Identification of Posaconazole polymorph in Noxafil® oral suspension

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Noxafil® is an azole antifungal agent available as concentrated solution to be diluted before intravenous administration (18 mg/ mL), delayed-release tablet (100 mg), or suspension for oral administration. Noxafil® oral suspension is a white, cherry-flavored immediate-release suspension containing 40 mg of posaconazole per mL as active substance. Posaconazole is a triazole antifungal agent containing 4 chiral centres. Four polymorphic forms of posaconazole (I , II, III[1] and IV [2]) are known but form I is the more stable.

In this study, identification of Posaconazole's polymorphic form I in the commercial oral suspension was attempted using X-ray Powder Diffraction (XRPD). X-ray diffractograms of Noxafil® oral suspension (40mg/ml) were compared against Form I and placebo patterns (Fig. 1) as well as against Form II, III and IV patterns (not shown). No match was found, an indication that the posaconazole wt % in the dispersion was too low to be detected by XRPD or that the compound is in an unknown state.

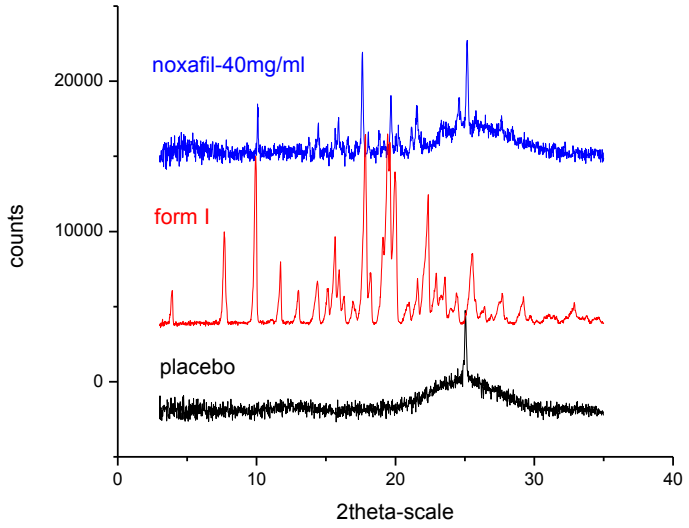

Figure 1. XRD diffraction patterns of Noxafil 40mg/ml Oral Suspension (blue line), Form I (red line) and placebo pattern**.**

In order to overcome this problem it was attempted to increase posaconazole's wt % in order to facilitate the detection of Form I. For this the suspension was left in fume hood for the water to be evaporated and the XRPD pattern of the concentrated dispersion was re-recorded (Fig. 2). The diffraction peaks of the evaporated pattern can easily be attributed to Form I. An alternative path that was explored was to centrifuge Noxafil® oral suspension. Posaconazole is not diluted in the placebo and thus the centrifuged material is expected to be more concentrated in the compound.

Indeed, the data obtained from both the experiments were compared to Form I pattern (fig.2) and the diffractograms were practically identical to each other. In order to secure that the phenomenon is reversible, the supernatant and centrifuged material was mixed again and the original pattern was observed. Re-centrifuging the re-constituted dispersion a Form I pattern was re-obtained.

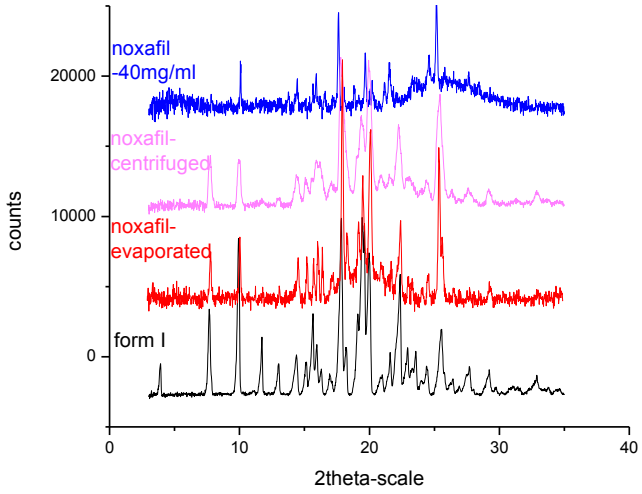

Figure 2.XRD diffraction patterns of Noxafil 40mg/ml Oral Suspension (blue line), Form I (black line), evaporated Noxafil 40mg/ml Oral Suspension (red line) and centrifuged noxafil pattern(pink line).

Summarizing, it can be presumed that both methods,evaporation or centrifuge reversibly, may constitute safe options in detecting Posaconazole polymorph I in Noxafil® oral suspension .

References:
1.EP1021439B1
2.EP2141159A1