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Polymorphic conversion of a hydrophobic drug in water: Posaconazole suspensions

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Active Pharmaceutical Ingredients (API) can exist in various crystalline forms (i.e., polymorphs). Metastable polymorphs may exhibit advantageous properties in terms of solubility and dissolution rate, however, they tend to convert to the thermodynamically most stable form. Since polymorphic transitions may not only have an impact on the performance of the drug product but also on its physical stability, in many cases the most stable polymorph is selected for formulation to prevent the risk of undesired transformations under processing and storage.

Posaconazole, a poorly water-soluble drug, is characterized by a plethora of polymorphs and hydrates. *Lykouras et al.* demonstrated that the most stable form of posaconazole (Form I) immediately converts to Form S in water.[1] Form S is contained in the marketed oral suspension of posaconazole.[2] However, there is still little knowledge about the nature and the stability of Form S.

The aim of our study was to gain understanding of the phase conversion of posaconazole crystal forms in water using Raman microscopy and Powder X-ray Diffraction (PXRD). For this purpose, an aqueous suspension of posaconazole Form I was monitored over a period of 5 weeks by Raman microscopy. In water, Form I instantaneously converts to Form S, which surprisingly undergoes a solvent-mediated phase transformation to Form A after 2 weeks. The experiment demonstrated that Form A is the most stable form of posaconazole in water. By Dynamic Vapor Sorption (DVS) it was found that both forms S and A are channel hydrates.

In the marketed oral suspension, Form S appears to be kinetically stabilized by the wetting agent polysorbate 80. An aqueous suspension of Form S in the presence of the excipient (0.25%) does not show any change in the X-ray diffraction pattern even after 5 weeks.

This study demonstrates the importance of carefully investigating the solid-state forms of an API to determine the most stable polymorph/hydrate under given conditions and to assess the risks related to the use of metastable forms.

[1] Lykouras, M., Orkoula, M., Kontoyannis, C. 2023. Formation and Characterisation of Posaconazole Hydrate Form. Pharmaceuticals. 16, 65.
[2] Lykouras, M., Fertaki, S., Orkoula, M., Kontoyannis, C. 2020. Sample Preparation of Posaconazole Oral Suspensions for Identification of the Crystal Form of the Active Pharmaceutical Ingredient. Molecules. 25, 6032.