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Pharmaceutical Cocrystals: A Novel Approach to Modify Physicochemical Properties of APIs

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ABSTRACT

Pharmaceutical cocrystals are crystalline molecules containing many constituents which are present in the same crystal structure arranged in a three-dimensional array representing a class of pharmaceutical materials which offers the vision to optimize physical properties. Co crystals has been gaining a lot of attention and interest from the pharma industries due to their ability to modify and enhance properties, such as solubility, dissolution, bioavailability, stability and process ability of the active drug. This review will focus on the advantages of cocrystals over other crystal forms such as solvates, hydrates and salts. It will present you the current perspective of the USFDA and EMA on pharmaceutical cocrystals and its design strategies along with the methods of preparation.

KEY WORDS: Pharmaceutical cocrystals, Hot melt extrusion, Physicochemical grinding, Physicochemical properties.

1. INTRODUCTION

The development of a new drug product from a novel molecule that is either synthesized, obtained from a natural source or produced by biotechnological processes is a complex procedure. The pharmaceutical industry has now moved from "trial-and-error" approaches to rational drug design and development. However, in some instances "trial-and-error" approaches are still used, where a molecule is passed through the development stages until desired properties are achieved. Drug candidates often reach to clinical trials without sufficient information on potential crystal forms, physical properties and manufacturing capabilities. Consequently, the lack of full characterization of the active drug through multiple perspectives leads to complex and costly problems in later stages of development, which could be avoided at an initial stage. Therefore, it is imperative to screen the existing solid state of an active pharmaceutical ingredient (API) in the initial stages of drug development, since it can influence API's physical, chemical, mechanical and biopharmaceutical properties and can also affect its stability and manufacturability (Rodrigues, 2018).

Pharmaceutical solids exists in either crystalline or amorphous nature (Rodrigues, 2018). Generally, crystalline forms of the API are preferred over amorphous forms, mainly due to their inherent stability and purity (Yadav, 2009). However, the crystalline materials have lower energy state compared to amorphous forms which provides them with lower solubility (Rodrigues, 2018). Approximately 40% of the marketed immediate release oral products have lower solubility and over 70% of the new chemical substances being identified by combinatorial screening program have lower water solubility (Gadade and Pekamwar, 2016). In this case, alternative solid forms may be investigated. This can be achieved by either modifying the physical characteristics of the API by increasing the particle surface area, improving solubility and/or wetting of the powder and improving the stability (Gadade and Pekamwar, 2016) or by the addition of a second component to alter the APIs physical chemistry in the form of pharmaceutical salts, hydrates or solvates. For ionisable drugs, preparation of salts using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability (Berry and Steed, 2017). Like the parent drug, salt forms of the drug may exist in several polymorphic, solvated and/or hydrated forms (Yadav, 2009). A pharmaceutical salt involves ionic interactions between an ionized molecular API (cationic or anionic form) and a counter ion. Polymorphism is another approach to modify the physicochemical properties of APIs (Rodrigues, 2018).

More recently pharmaceutical cocrystals have shown quite potential in improving different properties of APIs (Korotkova and Kratochvíl, 2014). Cocrystals are multicomponent compounds that are formed between a crystal of a drug and a coformer with specific stoichiometric compositions (Thakuria, 2013). Pharmaceutical cocrystals possess a tremendous potential in enhancing the physical properties of the API along with improving the absorption and permeation of the API through the GI tract, and therefore this field of study is currently experiencing speedy development (Karagianni, 2018). This review will deal with the comparative study of different physical forms of APIs such as salts, solvates, hydrates and cocrystals, along with the intermolecular interactions, regulatory classification and the application of the concepts of crystal engineering and principles of supramolecular chemistry in the design and development of pharmaceutical cocrystals.

Regulatory classification of pharmaceutical cocrystals: Pharmaceutical cocrystals represent an evolving class of compounds involved in the formulation of drugs with poor water solubility. It has become a topic of interest in the pharma industry, which can be traced from regulatory documents published by the United States food and drug administration (USFDA) and European Medicines Agency (EMA) (Gadade and Pekamwar, 2016).

The USFDA defines cocrystals as 'Crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ("coformers"), in the same crystal lattice'.

Pharmaceutical co-crystals have provided opportunities to increase the bioavailability and stability of the drug product and to improve the process ability of APIs during drug product manufacture through crystal engineering from the perspective of supramolecular chemistry.

For NDAs (New Drug Applications) and ANDAs (Abbreviated New Drug Applications) containing or professing to contain a co-crystal form, appropriate information needs to be submitted by the applicant that support the following:

- Data that proves that both the API and coformers are available in the unit cell.
- An inference that both the components do not have any ionic interactions especially in the case when the two components are ionic in nature.
- The USFDA in its guidance document 'Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry' characterizes pharmaceutical cocrystals as multicomponent materials where the ΔpKa (pKa (conjugate acid of base) - pka (acid)) ought to be less than one so that there won't be considerable proton transfer. If the ΔpKa is greater than one, there will be considerable proton transfer which may result in ionization and potential salt formation instead of a co-crystal.
- If the relative pKa values cannot predict between the salt form and the cocrystal form, spectroscopic and other meaningful approaches should be used to provide evidence to the contrary.
- Confirmation that the cocrystal dissociates significantly to give the parent API before reaching the target site.

If all of the above conditions are satisfied then the compound can be referred to as the pharmaceutical cocrystal. The pharmaceutical cocrystal is considered as a new polymorph of an API and not a new API by the FDA. The FDA considers co-crystalas a fixed-dose combination product and not a new single API if it contains two or more active pharmaceutical agents. (Services, 2018)

The European Medicines Agency, in its 'Reflection paper on the use of cocrystals of active substances in medicinal products' defines 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 (as with salts). (Madicines Agency, 2015)

In case of oral route of administration, cocrystal will not be considered as NAS (New Active Substance) since it will expose a patient to the same therapeutic moiety as with the salt form upon dissolution unless they are demonstrated to be different with respect to efficacy and/or safety. For other alternate routes of administration, the NAS status will be dependent on what form of the active moiety is actually present at the site of action in comparison to the authorised product. (Madicines Agency, 2015)

Salts, solvates (hydrates) and co-crystals: Since multitude of drugs that are marketed or in development phase are poorly water soluble, the most important concern is to improve properties such as the solubility of drugs. The extensive use of salts to improve solubility and dissolution rate is evinced by a wealth of marketed crystalline salts of APIs. (Pindelska, Sokal and Kolodziejski, 2017) Salt formation involves ionic interactions between an ionic drug and a counter ion similar to that of a reaction between an acid and a base involving either a transfer of proton or a neutralization reaction. (Monkhouse, 1977) For salt formation to take place, a difference of at least two units in the pKa values of the acid and the base is required. Salt formation is usually directed at a single acidic or basic functional group whereas cocrystals can deal with different functional groups simultaneously in a single drug molecule. (Yadav, 2009) Also, salt formation is only limited to ionic molecules whereas all types of molecules, at least in theory, can form cocrystals. There are very less number of acidic or basic counter ions that are explored in a typical API salt screen due to toxicological reasons, however, there are many molecules that can be used as coformers in cocrystal synthesis (Jones, 2006).

Solvates (hydrates) majorly differ from co-crystals in the physical state of the individual components (Morissette, 2004). One of the components is liquid in case of solvates (hydrates) whereas all the components in a cocrystal are solid at ambient temperature (Yadav, 2009). During crystallization, solvent may be incorporated in the crystal structure resulting in the formation of solvates. However, most of the solvents are biologically toxic and therefore, solvates are generally avoided in drug product development. Changes in temperature, pressure and/or relative humidity can cause conversion of hydrates to anhydrous crystal forms resulting in changes in the physical properties, for example, during storage, which can significantly affect the appearance and integrity of the dosage form (Jones, 2006). Cocrystals, however, are more stable especially because the constituents are solids at room temperature (Peddy Vishweshwar, 2006).

Pharmaceutical cocrystal design strategies: Crystal engineering can be used to design cocystals (Qiao, 2011) which involves cocrystallization using pharmaceutically acceptable/approved compounds with an aim to improve the physical properties of API without affecting its internal structure (Cheney, 2011). The important interactions involved in the formation of cocrystals are hydrogen bonding, van der Waals forces and π--π interactions. Crystal engineering involves modification in these intermolecular interactions resulting in the modification in the crystal packing (Qiao, 2011). The most common interaction observed in cocrystal structure is hydrogen bonding. Gadade and Pekamwar (2016) mentioned in its review the guidelines regarding hydrogen bond patterns that can be used to design pharmaceutical cocrystals. These rules are (a) hydrogen bonding involves acidic hydrogen atoms present in the molecule, (b) all good acceptors will be used in hydrogen-bonding when their hydrogen-bond donors are available, (c) preferentially hydrogen bonds are formed between the best hydrogen bond acceptor and the best hydrogen-bond donor.

Crystal engineering uses the theories of supramolecular chemistry for formation of cocrystals (Gadade and Pekamwar, 2016). The supramolecular synthon approach is a statistical analysis that utilizes the concepts of crystal engineering to analyze the supramolecular arrangements that an API might exhibit. The supramolecular synthon approach uses Cambridge Structural Database (CSD) which is a repository for small-molecule organic and metal-organic crystal structures to effectively choose coformers for crystal form screening if an appropriate supramolecular heterosynthon can be identified (Cheney, 2011). CSD is used to identify the most stable hydrogen bonding motifs for a particular API based on the structural property relationships observed in the classes of known crystal structures present in this database. The functional groups are classified depending on the groups contained on the host molecule and their contribution to crystal packing arrangement. Certain functional groups like amides, carboxylic acids and alcohols are particularly amenable to the formation of supramolecular heterosynthons (Gadade and Pekamwar, 2016).

Cocrystal formation can also be predicted from the pKa values of the individual components of the cocrystal. The difference in the pKa values of less than one between the two components is typically a criterion for selecting a coformer. Another criterion for predicting cocrystal formation is the miscibility of API and the coformer which is predicted by Hansen solubility parameters (HSPs) (Qiao, 2011). The HSP is calculated from the total energy of vaporization of a liquid comprising of several individual component forces. These forces arise from (atomic) dispersion forces, (molecular) hydrogen bonding (electron exchange) and (molecular) permanent dipole-permanent dipole forces. The difference in total solubility parameters (Δδt) of the API and conformer is calculated for the purpose of prediction of cocrystal formation. There are higher chances of cocrystal formation when the Δδt values are less than 7 MP0.5 and values greater than 10 MP0.5 show lesser probability of cocrystal formation. However, based on the results reported in the study, this approach has limited application in cocrystal prediction as only few coformers formed cocrystals, even though Δδt was less than 7MP0.3. Until it becomes possible to confidently predict which counter-molecules will form cocrystals with a given API, high throughput screening will continue to be of tremendous value to this research (Jones, 2006).

2. METHODS OF PREPARATION

The synthesis of pharmaceutical cocrystals from a mixture of solid starting materials has gained interest due to the advantages associated with these processes. Such synthesis requires no or negligible amounts of solvent, with excellent purity and quality. The high throughputs and fast processing times provides advantages over other processes. The techniques include Hot Melt and Mechanochemical Grinding.

Hot melt extrusion (HME) involves application of heat and pressure to the raw materials and forcing it through an orifice in a continuous process to give a product of uniform shape. Medina et al. pioneered to produce caffeine - AMG517 cocrystals by HME. Studies have shown that cocrystallization occurs gradually within the mixing areas of the extruder and materials are converted to cocrystals of comparable quality with those acquired through solvent crystallization. Some studies have shown that cocrystals formed by twin screw extruder (TSE) are better than that by single screw extruder because the cocrystals formed by the latter had shown broader melting endotherms and the presence of traces of amorphous drug resulting in lesser purity. A more recent approach that has been used to enhance the stability of cocrystals is matrix-assisted cocrystallization which involves coprocessing of drug - coformer pairs with inert excipients. However, this process results in the formation of amorphous drug material when co-processing with non-miscible carriers. This technology is, however, in its infancy and requires more studies for the synthesis of high quality cocrystals.

Another method of preparation of cocrystals is Mechanochemical grinding or dry grinding or solid state grinding which involves formation of cocrystals by chemical reaction that is induced solely by mechanical energy. Studies have shown that the synthesis of cocrystals of numerous drug and coformer pairs by dry grinding method afforded cocrystallization in more cases than their solution prepared counterparts (Douroumis, 2017).

Solvent-based methods are the most commonly used, especially in laboratory scale, because the process is less complex, process monitoring is possible and final product properties can be controlled by, for example,

changing the solvent and/or temperature. The most important step in these methods is solvent selection since the solvent can affect cocrystal characteristics such as crystal size, shape, purity, polymorphic form and the occurrence of solvates in the cocrystals. (Rodrigues, 2018) Solvent evaporation, ultrasound crystallization, freeze drying, antisolvent cocrystallization, spray-drying and high shear granulation are some of the techniques which use solvent for cocrystallization (Douroumis, 2017). Rodrigues (2018) have discussed advantages and disadvantages of these techniques.

3. CONCLUSION

The properties of API differ with different crystalline forms. Modification in these properties like solubility, bioavailability, chemical or physical stability can be brought about by crystal engineering to give salts, solvates, hydrates or cocrystals. One such approach to improve the bioavailability of hydrophobic drugs, especially neutral compounds or weakly ionisable compounds is pharmaceutical cocrystals. A number of cocrystallization techniques are available, each one with a set of benefits and flaws. However, these methods lack scalability which hinders their use in industry. Therefore, a great effort is necessary in this field, in order to apply cocrystallization as a routine method to improve drug properties.

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