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Improved Stability of TB Drug Fixed Dose Combination Using Isoniazid-Caffeic acid and Vanillic acid Cocrystal

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Abstract

The classic FDC of four TB drugs, namely Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA) and Ethambutol Dihydrochloride (EDH) has the twin issues of physical stability and rifampicin cross-reaction in the 4FDC. The major reason for these quality issues is the interaction between RIF and INH to yield isonicotinyl hydrazone (HYD) in drug tablets. Pharmaceutical cocrystals of INH with caffeic acid (PZA + EDH + RIF + INH-CFA cocrystal) and vanillic acid (PZA + EDH + RIF + INH-VLA cocrystal) are able to stabilize the FDC formulation compared to the reference batch (PZA + EDH + RIF + INH). Stability studies under accelerated humidity and temperature stress conditions of 40 °C and 75% RH showed that the physical stability of the cocrystal formulation was superior by PXRD and SEM analysis, and chemical purity was analyzed by HPLC. Changes in the composition and structure were monitored on samples drawn at 7, 15, 22, and 30 days of storage. FDC-INH-CFA cocrystal batch exhibited greater stability compared to FDC-INH-VLA cocrystal and FDC reference drug batches. The superior stability of INH-CFA cocrystal is attributed to the presence of stronger hydrogen bonds and cyclic O–H···O synthon in the crystal structure.

Key Words: Tuberculosis, Fixed dose combination, Isonicotinyl hydrazone, Isoniazid, Pyrazinamide, Rifampicin, Ethambutol Dihydrochloride.