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Pharmaceutical cocrystals/alloys and their structure-property relations

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Pharmaceutical cocrystal is a multicomponent crystalline solid composed of an API (active pharmaceutical ingredient) along with one or more GRAS (generally regard as a safe) coformers exist through noncovalent interactions in the crystal lattice. "Pharmaceutical cocrystal" was introduced into the terminology of pharmaceutical research by Almarsson and Zaworotko and has gained remarkable impetus from the last decade because of the potential implications to modify the properties of an API/bioactive molecule as functional materials in pharmaceutics. The principle advantages with cocrystals are the improving the physical/chemical stability, hygroscopicity, kinetic dissolution rate/thermodynamic solubility, permeability and enhanced bioavailability of APIs/bioactive molecules. All these properties will play a vital role in delivering an API/bioactive molecule by oral administration at right time, place and at the appropriate dose to improve the potency of the drug. Apart from fixed stoichiometry cocrystals, there are very few examples of multi-component solids forming solid solutions and alloys (multivariate stoichiometric cocrystals) in organic systems. Here we describe the cocrystals/alloys applications to improve the pharmaceutical properties of andrographolide (natural herb, AP), sulfamethizole (antibiotic, SMT) and nitazoxanide (anti-protozoan, NTZ). Andrographolide is derived from the leaves of Andrographis Paniculata, a plant known as "king of bitters". AP is known for diverse pharmacological activities, such as anti-viral, anti-inflammatory, anti-cancer, and anti-malarial. Despite being safe at high doses of 17 g/kg per day in humans, the efficacy of AP is limited in the clinical application by poor aqueous solubility (46 mg/L) and oral bioavailability of 2.67% because of rapid metabolism (chemical instability). Here we addressed the chemical instability and solubility through novel andrographolide-salicylic acid (AP-SLA) cocrystal.1 While SMT is a sulfonamide class antibiotic drug and it has better solubility (1.05 g/L at 37 °C) even though it has a short half-life (2.1 h) due to rapid metabolism leads to fast elimination. Most of the sulfonamide class drugs exhibit moderate to high solubility but bioavailability is limited due to rapid metabolism and fast elimination. As a result, the dosage strength of sulfonamide drugs has to be higher. Cocrystallization approach is adaptable to modulate the solubility towards higher or lower levels by rational selection of coformers to addressing the poor bioavailability of highly soluble drugs. We highlight the solubility lowering ability of cocrystals and salt of SMT which may be better solid forms than pure SMT.2 NTZ is a prodrug used as an anti-protozoan agent and its active metabolite is tizoxanide. However NTZ has poor aqueous solubility (7.55 µg/mL) and lower bioavailability (258 ng/mL). Two isomorphous cocrystals nitazoxanide with p-aminosalicylic acid (PASA) and p-aminobenzoic acid (PABA) as well as their alloys were prepared by grinding and slurry techniques. The cocrystals exhibit improved dissolution rate and pharmacokinetic properties compared to the reference drug and surprisingly the cocrystal alloy of NTZ-PABA: NTZ-PASA exhibited higher bioavailability of NTZ in sprague-dawley rats. This is the first report of cocrystal alloy pharmaceutical solid showed enhanced bioavailability and open opportunity for the repositioning of nitazoxanide as an anti-TB drug.3

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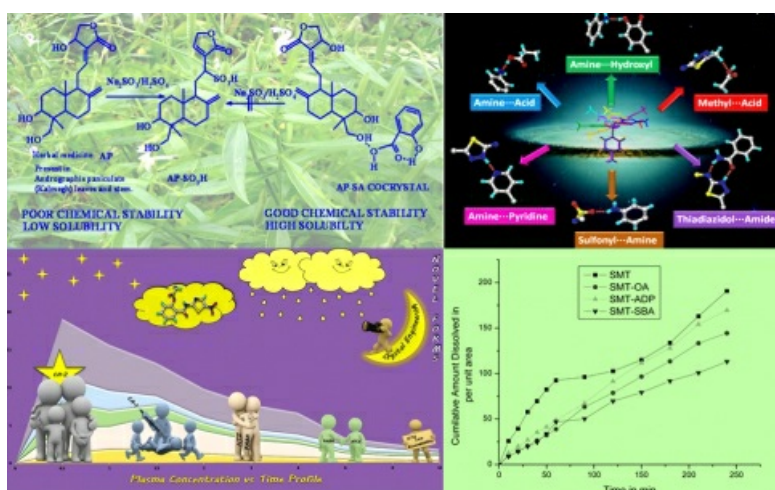
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