Mapping the Structural Landscape of Coumarin and its Derivatives

Makena M. Utech, Christer B. Aakeroy, and Abhijeet S. Sinha

Improving the physicochemical properties of active pharmaceutical ingredients (APIs) via co-crystallization is an area of pre-formulation that is rapidly attracting the interest of scientists across the globe. To put this problem in perspective, out of approximately 10,000 newly synthesized APIs, only a single compound is likely to make it to the market after being approved by the US Food and Drug Administration (FDA). Despite enormous sums of money invested by the pharmaceutical companies, a significant portion (approx. 30 %) of these molecules fail to even make it to clinical trials due to poor solubility and bio-availability (availability within our blood-stream). The existing methods such as salt formation, and encapsulation within host molecules are important, but the field is still left with the challenge of designing cheap and efficient ways to improve the physicochemical properties of active molecules, a fact that has hindered our ability to access APIs that can go a long way in curing different diseases. Co-crystallization is a conceptually simple technique for bringing together two or more molecules in a single crystalline lattice via weak non-covalent interactions such as hydrogen bonds (found in DNA). We are utilizing nutraceuticals, compounds that are readily available and occur naturally in common foods such as fruits and vegetables, as co-formers (partners) in the co-crystallization of APIs. The three most important benefits of utilizing nutraceuticals as co-formers for pharmaceutical co-crystallization are: (a) nutraceuticals that are bioactive can be co-administered with other bioactive molecules, thus facilitating the synergy between the two components; (b) APIs with poor physicochemical properties can be co-crystallized with nutraceuticals in an attempt to synthesize new crystalline forms with improved physicochemical benefits; (c) anti-oxidant behavior of nutraceuticals can be used to impart stability to APIs that are prone to oxidation.

Coumarins are naturally occurring nutraceuticals found in many plants such as in cinnamon, bison grass, and the tonka bean. The properties of this compound not only allow it to be used as a precursor for many anti-coagulants, but also in anti-cancer, antioxidant, and anti-inflammatory medications. In this project, four structurally different coumarins have been co-crystallized with API mimics to understand their structural preferences, *i.e.* hydrogen bonding patterns of these coumarins by themselves and with the mimics. Based on the information obtained, novel dual-drug crystalline materials will be designed, and the physicochemical properties of these materials will be examined. Twenty-five co-formers were pre-screened with the four coumarins (7-hydroxy-4-methylcoumarin, 7-hydroxycoumarin, 6,7-dihydroxycoumarin, and 5,7-dihydroxy-4-methylcoumarin) *via* mechanochemical solvent-drop grinding method. The resulting solids were analyzed by Infra-Red spectroscopy and differential scanning calorimetry (DSC). Slow evaporation of each positive combination of coumarin and co-former resulted in four single crystals that were analyzed by single-crystal X-ray diffraction. Trends were seen in the single-crystal structures with the electron donor hydroxy groups on the coumarins outcompeting the hydrogen bonding between coumarin molecules to form hydrogen bonds with the electron acceptor sites on the coformers. The ketone in the benzopyran backbone is also seen making short contacts with a C-H on other coumarin molecules to form the crystal lattice. These trends can be extrapolated to other similar molecules by using the conformer trends to find APIs that reflect those models in order to form cocrystals for the market.