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Commentary

Challenges in Translational Development of Pharmaceutical Cocrystals

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ABSTRACT

The last 2 decades have witnessed increased research in the area of cocrystals resulting in deeper scientific understanding, increase in intellectual property landscape, and evolution in the regulatory environment. Pharmaceutical cocrystals have received significant attention as a new solid form on account of their ability to modulate poor physicochemical properties of drug molecules. However, pharmaceutical development of cocrystals could be challenging, thus limiting their translation into viable drug products. In the present commentary, the role of cocrystals in the modulation of material properties and challenges involved in the pharmaceutical development of cocrystals have been discussed. The major hurdles encountered in the development of cocrystals such as safety of coformers, unpredictable performance during dissolution and solubility in different media, difficulties in establishing *in vitro–in vivo* correlation, and polymorphism have been extensively discussed. The influence of selecting appropriate formulation and process design on these challenges has been discussed. Finally, a brief outline of cocrystals that are undergoing clinical development has also been presented.

Introduction: Definition and Theoretical Aspects of Cocrystals

Cocrystals, although reported for long in literature, became popular only after 1990 when M.C. Etter extensively studied the role of hydrogen bond as a design element in the preparation of multicomponent crystals.[1,2] Attempts have been made to define cocrystals by the scientific community as well as by regulatory bodies. United States Food and Drug Administration (FDA) defined cocrystals as "dissociable API-excipient molecular complexes (with the neutral guest compound being the excipient called coformers) wherein both API and excipients are present in the same crystal lattice."[3] This definition by FDA in their guidance document has been a matter of debate and its consequences were thoroughly discussed in Indo-US Bilateral Meeting by several leading academic and industrial groups working in the area of cocrystals.[4] In a more recently published draft guidance by FDA, cocrystals are defined as "crystalline materials composed of two or more different molecules within the same crystal lattice that are associated by nonionic and noncovalent bonds."[5] It is also stated that if the solid form in a drug product is a new cocrystal entity, it is considered as a new polymorph (solvate/hydrate) of the active pharmaceutical ingredient (API). The scientific community has defined cocrystals as "solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio, which are neither solvates nor simple salts."[4] This definition excludes simple salts, hydrates, and solvates. However, from supramolecular perspective, the solvates or hydrates could be cocrystals in the case of "solvated/hydrated salt cocrystals."[6,7] Notably, the multicomponent systems such as solid solutions, inclusion complexes, and dispersions are not encompassed in this recently proposed definition of cocrystals. European Medicines Agency has adopted a similar definition in their reflection paper, which defined cocrystals as "homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio, where the arrangement in the crystal lattice is not based on ionic bonds, and components of a cocrystal may nevertheless be neutral as well as ionized."[8] Definitions by FDA present a simplistic view whereas other definitions include additional supramolecular features of cocrystals.

Cocrystal formation can be designed by applying the principles of supramolecular chemistry to manipulate solid-state properties of an API. Design strategies for cocrystals have been presented in many excellent publications and interested readers can refer them.[9-12] It mainly consists of selecting a suitable coformer based on the presence of compatible supramolecular synthon in the molecule of interest.[6] When same complementary functional groups are present between 2 molecules, such complexes are called as supramolecular homosynthons (carboxylic acid-dimer, amide-dimer), whereas heterosynthons form between different but complementary

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functional groups (carboxylic acid-amide, carboxylic acid-aromatic nitrogen, alcohol-aromatic nitrogen, and alcohol-amine). Cambridge Structure Database (CSD) helps in identifying hydrogen-bonding interactions and synthon competition in organic crystals of interest. It has been reported through CSD survey that probability of occurrence of carboxyl-pyridine heterosynthon is more likely than that of acid-acid homosynthon.[13] Aakeröy,[14,15] Vishweshwar,[16] and Almarsson's[17] concept of understanding the hierarchy of supramolecular synthons between the drug and coformer(s) coupled with the core concept of supramolecular chemistry by Desiraju[6] is the key in the design of cocrystal formation.

Another simple and prominent approach to predict cocrystal formation is ΔpK_a rule. A salt is formed if the difference between the p*K*a base and p*K*a acid (ΔpK_a) is >3, whereas a ΔpK_a <0 will generally result in the formation of a cocrystal. On the contrary, a ΔpK_a of 0-3 can result in complexes containing cocrystals or salts or shared protons or intermediate ionization states. The latter can be termed as salt-cocrystal hybrids. For example, salt-cocrystal continuum zone was observed in the p*K*a region of 0-2.5 in a study performed using 20 different theophylline (THP)-acid complexes.[18] Cruz-Cabeza[19] found that ΔpK_a >4 would exclusively result in ionized acid-base complexes, whereas for $\Delta pK_a < -1$ would result in nonionized acid-base complexes (cocrystals or solvates or hydrates). Hydrogen-bonding propensity can be helpful in the rational design of cocrystals. Other design approaches for cocrystals screening include lattice energy calculations,[20] Fabian's method[21] (based upon polarity and shape of coformer with respect to drug molecule), virtual cocrystal screening (based upon molecular electrostatic potential surfaces [MEPS],[22] and the conductor-like screening model for real solvents [COSMORS].[23]

Triggers Encouraging Research in the Area of Pharmaceutical Cocrystals

Pharmaceutical industry has been struggling with critical issues of poor physicochemical properties such as aqueous solubility, dissolution rate, permeability, stability, hygroscopicity, and processability of drug molecules.[24] Poor aqueous solubility remains one of the most prominent challenges.[25] Traditionally, poor aqueous solubility has been addressed by use of various solid form modifications of a drug such as metastable polymorph(s), solvates/hydrates, amorphous form, and salt formation. Each of the above approaches has its own advantages and challenges, thus leaving a scope for the introduction of novel approaches. Metastable polymorphs offer only marginal (commonly 1- to 2-fold) increase in solubility. Moreover, the poor physical and chemical stability of metastable polymorph may pose problems in processability and shelf-life stability.[26] Solvates/hydrates are not always preferred on account of their low thermal stability, variable stoichiometry, and limited gain in solubility.[27-29] Amorphous form increases the solubility of the poorly soluble compounds; however, it has the problem of physical instability (tends to devitrifies into crystalline form) as a result of its higher free energy and entropy.[30,31] Increased reactivity of an amorphous material leads to enhanced hygroscopicity and susceptibility to chemical degradation. Consequently, relatively few amorphous drug products are available in the market such as Ceftin® (cefuroxime axetil), Accolate® (zafirlukast), Rezulin® (troglitazone), and Accupril® (quinapril hydrochloride).[32] Use of the salt form is a well-established approach to improve physicochemical properties of a drug. Nevertheless, a major drawback of salt formation is that they are limited to those APIs that contain ionizable moieties and is governed by the ΔpK_a rule.[33] Cocrystals have provided a broad platform for modulation of material properties that are critical during pharmaceutical development and have emerged as a promising alternative to traditionally used solid forms. Advances in the area of crystal engineering, diversity of coformers, and regulatory acceptance have fueled research in the area of cocrystals as novel materials for pharmaceutical development.

Trend of Cocrystals in Patent and Non-Patent Literatures

Cocrystals are the novel solid forms of an API that have significant industrial utility and its synthesis involves nonobviousness. Therefore, cocrystals are patentable inventions, as they satisfy all the 3 eligibility criteria of novelty, industrial applicability, and nonobviousness. Speedy ascend in number of patent applications and publications in peer review journals in the last couple of decades underlines the attention received by cocrystals from both academia and pharmaceutical industry. Literature review on the term “cocrystal” in the scientific database (PubMed) showed an increase in number of scientific publications every year (total >2000 until April 2016; Fig. 1a). Moreover, the WIPO patent database depicted increasing intellectual property (IP) landscape every year (total >1650 until April 2016; Fig. 1b). The analysis of patent databases revealed that out of the total patents filed for pharmaceutical cocrystals, about 80% filings involved pharmaceutical industry or contract research organization, whereas only 20% of the filings were from sole academic institution and universities.

Modulation of Material Properties Using Cocrystals

The success of new chemical entity in pharmaceutical industry is governed by its selectivity, potency, and material (physicochemical) properties.[34] Latter includes properties such as solubility, dissolution rate, permeability, stability, hygroscopicity, melting point, and manufacturability. Poor solubility of a compound can lead to low and variable bioavailability. About 40% of marketed drugs have low solubility and around 70%-90% of the drugs in the development pipeline are anticipated to have low water solubility.[25] A recent study conducted on 812 drug candidates from AstraZeneca, Eli Lilly, GlaxoSmithKline, and Pfizer showed that poor pharmacokinetic and bioavailability have remained the third most common cause of failure of the molecules in phase I clinical trial.[35]

There is an increasing interest in crystal structure-property relationship of pharmaceutical solids as it allows engineering of supramolecular structure to attain materials with desired properties.[36] In the same framework, cocrystals are evolving as a promising approach to modulate material properties of a molecule by rational use of crystal engineering.[37,38] For example, melting point and aqueous solubility of hexamethylene bisacetamide, an anticancer compound, were systematically customized using a series of 5 diacids.[39] Authors demonstrated that cocrystallization with the diacid of shorter chain length can increase solubility and decrease the melting point of hexamethylene bisacetamide. Therefore, higher solubility of cocrystals was dialed-up by selecting the diacid of lower chain length as coformers. The strategy of synthesizing the cocrystals of similar crystal structure so as to maintain organization of individual building block within crystal lattice coupled with logical changes to the molecular nature of the coformers (diacids) resulted in cocrystals with the desired solubility.

Apart from solubility, cocrystals have also been investigated for modulation of other critical material properties of drugs. For instance, increased permeability (flux) of furosemide, a Biopharmaceutics Classification System (BCS) class IV drug, was achieved by cocrystallization with anthranilamide as a coformer.[40] Intrinsic dissolution rate (IDR) of megestrol acetate was enhanced by 3- to 4-fold as compared to the parent drug by cocrystallization with saccharin (SAC) as a coformer.[41]