

Synthesis and structural studies of novel solvates and cocrystals of genistein

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The exploration of new crystal forms of active pharmaceutical ingredients (APIs) and compounds which exhibited biological activities became the subject of interest in chemical research and pharmaceutical industry. It's estimated that about 40% of marketed drugs and between 70% to 90% of newly developed chemical molecules are classified as Classes II and IV in the Biopharmaceutical Classification System (BCS), characterized by low water solubility and poor bioavailability [1]. In recent years, there is a strong focus on developing methods to increase drug solubility and bioavailability, which are key factors determining its effectiveness. The synthesis of co-crystals made from an active ingredient and an appropriate coformer is among the most promising approach [2]. Beyond improving solubility [3], by creating new crystal forms, the final properties (e.g. hygroscopicity, toxicity, thermal and chemical stability) can be modified without changing the drug's chemical structure.

The main object of our study is genistein (Gen) - one of the natural isoflavonoid exhibited various biological activities. Genistein provides a huge potential for applications in various branches of medicine. It is considered a promising agent in treatment of cancer, diabetes, obesity and genetic diseases [4-6]. Similarly to most flavonoids, genistein is classified as Class II agent in the Biopharmaceutical Classification System (BCS). Its low water solubility leads to poor bioavailability, which limits its therapeutic effectiveness.

We investigated cocrystals of genistein with aromatic amides (nicotinamide, isonicotinamide) and synthesized new genistein solvates with selected isomers of lutidines. New crystal forms of genistein were characterized by single crystal X-ray diffraction (SC-XRD), powder X-ray diffraction (PXRD), thermal analysis (DSC and TG), infrared and Raman spectroscopy. In almost all the obtained crystal structures, there is one molecule of genistein and two molecules of the corresponding aromatic amine in the elementary unit cell. The exception is solvate of genistein with 2,5-Lutidine (Gen-2,5-Lut) where one molecule of genistein is accompanied by one molecule of the aromatic amine. Hirshfeld surface analysis and the associated two-dimensional (2D) fingerprint plots revealed that genistein has significant hydrogen bond donor capability when cocrystallized or forming solvates. Obtained new crystal forms revealed the presence of an O-H...N_{arom} heterosynthons between O7 and O4' hydroxyl moieties of genistein and the pyridyl ring of a coformer. Investigated compounds exhibited higher solubility than the pure genistein.

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