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REVIEW ARTICLE

PHARMACEUTICAL COCRYSTALS: AN OVERVIEW

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ABSTRACT

Pharmaceutical cocrystallisation has gained importance from both academic as well as industrial aspect as a technique for physicochemical property enhancement. This paper focuses on concepts, design strategies, methods of preparation, scale up and evaluation of pharmaceuticl cocrystals. Some examples of pharmaceutical cocrystals are also mentioned in this paper.

KEY WORDS: pharmaceutical cocrystals, cocrystallization, solubility enhancement

INTRODUCTION

The rate and extent of absorption of poorly water soluble drugs, on oral administration is often dependent on the rate of dissolution, which in turn, is dependent on solubility of drug. Rate of absorption and bioavailability of poorly water soluble drugs can be improved by enhancing the solubility. Many techniques like formulating a solid dispersion, complexing with β-cyclodextrin, formulating into liquid-sol compacts, nanosuspensions, super critical process, micronization etc have been utilised to enhance the solubility of poorly water soluble drugs. Cocrystallisation is one such technique (1, 2, 3).

COCRYSTALS AND COCRYSTALLIZATION:

The process of formation of cocrystals is known as cocrystallization (9).The pattern to describe cocrystals or its definition is rather a debatable issue (5, 11, 12, 13). However, cocrystals could be thought of as crystalline material comprising of two or more components [(4)]. A more restrictive definition of cocrystals can be given as "cocrystals are structurally homogenous crystalline materials containing two or more netutral molecular constituents present in definite stoichiometric amounts in a crystal lattice. Cocrystals are a result of formation of strong hydrogen bonds and non covalent interactions like halogen bonds, π-π interactions and columbic interactions between the building blocks of the cocrystals" (4, 5, 6, 7, 8) . From the above definition, a pharmaceutical cocrystal comprises of an API and a cocrystal former or coformer. Some researchers have also described conformers as stabilizers in cocrystallization process (4). From the definition of cocrystals it is clear that a cocrystal differs from API hydrate. But, an API hydrate may cocrystallise with a cocrystal former in a solid state (4).

Liquids and solids may also serve the purpose of cocrystal former (5). However, when cocrystal reactant components are solids under ambient conditions has practical advantages over liquid or gas coformers (4, 5): higher probability of being discovered and prepared, tend to have higher stability to heat in comparison to solvates or hydrates, a design aspect that distinguishes cocrystals from solvates and single component molecular solids (5).

PHYSICOCHEMICAL PROPERTIES OF COCRYSTALS:

Physicochemical properties of cocrystals are a combination of individual properties of both drug and cocrystal former. For most of the properties of cocrystals, when quantified, has a value that lies between conformer and pure drug. The previous statement is supported by the data of melting point analysis of cocrystals which usually, is found to be in between pure drug and cocrystal former. From stability point, Cocrystals are stable with respect to moisture under normal processing and storage conditions. Thermal stress and chemical stability are relatively less studied areas about crystal properties. Pharmaceutical cocrystallisation has emerged as a novel technique to improve the solubility of poorly water soluble drugs. Solubility of cocrystal product is usually more than that of pure drug but less than that of conformer. However, this is not always the case since there has been evidence of reduced solubility of cocrystal product in comparison to API. If solubility of cocrystal product is increased in comparison to API, intrinsic dissolution is also improved for cocrystals in comparison to pure drug and vice versa. Bioavailability is greatly improved for cocrystals in comparison to pure drug.

DESIGNING OF PHARMACEUTICAL COCRYSTALS:

Many, but not all molecules can form cocrystals. Designing and preparation of pharmaceutical cocrystals is a multi-step process. These are: *Step 1:* conducting a research or literature review for an API with respect to its solubility and chemical functionalities present, chemical properties of the API. *Step 2:* selection of cocrystal former.

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Cocrystal former is selected on the basis of the chemical functionalities present and possible interactions between the functionalities of the cocrystal former and API. This is a critical step since the cocrystal selected has a great influence on the success of the process and yield of the product. This is also a time consuming step since the cocrystal selected on the basis of theories or principles may not actually yield a product. *Step 3:* selection of process for the preparation of cocrystals. *Step 4:* screening of cocrystals. *Step5:* evaluation of cocrystals (10, 4, 5).

The above mentioned steps are time consuming and tiring. The time and labour involved in these steps can be reduced with the help of crystal engineering. The concept of crystal engineering was first introduced by Pepinsky in 1995 (14, 4). Crystal engineering can be defined as the application of the concepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are actual manifestations of the self assembly (4, 16, 17, 18, 19). Crystal engineering experiment involves CSD (Cambridge Structural Database) surveys followed by experimental work to prepare and characterise new compounds. The new compounds obtines this way are called supramolecular synthons (15, 4). Supramolecular synthons were defined by Desiraju as structural units within supramolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interactions (15, 4).

Hydrogen bonds play an important role in designing of most of the pharmaceutical cocrystals (4, 20, 21). The following are the guidelines to predict the formation of hydrogen bonds: (a) all good proton donors and proton acceptors are used in hydrogen bond formation, (b) for a six membered ring, intramolecular hydrogen bonds are preferred over intermolecular hydrogen bonds and (c) the best proton donors and proton acceptors remaining after the formation of intramolecular hydrogen bonds form intermolecular hydrogen bonds with each other (4, 22).

pKa can also be used to predict the posiibility of cocrystal formation. The difference in the pKa value i.e., ΔpKa greater than 3 is the accepted criterion for selecting the counter ions for salt formation. The same crierion is used for selection of cocrystal former. There are many exceptions to the use of ΔpKa method (4, 23).

METHODS OF PREPARATION OF COCRYSTALS:

(A) **SOLUTION COCRYSTALLISATION (24-28)**

This technique employs one of the following strategies: (1) use of solvents or solvent mixtures whereby cocrystal congruently saturates or (2) use of non-equivalent reactant concentrations in order to reach the cocrystal stability. Solution cocrystallisation can be carried out by (1) evaporative cocrystallisation where two components of the cocrystal system are dissolved in a solvent and crystallisation is induced by evaporation of solvent; (2) reaction cocrystallisation where one component is added to a saturated or near saturated solution of the other componentand the product (cocrystal) is obtained by reaction between these two components, and (3) cooling crystallisation where crystallisation is induced by varying the temperature of the crystallisation system.

(B) GRINDING METHOD (29-31):

Cocrystallisation by grinding can be achieved by two methods: (a) neat/dry grinding which involves mixing of two cocrystal components in stoichiometric ratios and grinding them, and (b) liquid assisted grinding which involves grinding of two cocrystal components in stoichiometric ratios by adding small amount of suitable solvent.

(C) OTHER METHODS

Supercritical fluid technology has been utilised in preparation of cocrystals [32, 33]. Indomethacin-sacchrin cocrystals have been prepared by supercritical fluid technology. Ultrasound technology has been utilised to prepare cocrystals (34, 35, 36).

EVALUATION OF COCRYSTALS:

Practical yield, drug content, crystal size and solubility study are preliminary studies that are required to be performed for a cocrystal product. Practical yield gives an idea whether the process can be applied for commercial production or not. Percentage drug content gives the value of drug recovered in final product form while solubility study confirms whether process was successful or not. Crystal size at preliminary level may be evaluated by optical microscope using stage micrometer and eye-piece micrometer. Cocrystals are also evaluated for *in vitro* dissolution studies, stability studies and bioavailability studies.

IR spectroscopic technique is usually employed in determining the chemical conformation of compounds. It is useful 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^{-1} while a weak C–O stretch around 1200 cm^{-1}; but, if deprotonation has occurred, a carboxylate anion (–COO−) has only a single C–O stretch in the fingerprint region of 1000–1400 cm^{-1} (37).

DSC is the preferred for obtaining melting point data and thermal data such as enthalpy of melting. DSC has recently been used as a tool for rapid cocrystal screening (38, 39).

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

Single X-ray diffraction (SXRD) is a technique for determination of the solid-state structure of cocrystals at an atomic level. The problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, powder X-ray diffraction (PXRD) are utilised more frequently to verify the formation of cocrystals (41).

Raman spectroscopy is used to study vibrational, rotational, and other low frequency modes in a system. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products (27, 42, 43).

Terahertz time-domain-spectroscopy (THz-TDS) has emerged as an alternative to powder X-ray diffraction in the characterisation of molecular crystals. It has been demonstrated that terahertz spectroscopy has the ability to distinguish between chiral and racemic hydrogen-bonded cocrystals that are similar in molecular and supramolecular structure (40).

SOME EXAMPLES OF PHARMACEUTICAL COCRYSTALS:

Pharmaceuticl cocrystals have been prepared for carbamazepine, indomethacin, ibuprofen, β-lapachone and few other drugs with improved physicochemical properties.

CONCLUSION:

Pharmaceutical cocrystals are gaining importance for solubility, bioavailability and stability enhancement. Though much work is done, pharmaceutical cocrystals largely remain as an area unexplored. Researchers are investigating new techniques and API to develop successful pharmaceutical cocrystals.

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