Poster Presentation

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New polymorph of ambrisentan: structural and biopharmaceutical implications

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The poor performance of biopharmaceutical classification system (BCS) class II drug molecules is a major hurdle in the design and development of pharmaceutical formulations. Solid state transformation of a drug into different polymorphs exhibits different biopharmaceutical properties. Ambrisentan (AST; US trade name Letairis) was approved by the US FDA for the treatment of pulmonary arterial hypertension (PAH) in June 2007. AST belongs to a BCS II category drug (low solubility and high permeability). Cambridge structural database (CSD) search revealed that only one crystal form (form I; CCDC 917075) has been deposited having orthorhombic crystal system. In the present investigation, new polymorph (form II) was isolated by solution crystallization (1, 2-dicholoroethane) having monoclinic (P21/c) crystal system. Single crystal data revealed that form II has different packing as compared to marketed form I, however, both forms revealed similar hydrogen-bonded network sustained by OH...Narom motif. Both forms were fully characterized by various analytical tools such as differential scanning calorimetry (DSC), hot stage microscopy (HSM), powder x-ray diffractometry (PXRD), and 13C solid-state nuclear magnetic resonance (ssNMR). The thermodynamic relationship between two forms was established using thermochemical as well as solution calorimetric study. The apparent solubility and intrinsic dissolution studies were performed in 0.1 N HCl (pH 1.2) that revealed form II shows significantly higher solubility than marketed form (up to 1.4 times). A mechanistic understanding of enhanced dissolution of this form was generalized by surface imaging using atomic force microscopy (AFM) together with scanning electron microscopic (SEM) examination of the solid residue of intrinsic dissolution discs. This study further corroborated that apart from thermodynamic characteristics, the difference in the surface chemistry of form II aids in augmenting dissolution rate as compared to market form. Phase transformation experiment using slurry method/ liquid assisted grinding suggested that form II transformed to form I after 2 hours of slurry experiment and 30 minutes of grinding. Further, form II showed higher Cmax and AUC in oral bioavailability study than marketed form. Thus, form II is a promising for development into a more bioavailable solid dosage form of AST.

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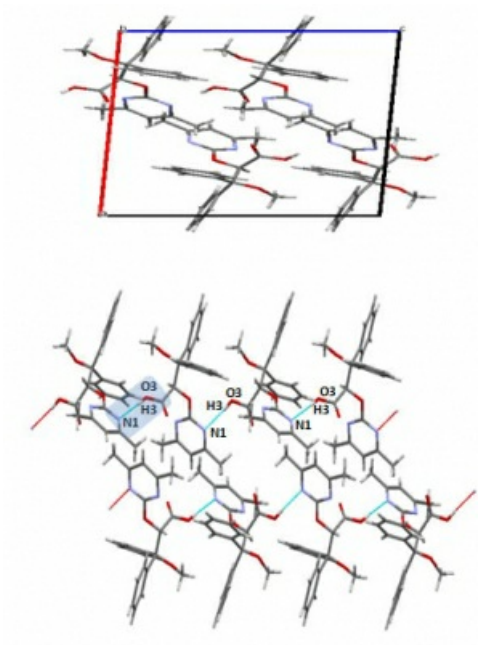

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