molecular pharmaceutics

editorial

Cocrystals: Molecular Design of Pharmaceutical Materials

Hydrogen bond based design of molecular networks has emerged as a powerful tool in the discovery of cocrystals. Pharmaceutical cocrystals are crystalline molecular complexes that often rely on hydrogen-bonded assemblies between neutral molecules of an active pharmaceutical ingredient (API) and other components with well-defined stoichiometries. Compared to a cocrystal where molecules interact by non-ionic interactions and components are in the neutral state, in a crystalline salt the interactions are charge assisted and the components are in the ionized states. This means that cocrystals offer the advantage of generating solid forms of APIs even when these lack non-ionizable functional groups and in this way produce materials with strikingly different properties that are not available in single API solid phases (polymorphs and amorphous forms), or in API solvates, or salt forms.

This special issue "Pharmaceutical Cocrystals" presents two reviews and several articles that highlight the molecular basis of cocrystal design, preparation, and behavior. In the review "Sulfa Drugs as Model Cocrystal Formers" Caira summarizes molecular interactions in cocrystals with sulfa drugs, earlier exploratory studies, and more recent systematic investigations of cocrystal formation processes. Beyond scientific advantages, cocrystals also present unique regulatory issues and intellectual property opportunities as presented by Trask in the review "An Overview of Pharmaceutical Cocrystals as Intellectual Property".

Central to the formation of cocrystals is the identification of robust intermolecular interactions or synthons that will produce a supramolecular assembly. While prediction of the three-dimensional arrangement of molecules in a crystal is a very difficult task at the present time, the success of cocrystal design relies on establishing the rankings among noncovalent bonds, and in particular hydrogen bonds, used to build supramolecular assemblies. The recent flurry of research activity in cocrystals has focused on this very important topic as reflected by the articles in this special issue. In "Hierarchy of Supramolecular Synthons: Persistent Hydroxyl···Pyridine Hydrogen Bonds in Cocrystals That Contain a Cyano Acceptor" by Bis et al., "Amide−*N*-Oxide Heterosynthon and Amide Dimer Homosynthon in Cocrystals of Carboxamide Drugs and Pyridine *N*-Oxides" by Babu et al., and "Co-Crystals of Caffeine and Hydroxy-2-naphthoic Acids: Unusual Formation of the Carboxylic Acid Dimer in the Presence of a Heterosynthon" by Bučar et al., the robustness of supramolecular synthons (molecular recognition elements) is evaluated by studying hydrogen bond motifs and their frequencies in crystal structures reported in the Cambridge Structural Database and by characterization of structures of new cocrystals.

Because hydrogen bonds rely on donor and acceptor character of functional groups, it is important to establish whether a reaction will result in cocrystal or in salt formation. Two articles investigate the classification and design elements of cocrystals and salts. Childs et al. examine how ΔpK_a and crystal structure environment determine the extent of proton transfer, and consider the relatively narrow region between salt and cocrystal categories in "The Salt−Cocrystal Continuum: The Influence of Crystal Structure on Ionization State". Aakeröy et al. address the question of how proton transfer affects the reliability and predictability of intermolecular interactions within and composition of an organic molecular solid, whether a cocrystal or a salt, in "Cocrystal or Salt: Does It Really Matter?". Ma and Moulton present the design and synthesis of coordination molecular complexes composed of API, metal, and ancillary ligand and show how the choice of ancillary ligand affords a large degree of control on partition coefficient, in "Supramolecular Medicinal Chemistry: Mixed-Ligand Coordination Complexes".

How cocrystals form and develop is fundamental not only for the success of cocrystal discovery but also for the prediction of cocrystal behavior and stability. Moisture sorption is shown to spontaneously form cocrystals as a result of the supersaturation generated by reactant dissolution in a deliquesced phase as presented by Jayasankar et al. in "Mechanisms by Which Moisture Generates Cocrystals". In "Screening for Pharmaceutical Cocrystal Hydrates via Neat and Liquid-Assisted Grinding", Karki et al. studied the propensity of cocrystals to form hydrates by comparing crystal structures and hydrogen bond interactions. Screening for cocrystals can also lead to the discovery of new crystal forms of reactants as shown by Wenger and Bernstein in "Cocrystal Design Gone Awry? A New Dimorphic Hydrate of Oxalic Acid". Cocrystals also play a major role in changing dissolution and bioavailability. Remenar et al. in "Celecoxib:Nicotinamide Dissociation: Using Excipients To Capture the Cocrystal's Potential" show that cocrystals can increase solubility and dissolution rate and that a phase transformation to a less soluble form of a component will need to be prevented in order to take full advantage of the higher cocrystal solubility.

The articles in this special issue illustrate the opportunities that application of design elements affords in generating

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supramolecular assemblies and cocrystals of APIs. I hope that the insights presented here serve as an inspiration for future developments of pharmaceutical materials. While much is known about the molecular basis for cocrystal formation, the correlation between structure and function is yet to be discovered. The power of supramolecular design of pharmaceutical materials lies ultimately in our ability to anticipate their properties. We are entering a very promising stage where interdisciplinary teams including chemists, engineers and pharmaceutical scientists can offer industry-leading understanding of design and development of materials for a new generation of therapies.

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