Improving the stability, bioavailability of TB FDC drug

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The physical stability and bioavailability of a fixed-dose combination (FDC) drug containing four anti-TB medicines — rifampicin, isoniazid, pyrazinamide and ethambutol — has been vastly improved from 3-4 days (at 40 degree C and 75% relative humidity) to over 30 days by turning to crystal engineering.

The use of FDC containing two, three and four anti-TB drugs for the treatment of TB was recommended by the World Health Organisation in 1994. The four-drug FDC was included in the WHO Model List of Essential Drugs in 1999.

The four-drug FDC suffers from stability and quality issues. The FDC tablets tend to undergo discolouration and become sticky, gummy mass thereby affecting its quality. The use of poor quality drugs can lead to treatment failures and development of drug resistance.

A team led by Dr. Ashwini Nangia from Pune's National Chemical Laboratory addressed the problem of stability and poor bioavailability by making cocrystals (hydrogen-bonded multicomponent crystal) of isoniazid with either caffeic acid or vanillic acid. The results of the study were published in the *Journal of Pharmaceutical Sciences*.

"Rifampicin tends to cross react with isoniazid and this leads to changes in colour and composition of the four-drug FDC drug, and erratic bioavailability and therapeutic action," says Dr. Nangia. By using caffeine and vanillic acid to form cocrystals with isoniazid, the researchers were able to inhibit cross-reaction between isoniazid and rifampicin.

While FDC tablets used as control turned to liquid-like state within one week, the FDC containing isoniazid cocrystal remained stable for up to 30 days.

Whereas the cocrystal formed using vanilic acid showed slight colour change within one week and became dark brown at the end of four weeks, caffeic acid cocrystal showed slight change in colour after one week but remained in solid form for up to four weeks. As a result, caffeic acid cocrystal showed better stability.

"The reason why caffeic acid cocrystal performs better than vanilic acid cocrystal is due to better and strong hydrogen bonding in the crystal structure. This is absent in the vanillic acid cocrystal," he says.

"We have tested the stability for one month. We expect the stability to be much longer because excipients [substances included for the purpose of long-term stabilisation] and additives will be added which make the formulation stable. Secondly, the tablet will be in closed strip and so the degradation will be much slower. The cocrystal FDC is much more stable than the drug mixture and hence should be explored in further formulation development," says Dr. Nangia.

The researchers plan to test the stability of the four-drug FDC cocrystal for longer term and in new environments. "It is expected to perform superior to the drug combinations," he says.

The device was tested in the open ocean at a depth of 1,600 to 2,300 ft.

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