REGULATORY AND STRATEGIC ASPECTS IN PREPARATION OF COCRYSTALS

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ABSTRACT
Cocrystal is a concept in which the drug and coformer lives in same structure. It is formulation which is gaining the more attention from researchers of pharmaceutical and chemical sciences. Cocrystals increases the physiochemical properties of the drug. During the preparation of the pharmaceutical product, it is necessary to increase the physicochemical properties of active pharmaceutical ingredients. Pharmaceutical cocrystals can be employed to improve many physicochemical characteristics of a drug that contains solubility, dissolution, bioavailability and stability of pharmaceutical compounds while maintaining its therapeutic activity. It is very advantageous and easy process for production of pharmaceutical compounds.

The preparation of polymorphic forms, solvates, hydrates and salts of cocrystals during the synthesis are also increases the properties. The rules and processes like hydrogen bonding rules, solubility, screening through the CSD database and thermodynamic characteristics can be utilized for the rational design of cocrystals and selection of coformers for synthesis multi-component cocrystals. In this paper, we discuss with the synthesis, strategic aspects of formulation, design, and characteristics of cocrystals along perspectives on its regulatory and intellectual property considerations.

KEYWORDS
Cocrystals, Conformers, Solubility, Efficacy, Crystallization, Physiochemical properties.

I INTRODUCTION (1)
In recent decade many new chemical entities coming into poorly soluble drug category which commonly leads to poor oral bioavailability. According to biopharmaceutical classification system the drugs are classified into four major categories according to their solubility and permeability BCS Class II and class IV drugs having low aqueous solubility leading to poor absorption and bioavailability which resulting in many challenges for drug development process. Increasing bioavailability of inadequately water-solvent BCS class II and BCS class IV drugs are very important to improve efficacy of drugs.

Physical property improvement gaining more interest to pharmaceuticals as the majority of formulations are formulated as solid forms. The physical properties of the solids having direct impact on the processing, delivery, performance of the medicine. To give a proper crystal structure directly affects the solubility and
other physiochemical properties of a given solid in solution. Drug products require a certain solubility to be bioavailability in the body. It is estimated that approximately 40% of existing drug products and up to 90% of new chemical products have limited aqueous solubility and hence cannot be delivered to the body causes many problems. Cocrystal formation with a suitable coformer have potential of increases solubility by modification of the underlying crystal structure and bioavailability increases.

In recent years maximum development and interest area are being diverted to co-crystallization. Cocrystallization can be achieved only when the physiochemical properties of the formulation are increases. Co-crystals consists of two components that are the drug and the former.

Pharmaceutical cocrystals are defined as crystals that comprise two or more discrete neutral molecules at a stoichiometric ratio and bond together via noncovalent bond interactions in which at least one of the ingredients is drug and the others are pharmaceutically acceptable ingredients. Since many years, it was realized that cocrystal engineering may be capable approach to improve the physicochemical properties of pharmaceuticals, which was mentioned to several representative pharmaceutical cocrystal papers.

II SCIENTIFIC DEFINITION OF COCRYSTALS

Solids possess the characteristic that the atoms, ions or molecules are tightly packed and cannot move freely within a given space. This state of matter can be further divided into sub-groups depending on the arrangement of the components of the solid. Solids that do not display any form of order are known as amorphous solids. On the other hand, solids in which the compounds are arranged in regular patterns are known crystalline solids.

Crystals are composed of a lattice in which the atoms, ions or molecules are arranged in a defined stoichiometric ratio and interact with each other via different types of atomic interactions. The group of crystals can be divided into many sub-groups. The categorization depends on the number of partners like acceptor and donor involved in the formation of the crystal lattice. Crystals composed of a single entity are the simplest example of a crystal. In contrast to single entity crystals, crystalline structures that are formed by two or more components can be formed by different interaction types such as covalent, non-ionic and van der Waals interactions. Crystals formed by ionic interactions are known as ionic solids, which are also often referred to as salts. Examples of solids with crystalline character that are formed by non-ionic interactions of compounds like solvates, hydrates and cocrystals.

III SELECTION OF COFORMERS

Coformer with its drug compatibility should be studied before to its pharmaceutical co-crystal development and are the main challenges to be solved and problems improved. Coformer screening is the most important factor used for selecting the coformer that can be used in formulation as a co-crystal with the drug. Then this candidate is then studied for its physicochemical and pharmacological properties prior to its development to a suitable dosage form. Generally, the coformers are selected from the substances which are approved as generally recognized as safe (GRAS) list given by USFDA so because of this, these coformer do not affect the pharmacological activities of the main API.
IV METHODS OF COCRYSTAL PREPARATION (2,3)

SOLVENT BASED CO-CRYSTALLIZATION METHODS

Solvent-based methods are most commonly used due to the ability to monitoring the process and controlling the properties of the formed product. Solvent selection is important step in these methods. As the solvent shows its impact on crystal size, shape, purity, polymorphic form and other co-cystal characteristics. Many literatures reported the importance of solvent selection in solvent-based co-crystallization method. Some examples are solvent evaporation, cooling co-crystallization, reaction crystallization, anti-solvent addition, ultrasound-assisted co-crystallization.

1. Solution based method
   a. Solvent evaporation method
   b. Antisolvent method
   c. Cooling crystallization
   d. Reaction cocrystallization
   e. Slurry conversion

SOLVENT FREE CO-CRYSTALLIZATION METHODS

Solvent free co-crystallization methods are gaining an interest in the industry and due to the feasibility of being kindred with green chemistry principles. These principles endorse efficient co-crystal production with less toxic bi-products. Mechano-chemical methods, neat grinding, liquid assist grinding, polymer assistant grinding, hot-melt extrusion, spray congealing co-crystallization are some of the methods classified under solvent-free co-crystallization.

1. Solid based methods
   a. Contact cocrystallization
   b. Solid state grinding
   c. Neat grinding
   d. Liquid assisted grinding
   e. Melting crystallization
V PHYSIOCHEMICAL PROPERTIES OF COCRYSTALS (4-7)

1. Solubility

Cocrystallization technique which is having main use that is improve solubility of the drug. Which increase solubility along with coformers which is not possible for only drug, drugs which are from BCS II category, cocrystals are very useful formulation for improve their solubility.

2. Stability

It is an important parameter to for any formulation. Hence in case of cocrystals, it is also important to ensure the chemical stability, solution stability, thermal stability, and relative humidity stability.

3. Bioavailability

Bioavailability is the amount of drug available in systemic circulation. Cocrystals increases the bioavailability of drug which is very useful for any formulation.

4. Intrinsic dissolution

Co-crystallization is a new technique for solubility enhancement mainly used in case of BCS class II drugs. There are many examples that proves the cocrystals increase the intrinsic dissolution rate and achieves many times higher dissolution rate.

5. maximum wavelength

When the co-crystal solution is placed for UV scan, the scan gives the peak showing maximum wavelength of the API. If the conformer is also an API the scan will show two peaks of lambda max of both the API.

6. melting point

Melting point is also in the physiochemical properties, because of this temperature is in solid liquid equilibrium. When the co-crystals are formed the melting point changes and comes in between the melting point of two individual molecules. If such results are obtained, it can be confirmed that the co-crystals are formed.

VI FACTORS DETERMINING COCRystallIZATION (8-12)

ΔpKa RULE

ΔpKa value has been used check cocrystal development ability of a coformer with a given API with suitable coformer. pKa value indicates the ability of an acid molecule to give up a proton. When the difference between pKa value of API and pKa value of coformer (ΔpKa) is in range of negative, there will be no proton transfer. Hence, one can possibly expect cocrystal formation in such a situation of cocrystal formation. On the other side, salt formation is observed when ΔpKa value is greater than 3 due to completion of proton transfer. According to scientists Berry and Steed, when ΔpKa value stays close to that of a base, then the system forms a salt and when it remains close to the acid, then the system forms a cocrystal. Salt-Cocrystal Continuum is interesting part of multicomponent pharmaceutical solids which comes under cocrystal/salt category. When a multicomponent solid form present in mixed ionization states, it is not easy to understand whether formed solid form is a salt or cocrystal. This mainly possible when the difference in pKa value of the drug and coformer lies between 0 and 3. Investigated the influence of crystal structure on the ionization states of the salt-cocrystal continuum. When the ΔpKa value ranges between 0 and 3 (partially ionized states), in such cases, these solid forms were referred to as Salt-cocrystal continuum.
HYDROGEN BOND DONORS AND ACCEPTORS

The number of hydrogen bond donors and acceptors in a coformer and drug molecules also determines the formation of the crystals in a cocrystallization event. Molecules that can form multiple hydrogen bonds they also form cocrystals with the suitable coformer molecules. There are rules like Etter and Donohue framed Hydrogen Bond Rules from these rules predict the circumstances under which hydrogen bond interactions that forms into cocrystals.

These rules are as given below:

1. Mostly all good proton donors and acceptors are involved in hydrogen bonding.
2. Six-membered ring intramolecular hydrogen bonds are formed first in preference to intermolecular hydrogen bonds.
3. The best proton donors and acceptors become available after intramolecular hydrogen bond formation the involved in intermolecular hydrogen bonds.
4. All acidic hydrogen atoms are involved in hydrogen bonding in the crystal structure of cocrystallization.

MOLECULAR RECOGNITION POINTS

Almarsson and Zaworotko pointed out that the API molecules contain certain functional group in their structure which interacts with the coformer and thereby produce a supramolecular unit called supramolecular synthons. Synthons defined as “Structural units within supramolecules which can be formed by known or conceivable synthetic operations involving intermolecular interactions”. Scientist Desiraju defined supramolecular synthons as spatial arrangement of intermolecular interactions which serves as a base for any supramolecular synthesis. Thus, synthons are elements in crystal engineering which are not same as intermolecular interactions. Sometimes, a synthon can also be seen as a single interaction in a few supramolecular structures. depends on the drug and coformer complementary functional groups these supramolecular synthons are differentiated into two parts that are homo synthons and heterosynthons. Homosynthons are prepared by interaction between self-complementary functional groups like acid-acid and amide-amide groups. whereas the heterosynthon formation occurs due to the interaction between two different functional groups such as acid-amide, acid-pyridine and amide-pyridine groups. Heterosynthons could also be formed due to halogen bonding results.
FLEXIBILITY OF SYNTHON-FORMING FUNCTIONAL GROUPS

Some other molecular recognition points, the position of functional groups and the conformational flexibility of participating molecules also play an important role in determining success rate of a cocrystallization. Scientists Nangia and coworkers found that resorcinol can cocrystallize with curcumin whereas hydroquinone and catechol could not cocrystallize with curcumin though all the three molecules possessed same functional groups. That understanding the rationale behind formation of supramolecular synthons in the crystal lattice of the cocryystals is highly necessary for cocrystal formulation design and development. carried out an extensive study to understand how polymorphic compounds serve as good cocrystallizing coformers and emphasized the significance of flexibility of synthon-forming functional groups of coformers during any cocrystallization. They experimentally studied the cocystal forming ability of three compounds, isonicotinamide, 2-amino 3-nitropyridine, 4-chlorobenzamide and maleic hydrazide. It was observed in their study that isonicotinamide, 2-amino 3-nitropyridine and 4-chlorobenzamide participated actively in intermolecular hydrogen bonding with a variety of aliphatic and aromatic carboxylic acids and thereby favored the formation of binary/ternary cocryystals whereas maleic hydrazide was not found suitable candidate for cocrystallization with aromatic or aliphatic compounds having acid, amide and oxime functional groups. This was attributed to the flexibility of functional groups in coformers in addition to their polymorphic nature. Isonicotinamide, 2-amino 3-nitropyridine and 4-chlorobenzamide exhibit hydrogen bonding between different functional groups in each of their polymorphs whereas all the three polymorphs of maleic hydrazide always exhibited the primary hydrogen-bonding interactions between same functional groups which decreases the possibility of formation of new hydrogen bond synthons with the other molecules.

CARBON CHAIN LENGTH OF DICARBOXYLIC ACID COFORMERS

Carboxylic acids are most commonly used coformers for cocrystallization of many small molecules since they can form heterosynthons with molecules containing amide and pyridine functional groups and homosynthons with API molecules containing acid functional group. However, the cocystal forming tendency of carboxylic acids also depends on the length of carbon chain present in the compound. while investigating cocrystallization of itraconazole with different aliphatic dicarboxylic acids containing carbon chains of varying length observed that as the length of carbon chain in the coformer molecules increases, the packing of these molecules within the crystal lattice of drug molecules becomes more difficult due to steric hindrance and incompatibility of large carbon chain to exactly fit into the crystal lattice of drug.

EFFECT OF SOLVENTS

Solubility of the API and coformer in a solvent used for cocrystallization plays a significant role in determining rate of cocrystallization experiment. The solubility of the individual components must be determined to cocrystallization experiments. The Phase Solubility Diagram, also called as Ternary (API-Coformer-Solvent) Phase Diagram can be constructed using this data which then plays as a fundamental tool to identify region of cocystal development, understand the solution chemistry and solubility behavior of cocryystals. The polarity of the solvent system, solubility of API and coformer, temperature and pH are the important parameters which determine the cocystal forming zone in a ternary system. Robertson and his coworkers observed that the polarity of the solvent determined the type of non-covalent interactions and thereby controlling intermolecular interactions in the cocystal phases. It was summarized that the hydrogen-bonded cocryystals formation was favored by less polar solvents (such as toluene) whereas the more polar solvents (such as chloroform, dichloromethane, acetone, acetonitrile, nitromethane and 1-propanol) favored the formation of halogen-bonded cocryystals and in some cases, mixed halogen and hydrogen-bonded cocryystals. This is mainly attributed to the influence of polarity of the different solvents on the strength of intermolecular interactions.
PKA BASED MODEL

Proton transfer is the term that occurs in the case of salts. The equation involved in the prediction of co-crystal formation is \( \Delta pK_a = [pK_a(\text{base}) - pK_a(\text{acid})] \). The transfer of proton can be seen if the difference in the pKa value is more than 3. If the \( \Delta pK_a \) value is less than zero, then co-crystal might be formed and the higher value that is more than 3 results in the formation of salts. If the \( \Delta pK_a \) is in between 0-3, then either co-crystal or salt can be expected. For example, succinic acid (pKa 4.2) forms co-crystal with urea base (pKa 0.1) while the salt is formed by using L-lysine base (pKa 9.5)

CAMBRIDGE STRUCTURAL DATABASE

Cambridge structural database (CSD) can incorporate to assess the intermolecular hydrogen bonding possibility between different molecules. CSD single crystal x-ray crystallography can be employed for characterizing the crystal structure of a compound. The resolved structure can be saved in CSD and information can be searched, retrieved, and utilized from the database at any time. ‘Atoms’ and ‘powder cell’ are two examples of the software which can be used to visualize the structure by the information obtained from the CSD.

Proper knowledge of intermolecular interactions is required for the synthesis of supramolecular synthons. Designing of synthons can be done by utilizing the information about hydrogen bond patterns of crystal lattice which can be done by CSD. Intermolecular interactions on crystals can be studied by using which provides the information for systematic analysis of a wide range of related structures which could not be done by other methods. CSD contains information about the functional groups that result in the formation of supramolecular synthons.

HANSEN SOLUBILITY PARAMETER (HSP)

To predict the miscibility of a drug and coformer and co-crystal formation is become possible by using HSP. The group contribution method is commonly used to determine the HSP and for this only structure compound is needed. Many methods like Fedors method, Hoy’s method, and Van Krevelen’s method are used in HSP for calculation purpose.

Prediction of co-crystal formation by using Hansen solubility parameter was reported by Mohammad. This concept was actually proposed by Hansen for polymer solubility prediction in paints. HSP indicates that several individual forces compose the total energy of vaporization. The co-crystal formation can be predicted by calculating the difference in total solubility parameter (\( \Delta \delta_t \)) for API and co-former.

HYDROGEN BONDING (12)

From the various studies, it is found that the hydrogen bond donors and acceptors of the partners shall make cocrystals. Moreover, the best hydrogen bond donors and acceptors interact within the crystal structure cause to formation of co-crystals. The formation of hydrogen bonding can be confirmed by various methods like FTIR spectroscopy.
SUPRAMOLECULAR SYNTON APPROACH

Supramolecular synthons were used for screening the coformers. Supramolecular synthons are further categorised into two groups namely supramolecular homosynthons and supramolecular heterosynthons. The former are identical functional groups like two carboxylic acid groups whereas the later consist of different functional groups like carboxylic acid and amide group.

BINARY AND TERNARY PHASE DIAGRAMS

These phase diagrams illustrate the solubility of either API coformer (Binary) or API-coformer-solvent (Ternary). DSC analysis can be employed for the construction of binary phase diagram. A ‘W’ shaped diagram will obtain in case of cocrystal formation rather than a ‘V’ shaped diagram, which is found when eutectic mixture is formed between the API and coformer. Yamashita et al carried out the coformer screening of salts and co-crystals based on binary phase diagram. Ternary phase diagram (TPD) is a solute-solute-solvent triangular phase diagram that is used for coformer screening in the solution co-crystallization. Hong et al have used TPD for the successful preparation of myricetin co-crystals.

VII THE FUTURE OF COCRYSTALS

Recent developments suggest that the field of pharmaceutical cocrystal is important field, not least in finding new crystal forms and the potential IP that might accompany such discoveries. There is also a developing understanding of how cocrystals behave in physiological environments and particularly how cocrystallisation could be applied to alternative routes of delivery. We also note that tentative steps have been taken by the pharmaceutical industry in the field of cocrystallisation, but there are still outstanding challenges, particularly with regards to continuous manufacturing. A recent review discusses how emerging process analytical technologies and continuous processing techniques can be applied to cocrystallisation. Clinical trials ClinicalTrialsRegister.eu and ClinicalTrials.gov were searched using the terms, ‘Cocrystal’ OR ‘Co-crystal’ and the results were compiled. Cocrystals of commonly prescribed drugs.

VIII CONCLUSION (13-16)

The importance of crystal engineering through cocrystallization in pharmaceutical field can be understood by looking at regulatory cocrystal considerations and CSD database growth. On the one hand, cocrystals are unexpectedly formed during processing. Application of pharmaceutical cocrystals is very important alternative way to improve the bioavailability of poorly water-soluble drugs, especially for these neutral compounds or those having weakly ionizable groups. Although, the definition of the term “pharmaceutical cocrystal” is still under discussion, it is clear that these substances are very useful, and it is important to explore new cocrystals of an API to improve or obtain some properties, such as habit, bulk density, solubility, compressibility, friability, melting point, hygroscopic and dissolution rate. There are many cocrystals formulation methods and they are easy to prepare, they having many characteristics for improving physicochemical properties of drug. Cocrystals investigation and production are very interesting for researchers.
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