

*Salt-cocrystal continuum of epalrestat-cytosine binary solid*Battini Swapna¹, Ashwini Nangia¹¹University Of Hyderabad, Hyderabad, India

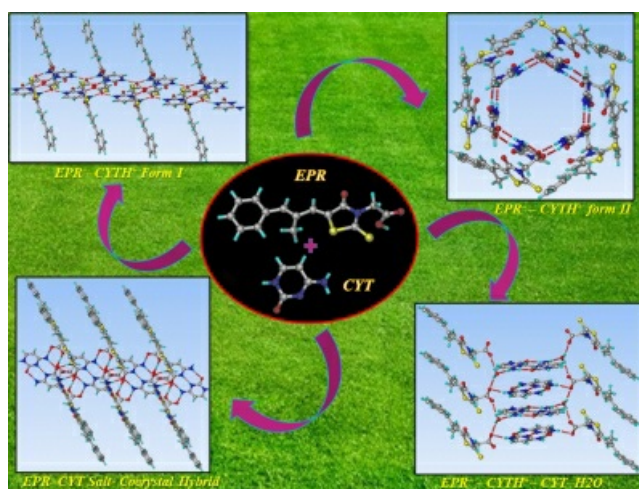
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Epalrestat (5-[(1Z,2E)-2-methyl-3-phenylpropenylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid; EPR), a potent aldose reductase inhibitor, is used to treat diabetic complications such as diabetic neuropathy, nephropathy etc. Crystal structures of guest free form, ethanol and methanol solvates of EPR have been reported. Recently from our group color polymorphs and Z,Z isomer of EPR have been reported. Cytosine (CYT) is a pyrimidine nucleobase, which form H-bonds with its complementary purine nucleobase guanine in the Watson & Crick base pairing for deoxyribonucleic acid (DNA) structure. Design and synthesis of supramolecular solid forms such as salts, cocrystals, polymorphs, hydrates and solvates of active pharmaceutical ingredients (APIs) are very important in the pharmaceutical industry to enhance the physicochemical and pharmacokinetic properties of APIs. The pKa values of EPR and CYT are 3.70 and 2.35. Thus, ΔpK_a value would be 1.35. Therefore, the resultant crystallization outcome of EPR and CYT would be either salt or cocrystal or salt cocrystal hybrid. In this article, we have successfully prepared novel salt polymorphs $EPR^- - CYTH^+$ form I and form II, salt-cocrystal hybrid and salt-cocrystal hydrate ($EPR^- - CYTH^+ - CYT - H_2O$) forms of anti-diabetic drug epalrestat (EPR) with pyrimidine nucleobase cytosine (CYT) by various techniques such as solvent assisted grinding, solution crystallization and controlled heating experiments. We observed the inclusion of lesser amounts ethanol and n-propanol solvent molecules in the structural voids of $EPR^- - CYTH^+$ form II and we calculated the stoichiometry of $EPR^- - CYTH^+$ form II ethanol solvate and $EPR^- - CYTH^+$ form II n-propanol solvate as 1:1:0.036 and 1:1:0.043 from ¹H NMR spectroscopy. 2-Amino-pyrimidinium-carboxylate two point heterosynthon was observed in the crystal structure of $EPR^- - CYTH^+$ form I and $EPR^- - CYTH^+$ form II. Rarely seen $CYTH^+ \dots$ $CYTH^+$ base pairing was observed in the crystal structure of salt-cocrystal hybrid and salt-cocrystal hydrate. $EPR^- - CYTH^+$ form I and $EPR^- - CYTH^+$ form II exhibits conformational difference and belongs to conformational polymorphs. All these forms were characterized by spectroscopic (FT-IR, ¹H solution NMR), thermal (DSC, HSM, TGA), powder X-ray diffraction (PXRD) and single crystal X-ray diffraction techniques.

(1) Desiraju, G.R. & Kishan K. V. R. (1989). J. Am. Chem. 111, 4838.

(2) Swapna, B., Suresh, K. & Nangia, A. (2016). Chem. Commun. 52, 4037-4040.

(3) Swapna, B. & Nangia, A. (2017). (Manuscript under Submission)



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