisted grinding[41] and they can alter physicochemical properties of API's. Stability of solvates will be different from unsolvated forms because of presence of solvent in crystal lattice. Solvates/hydrates are quite unstable, because they lose solvent/water at high temperature and low humidity during storage and the physiochemical properties will be different for hydrated/dehydrated forms.[6] Different polymorphic cocrystals and solvates of caffeine and anthranilic acid were prepared by using different solvents via liquid assisted grinding.[26]

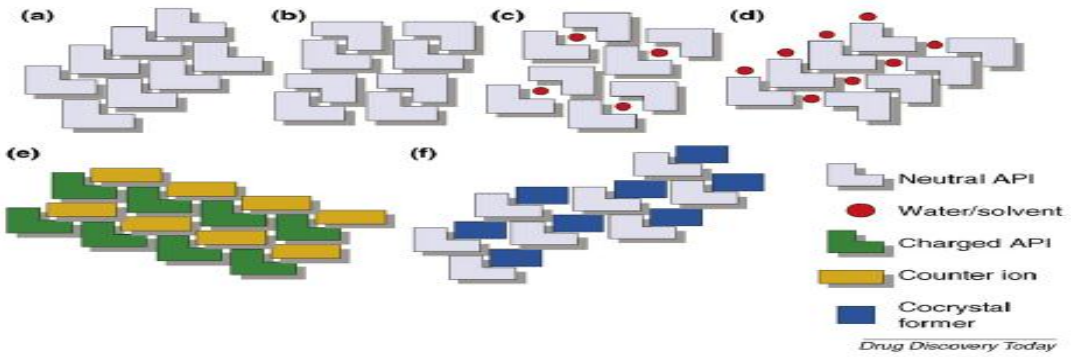

Fig. 1: Schematic representation of (a) pure API; (b) polymorphs of API; (c) clathrates solvate/hydrate of API, (d) solvates/hydrates of API, (e) salt of API, (f) pharmaceutical cocrystals of API.

Pharmaceutical cocrystal design strategies

Pharmaceutical cocrystals have rapidly emerged as a new class of API solids demonstrating great promise and numerous advantages. Much work has focused on exploring the crystal engineering and design strategies that facilitate formation of cocrystals of APIs and cocrystal formers. Pharmaceutical cocrystal design and preparation is a multi-stage process, as schematically illustrated in Fig. 2.[7] In order to get a desirable cocrystal product of an API with limited aqueous solubility, the first step is to study the structure of the target API molecule and find out the functional groups which can form intermolecular interaction with suitable coformers. Intermolecular interaction includes van der waals forces, p-p stacking and most common hydrogen bonding.

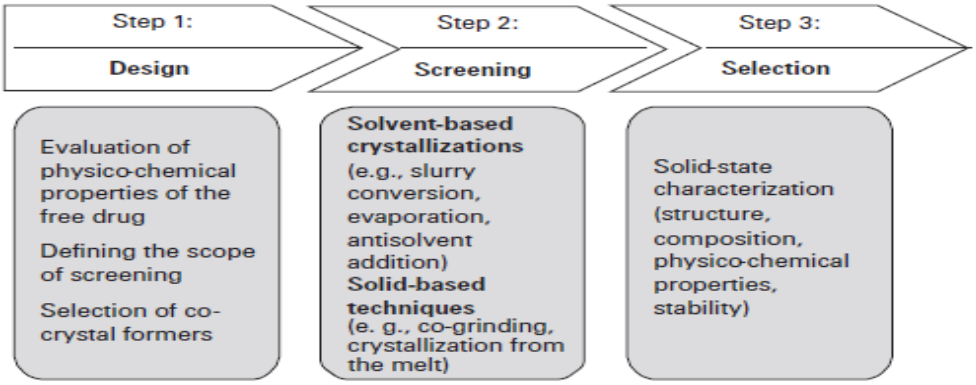

Fig. 2: A general guideline for Cocrystal design and screening.

1. Coformer selection

One of the main challenge in pharmaceutical Cocrystal development is the selection of coformers that are compatible with particular API.[8] For selection of suitable coformers and screening of cocrystals, researchers have used some different knowledge based approaches which include supramolecular synthone, hasen solubility parameter, Cambridge Structure Database (CSD), p*K*a based models, hydrogen bonds, Fabian's method etc.

1.1. Supramolecular synthone approach

A pharmaceutical cocrystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure.[8] Crystal enginerring also involves the basic understanding of synthons formation by using non covalent interaction.

The term synthon was coined by Corey and defined as "structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions". When crystal patterns repeat regularly, the pattern of interactions can be called a supramolecular synthon.

Supramolecular synthons are further categorized into:

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

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

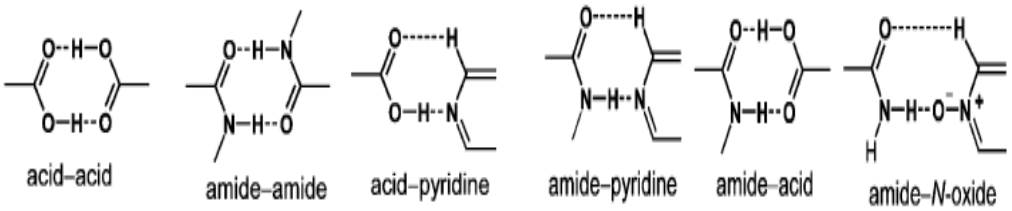

Fig. 3: Most common supramolecular synthon.

1.2. Hansen solubility parameter

Miscibility of a drug and coformer, as predicted by Hansen Solubility Parameters (HSPs), can indicate cocrystal formation and guide cocrystal screening. Predicting the miscibility of cocrystal components using solubility parameters can guide the selection of potential coformers prior to exhaustive cocrystal screening work.[10]

Cambridge structural database

The Cambridge Structural Database (CSD) is a repository for small molecule crystal structures. Scientists use single-crystal x-ray crystallography to determine the crystal structure of a compound. Once the structure is solved, information about the structure is saved but in CSD scientists can search and retrieve structures from the database. Scientists can use the CSD to compare existing data with that obtained from crystals grown in their laboratories.[8]

1.4. Hydrogen bond

For most pharmaceutical cocrystal structures, hydrogen bonds take an important role in directing intermolecular recognition between an API and a coformer molecule. Following guidelines were proposed to facilitate the design of hydrogen bonded solids: (a) all good proton donors and acceptors are used in hydrogen bonding; (b) if six-membered ring intramolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen bonds (c) the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation, form intermolecular hydrogen bonds to one another.[11]

1.5. Δ pKa

Cocrystal formation is expected for $\Delta pKa < 0$ and salt formation for $\Delta pKa > 3$. A ΔpKa in the region 0-3 is howere less conclusive with salt or Cocrystal formation being possible.[12]

Howere, many problems using this ΔpKa evaluation method are found and the criteria is not always applicable.

1.6. Fabian's method

Different sets of reliable cocrystal 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 cocrystals. The strongest descriptor correlation was related to the shape and polarity of cocrystal formers.

Mechanisms by which cocrystals enhance solubility

Solubility is determined by two independent factors: the strength of the crystal lattice and the solvation of cocrystal components. To increase solubility, one can lower the lattice energy and/or increase the solvent affinity.[1] Cocrystals have the ability to influence both factors to different extents.[12-14] Cocrystal solubility is also related to coformer solubility and most importantly, the conformer solubility must be approximately 10 fold higher than the API to increase the solubility of the Cocrystal compared to drug.[3]

Cocrystallization methods

Various methods of Cocrystal formation are reported, the most common formation methods are based on solution and grinding.[11]

1. Grinding method

(a) Neat grinding (dry grinding): In this method stoichiometric amount of Cocrystal forming agents are grind together by using mortar pestle or mechanically, using ball mill etc. this method requires one or both reactant having sufficient vapour pressure in solid state.

(b) Liquid assisted grinding (solvent drop or kneading or wet cogrinding): In this method, Cocrystal forming agents are grind together by adding suitable small amount of solvent. Selection of solvent is very important and it should be able to dissolve at least part of the original components. Very less solvent is required in this method, so it is cost-effective, environmentally friendly and reliable method for the discovery of new Cocrystal.

2 Solution methods

In practice, solution cocrystallisation is based on the following two strategies [15]: (1) use of solvents or solvent mixtures where the cocrystal congruently saturates and thus the components have similar solubility, or (2) use of non-equivalent reactant concentrations in order to reach the cocrystal stability region in non-congruently saturating solvents, which can be illustrated by isothermal ternary phase diagrams (TPDs).

a) Evaporation cocrystallisation: Cocrystallisation by evaporation of stoichiometric solutions is based on strategy 1 and it is the most important tool for cocrystals screening. In order to design successful cocrystal screening experiments, it is very important to consider reactant solubility's.

b) Reaction crystallisation: In reaction crystallization, a solution of one reactant often is mixed with a solution of the other, and the crystallizing substance is formed by a chemical reaction in concentrations exceeding the solubility. The reaction is fast or very fast, and the mixing conditions influence the product size distribution.

c) Cooling crystallization: Another solution method called cooling crystallisation involves varying the temperature of the crystallisation system. First, large amounts of reactants and solvent are mixed in a reactor typically a jacketed vessel, and then the system is heated to a higher temperature to make sure all solutes are totally dissolved in the solvent and is followed by a cooling down step. Cocrystals will precipitate when solution becomes supersaturated with respect to cocrystal as the temperature drops down.

3. Ultrasound assisted solution cocrystallization

Sonochemical method has been developed for the preparation of cocrystals of very small size i.e. for preparation of nanocrystals[18]. In this method, API and cocrystal former are dissolved together in a solvent and the solution is kept in a sonoreactor to form the solution turbid. Cold water is supplied during the sonication to maintain the constant temperature of sonicator and prevent fragmentation. The solution is kept overnight for drying. Pure cocrystals were obtained by this method and the purity of cocrystals can be assessed by using X-ray diffraction study.

4. Supercritical fluid atomization technique

In supercritical atomization technique, the drug and coformers are mixed with each other by using high pressurized supercritical fluid i.e. CO2. Cocrystals are prepared by atomizing this solution with the help of atomizer. In supercritical antisolvent (SAS) method, the cocrystals are prepared from solution by the antisolvent effect of supercritical fluid.[17]

5. Spray drying technique

In spray drying process, cocrystals are prepared by spraying the solution or suspension of drug and coformer with hot air stream to evaporate the solvent. This is the most preferred technology because this is a fast, continuous, and one-step process. Thus, spray drying process will offer a unique environment for the preparation and scale-up of cocrystals.

6. Hot melt extrusion technique

In hot melt extrusion technique, the cocrystals are prepared by heating the drug and coformers with intense mixing which improved the surface contacts without use of solvent. The limitations of this method include both coformer and API should be miscible in molten form and not used for thermolabile drugs.

7. Miscellaneous Cocrystal Preparation

a) Laser Irradiation

This method consists of using a high-power CO_2 laser to irradiate powder blends of cocrystal formers and induce their recrystallization to a cocrystal structure.

b) Electrochemically Induced Cocrystallization

Urbanus et al. demonstrated the potential of using cocrystallization combined with electrochemistry for in situ product removal of carboxylic acids. Proof-of-principle was established using a cinnamic acid and 3-nitrobenzamide cocrystal system. This work showed that electrochemistry can be used to locally shift the pH to obtain neutral carboxylic acids and generate a local driving force for cocrystallization.

c) Resonant Acoustic Mixing

Resonant acoustic mixing has been used to mix the target molecule and coformer in the presence of a liquid to form a cocrystal in the absence of any grinding media. In this method, mechanical energy is transferred acoustically into a wetted powder mixture, encouraging intimate mixing of the components.

d) Spray Drying

Spray drying is a continuous single-step method of transformation of liquids (solutions, suspensions, slurries) to solid powders. It is advantageous due to its continuous, highly controllable, and fast process. Although spray drying has been widely used in formulating amorphous solid dispersions because of the fast solidification process, it has also been employed in synthesis of cocrystals.

e) Freeze-Drying

Freeze-drying, technically known as lyophilization, has been mostly used as a processing technique to preserve a wide variety of products, which include food and pharmaceuticals. This process works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase. It has also has been demonstrated recently to be a feasible method for the preparation of new solid forms of cocrystal systems.

f) Electrospray Technology

Electrospraying is a process of simultaneous droplet generation and charging by means of an electric field. In this process, a solution containing the dissolved substances flows out from a capillary nozzle, which is maintained at high potential, through an electric field, which causes elongation of the solution droplets to form a jet. The solution jet is dried, and the generated particles are collected on a charged powder collector.

Cocrystal characterisation techniques

The cocrystal characterization is involves structural assessment and properties evaluation. There are several analytical techniques which are used for characterization of crystal structures and properties.[20] The basic physicochemical properties of cocrystal can usually be characterized by powder X-ray diffraction (PXRD), single crystal X-ray diffraction (SXRD), infrared spectroscopy (IR), Raman spectroscopy, differential scanning calorimetry (DSC), solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), and terahertz spectroscopy.

Physicochemical properties of cocrystals

The physical and chemical properties of a cocrystal need to be investigated in the same manner as any other solid form in order to determine developability into a marketed dosage

form.[21] Physicochemical properties, such as crystallinity, melting point, solubility, dissolution, and stability, have been studied extensively by researchers.[23]

1. Melting point

The melting point is a fundamental physical property, which is determined by the temperature at which the solid phase is at equilibrium with the liquid phase. Melting point is important tool in characterization and identification of purity of compounds. It is also very valuable due to its correlations to aqueous solubility and vapor pressure.[23]

2. Stability

Stability is a very important parameter when evaluating the properties of a pharmaceutical cocrystal. Usually, the stability testing of a newly developed cocrystal includes four aspects: relative humidity stress, thermal stress, chemical stability, and solution stability.[11]

3. Solubility

One of the main reasons to investigate cocrystals is to increase the solubility of a poorly soluble compound.[23] Traditional methods for improving solubility of poorly water-soluble drugs include salt formation, solid dispersion (emulsification), and particle size reduction (micronisation). However, there are practical limitations with these techniques.[22]

4. Intrinsic dissolution

Intrinsic dissolution measures the rate of dissolution of a pure drug substance from a constant surface area, which is independent of formulation effects and measures the intrinsic properties of the drug as a function of dissolution media, e.g. pH, ionic strength and counter-ions.[11] Solution concentration is measured over time to determine the dissolution rate (in mg/cm^2 ·min). Intrinsic dissolution rate is a good indicator for in vivo performance of APIs.[25]

5. Bioavailability

Bioavailability is a measurement of the rate and extent of the active drug that reaches systemic circulation.[26] Animal bioavailability is an important parameter to consider when preparing new forms of a compound.[23] The ultimate goal for cocrystal investigation is to improve the bioavailability of an API.

Advatages of cocrystals

Cocrystals are stable crystalline form as compaire tp amorphuous.

It enhance solubility of poorly water soluble drugs.

It also enhance bioavailability of drugs.

Cocrystal formation techniques may be used for purification steps.

Drawbacks

There are some reports of cocrystal inadvertently reducing Solubility and exposure in human subjects.[29]

Cocrystals are non-ionic and have a tendency to have lower melting points than corresponding salts. In general APIs that exhibit lower melting points often exhibit plastic deformation during secondary processing which can cause both caking and aggregation of suspensions, and impacts on both flow and compressibility performance during tabletting.[30]

CONCLUSION

Cocrystallization offers one of the most promising approaches to improve physicochemical properties of APIs. A wide range of options exist to prepare cocrystals ranging from routine lab scale synthesis methods to potentially large scale continuous production methods. This review offers standard descriptions and examples of established and emerging cocrystal preparation routes. As cocrystals continue to gain interest and prove their value, the range of demonstrated cocrystal application areas continues to expand. All demonstrated application areas for pharmaceutical cocrystals are included in this review with the aim of highlighting the wide ranging potential of these materials. It is anticipated that cocrystals will become more and more routine in pharmaceutical development as their benefits continue to be demonstrated and routine routes of manufacturing are proven.

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