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Cocrystals: The Path to Improve Intellectual Properties of API

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ABSTRACT

Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the Active Pharmaceutical Ingredient (API). Co-crystals can be constructed through several types of interaction, including hydrogen bonding, pi-stacking, and van der Waals forces. Co-crystals high throughput provides information on relationship between formation and chemical structure of the API. Poor dissolution rate, solubility, chemical stability and moisture uptake influence therapeutic efficacy of many pharmaceuticals and significantly lower the market value of a drug. Multi-component crystals e.g. solvates, hydrates, co-crystals, salts play important role in the design of new solids, particularly in the pharmaceutical area.

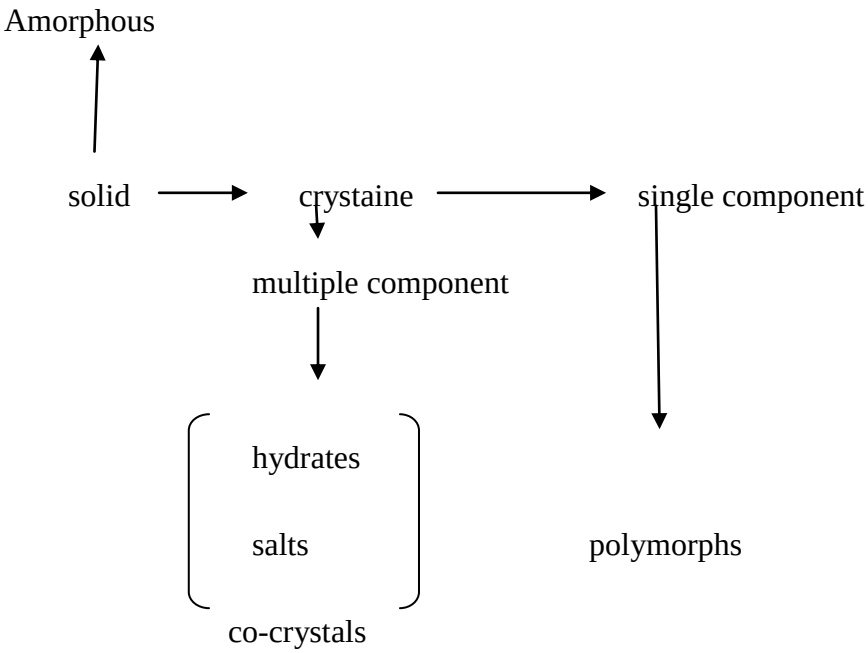
INTRODUCTION:

Co-crystallization alters the molecular interactions and composition of pharmaceutical materials and is considered better alternatives to optimize drug properties. Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former. Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API. Co-crystals can be constructed through several types of interaction, including hydrogen bonding, pi-stacking, and van der Waals forces. Cocrystals high throughput provides information on relationship between formation and chemical structure of the API and conformer. Factors affecting co-crystal stability are reported and a co-crystal is only expected to form if it is thermodynamically more stable than the crystals of its components. Phase transformations induced during processing/storage affects the mechanisms of conversion of crystalline drugs to co-crystals. Pharmaceutical co-crystals could play a major part in the future of API formulation and can be employed for chiral resolution.

Poor dissolution rate, solubility, chemical stability and moisture uptake influence therapeutic efficacy of many pharmaceuticals and significantly lower the market value of a drug Multi-component crystals e.g. solvates, hydrates, co-crystals, salts play important role in the design of new solids, particularly in the pharmaceutical area.

Co-crystals:

Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Co-crystals have regained attention as attractive alternate solid forms for drug development. Physiochemical properties of pharmaceuticals can be improved by obtaining co-crystals using co-crystallization. Co-crystallization with pharmaceutically acceptable compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior.



New opportunities for producing a larger diversity of solid forms of drug substances exhibiting the proper balance of important properties for development into a viable and effective drug product may be met by co-crystals. Furthermore, exploring the co-crystallization potential around an API increases the intellectual property protection over a particular drug product; thus, reducing the risk of costly litigation and market erosion.

Co-crystallization is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single component crystals and their polymorphs) or with different molecular components (multiple component crystals or co-crystals) in the crystalline state.

The components in a co-crystal exist in a definite stoichiometric ratio and assemble *via* non-covalent interactions such as hydrogen bonds, ionic bonds, π-π or van der Waals interactions rather than by ion pairing. Generally, co-crystals in their pure states are solids at room temperature and by convention, these normally exclude salts. Co-crystals can have different properties than the crystals of individual components. Further, co-crystals have different crystal structures than the pure components, contain different intermolecular packing patterns, and as such, they often exhibit widely different physical properties than the pure components. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionization sites in the API.

Co-crystals with the same API will have strikingly different pharmaceutical properties (melting point, solubility, dissolution, bioavailability, moisture uptake, chemical stability, etc.), depending on the nature of the second component. Some of the co-crystals formed had higher and some lower melting points as compared to their pure components, for example, succinic acid (M. P. 135.3), urea (M. P. 188.9), co-crystal of succinic acid-urea (M. P. 149.9).

PHARMACEUTICAL CO-CRYSTALS:

The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former. Co-crystal former may be an excipient or another drug. Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API. Scientists showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical co-crystal formation improved the performance of a drug known to have poor solubility. Pharmaceutical co-crystallization is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability hygroscopicity, and compressibility without alternating their pharmacological behavior. The expanding scope of crystal form selection, emergence of crystal engineering in pharmaceutical science and pharmaceutical co-crystals were reviewed. Some common aspects of co-crystal formation, screening strategies and outline methodologies for co-crystal functionality were reported. The use of co-crystals in drug design and delivery and as functional materials with potential applications as pharmaceuticals has recently attracted considerable interest. Pharmaceutical co-crystals have been described for many drugs such as acetaminophen, aspirin, ibuprofen, flurbiprofen etc. Co-crystals of antitubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool.

The use of hydrogen bonding rules, synthons and graph sets may assist in the design and analysis of co-crystal systems. In general, though, prediction of whether co-crystallization will occur is not yet possible and must, at present, be answered empirically. Co-crystal formation may be rationalized by consideration of the hydrogen bond donors and acceptors of the materials that are to be co-crystallized and how they might interact. Following the extensive examination of preferential packing preferences and hydrogen bond patterns in a number of organic crystals, Etter and co-workers proposed the deliberate design of hydrogen

bonded solid. All good proton donors and acceptors are used in hydrogen bonding, six-membered ring intermolecular hydrogen bonds form in preference to intermolecular hydrogen bonds, the best proton donor and acceptor remaining after intermolecular hydrogen-bond formation will form intermolecular hydrogen bonds to one another (but not all acceptors will necessarily interact with donors). These observations help to address the issue of competing hydrogen bond assemblies observed when using a particular co-crystallizing agent.

A detailed understanding of the supramolecular chemistry of the functional groups present in a give molecular is the prerequisite for designing the co-crystals because it facilitates the selection of the suitable co-crystal former. Supramolecular synthons that can occur in common functional group in order to design new co-crystals and certain functional groups such as carboxylic acids, amides and alcohols.

Methods of preparation of co-crystals:

Co-crystals can be prepared by solvent and solidly based methods. The solvent-based methods involve slurry conversion solvent evaporation, cooling crystallization and precipitation. The solid based methods involve net grinding; solvent-assisted grinding and sonication 80^0 to 85^0 C.

Examples:

1) Co-crystals of Aceclofenac:

Acelofenac is an orally effective nonsteroidal anti-inflammatory drug of phenylacetic acid group, which possesses remarkable anti-inflammatory, analgesic and antipyretic properties. Aceclofenac exhibits slight solubility in water and as a consequence, it exhibits low bioavailability after oral administration. Co-crystal of aceclofenac prepared by simple solvent.

2) Co-crystals of Theophylline:

Theophylline is useful in treatment of respiratory disease such as asthma. From the physicochemistry standpoint, theophylline represents challenge to formulators in that it is known to interconvert between crystalline anhydrate and monohydrate forms as a function of relative humidity. The possibility of crystalline hydrate formation complicates design of a

consistent, reproducible for an API in the drug development process. The co-crystals of the theophylline were prepared with oxalic acid, malonic acid, maleic acid, glutaric acid by solvent evaporation technique.

3) Co-crystals of Indomethacin:

Indomethacin, a Non-Steroidal Anti-Inflammatory Drug (NSAID), is widely prescribed for patients with arthritis. Indomethacin is practically insoluble in water and poses severe challenges in the formulation development. Various co-crystal formers, including saccharin, were used in the screening for indomethacin co-crystals in series of solvents.

4) Co-crystals of Pyrazinamide:

Pyrazinamide is a first line drug recommended by WHO for tuberculosis treatment, and diflunisal, a nonsteroidal anti-inflammatory substance. The co-crystal of pyrazinamide prepared by neat grinding method with ethanol.

5) Co-crystals of Ibuprofen:

Ibuprofen (IBP) was selected as the API meanwhile glycine (GLY), L-alanine (ALA) and L-proline (PRO) were selected as co-crystal former (CCF) agents. Ibuprofen was used as an API while amino acid as CCF is believed to improve the solubility of the API by co-crystallization process.

CONCLUSION:

Co-crystals are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs. Co-crystals have the potential to be much more useful in pharmaceutical products than solvates or hydrates. The co-crystal in API formulation includes the ability to fine-tune physical properties, characterization of API, identify and develop new, proprietary forms of prescribed drugs and the opportunity to generate intellectual property. The co-crystal gives vital information on relationship between formation and chemical structure of the API and co-former.

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