IDENTIFICATION AND CHARACTERISATION OF POSACONAZOLE POLYMORPH IN ORAL SUSPENSIONS

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The ability of a compound to exist in various crystal structures due to different packing conformations of its molecules is known as polymorphism. The study of the crystal form of an Active Pharmaceutical Ingredient (API) in the final formulation is crucial because properties such as API solubility and bioavailability depend on the crystal structure. However, the identification of APIs' polymorph in pharmaceutical oral suspensions is often challenging due to the low API's concentration in the dispersion medium, the possible phase transformation in the presence of the liquid dispersant and the inability of chromatographic techniques to characterize solid phases and distinguish between different polymorphs.

Posaconazole is an antifungal drug, commercially available also as a 40 mg/mL oral suspension. Until recently, 14 different forms (10 polymorphs, 3 solvates and 1 amorphous form) of posaconazole have been described in literature. Posaconazole Form I is used to produce its oral suspensions. A polymorphic conversion was detected in the final formulation after its direct analysis via X-Ray Powder Diffraction (XRPD). A method was developed in order to identify and characterize the crystal phases in the suspension without endangering transformation during the isolation and characterization process analysis. For this purpose, posaconazole oral suspensions were centrifuged to remove excess water, the precipitates were isolated, covered with low-density polyethylene (LDPE) cling film to avoid transformation to another crystal phase and their XRPD diffractograms were recorded. Posaconazole in its oral suspension was identified as Form-S, which was found to be very unstable when exposed to open air at ambient temperature and it was quickly transformed to the initial Form I.

Among the excipients of posaconazole oral suspensions, water was found responsible for this polymorphic conversion. Hence, pure posaconazole Form-S was isolated by filtering under vacuum a posaconazole Form I aqueous dispersion. Pure Form-S was subsequently characterized using XRPD, Raman spectroscopy, Attenuated Total Reflectance (ATR), Optical Microscopy, Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). Significant differences in the Raman spectra of the two polymorphs were found. Hydrogen bond vibrations observed in the ATR spectrum confirmed the suspicion of modification of Form I to Form S due to interactions with water molecules. From XRPD it was found that Form-S adopts a monoclinic crystal lattice with unit cell dimensions a = 12.3799 Å, b = 6.3053 Å and c = 23.1258 Å, angle $\beta = 93.140^{o}$ and volume V = 1802.47 Å. The results of thermal analysis and optical microscopy revealed that Form-S is a trihydrate form of posaconazole, with its molecules shaping a loosely connected crystal net, surrounded by water molecules. In all cases the transformation kinetic from one form to another was also studied.