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Article

Mechanosynthesis, Characterization, and Physicochemical Property Investigation of a Favipiravir Cocrystal with Theophylline and GRAS Coformers

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Poonam Deka,[‖] Diptajyoti Gogoi,[‖] Khaled Althubeiti, Dharmaraj R. Rao, and Ranjit Thakuria*

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ABSTRACT: Five cocrystals of antiviral drug favipiravir (Fav) with respiratory drug theophylline (Theo) and GRAS coformers, viz., *p*-aminobenzoic acid (PABA), 4-hydroxybenzoic acid (4HBA), gallic acid (GA), and ferulic acid (FRA), were successfully synthesized using mechanochemistry as well as solution crystallization. All the synthesized cocrystals were characterized using PXRD, SCXRD, and thermal analysis. A physicochemical property investigation showed an excellent correlation of coformer solubility with cocrystal solubility. Moreover, cocrystal solubility can be tuned based on the selection of coformers during cocrystallization as well as the pH of the medium. Crystal structure analysis depicts amide−amide homosynthon formation in the Fav·Theo cocrystal and an acid−amide heterosynthon in the case of cocrystals with GRAS coformers. Incorporation of nutraceuticals (GA and FRA) provides an additional health benefit, whereas Fav·Theo cocrystal may be a potential formulation to treat patients suffering from chronic obstructive pulmonary disease (COPD) or asthma along with viral infections.

INTRODUCTION

6-Fluoro-3-hydroxypyrazine-2-carboxamide commercially known as favipiravir (Fav) is a new broad-spectrum antiviral drug that selectively and strongly inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses.[1,2] It was first developed and manufactured by Toyama Chemicals in Japan during 2014 and is effective against a wide range of influenza viruses and subtypes. Fav came into much attention during the year 2020 for its use as a drug against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, more commonly known as COVID-19.[3−6] A docking study carried out by Ataseven and co-workers[7] also showed high potential of a Fav analogue against RdRp of different virus types compared to existing drug molecules such as lopinavir, ritonavir, etc. Moreover, it is also used against other viral infections like Ebola, Lassa, and Nipah in recent times.[8] The anhydrous form of Fav was first reported by Shi et al.[9] solved in the orthorhombic $Pna2_1$ space group containing one molecule in the asymmetric unit. Structure analysis showed the molecule to be nearly planar with an intramolecular O−H···O hydrogen bond in an enol-like tautomeric form (Scheme 1a). Gas phase analysis showed better stability of the enol-like form compared to the keto form.[10] During preparation of this manuscript, Vologzhanina and co-worker reported[11] a new tetragonal polymorph of Fav solved in the $P4_2/n$ space group containing an amide−pyrazine (N−H···N) hydrogen bond that connects adjacent molecules. Based on periodic density functional theory (DFT) calculation, they established the newly synthesized polymorph to be metastable in nature and readily convertible to the orthorhombic form under room temperature. Unlike its structural analogue pyrazinamide (α, β, and δ polymorphs),[12] the Fav anhydrous form does not contain the commonly encountered amide−amide dimer synthon. A Cambridge Structural Database (CSD) search (version 5.42; performed on Nov. 2020 update) on Fav multicomponent solids (salts, cocrystals, solvates, eutectics, or coamorphous) showed no results until date. Moreover, moderate solubility and a relatively unexplored physicochemical study of the anhydrous form[13] lead us to explore possible crystal structure landscape of Fav. Based on a complementary hydrogen bond, a few GRAS (generally regarded as safe) coformers (see Scheme 1b) along with theophylline (Theo), a phosphodiesterase inhibiting drug, were considered as potential coformers to

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