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Synthesis, characterization and anti-tuberculosis activity of a new isoniazid-oleanolic acid co-crystal system

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Tuberculosis (TB) is a highly endemic disease worldwide. One of the commonly used first-line drugs for anti-TB therapy (ATT) is isoniazid (INH). Isoniazid is known to be majorly metabolized and detoxified in the liver by both phases I and phase II group of drug metabolizing enzymes. The drug and along with its metabolite are toxic and during its assimilation process cause injury to the liver. The work presented here involves the investigation of co-crystals involving isoniazid and oleanolic acid. A 1:1 co-crystal involving isoniazid, foremost first-line drugs recommended by the World Health Organisation for the treatment of tuberculosis, which causes damage to the liver and oleanolic acid, hepatotoxicity naturally occurring compound, have been synthesized for the first time. Considering the drug combination perspective, this is an interesting pharmaceutical co-crystal because of the known side effect of isoniazid therapy which might be improved upon by the presence of the oleanolic acid. The co-crystal compound was characterized using PXRD, TGA, and SEM which were further evaluated for in vitro anti-TB and cytotoxicity index, using Human Embryonic Kidney (HEK 293) and Human Hepatocellular carcinoma (HepG2) cells. The PXRD of the synthesized co-crystal compound maintained crystalline nature like isoniazid for the three methods, TGA for all the three methods have cleavage values from 220°c-360°c, and the SEM images obtained from the three synthetic methods appears rod-like in nature. The co-crystal of OA with INH, increased the anti-TB MIC values for the three synthetic methods used as follows (a) Solvent evaporation(1.06µM); (b) Solvent drop (0.50µM); (c) Direct grinding (0.61µM). The cytotoxicity test of the co-crystal system on the two-human cell lines (HEK 293 and HepG2) was found to be IC50 ≥ 300ug/ml. The current work indicates, a co-crystal compound of OA with INH is probable and could be utilized to design better treatment for tuberculosis disease.

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