The Polymorph Myth Dispelled: True Forms of Oxytetracycline Hydrochloride

M. Pęczek[1], H. Butkiewicz[1], T. Bizoń[1], D. Trzybiński[1], M. Malińska[1], A. Ø. Madsen[2], A. A. Hoser[1]

[1]University of Warsaw, Faculty of Chemistry, Pasteura 1, 02-093 Warsaw, Poland, [2]University of Copenhagen, Department of Pharmacy, Universitetsparken 2, 2100 Copenhagen, Denmark

me.peczek@student.uw.edu.pl

Polymorphism describes the ability of a compound to crystallize in more than one distinct form. This phenomenon is especially significant in the pharmaceutical field, as different polymorphs can display diverse physical characteristics, such as solubility and bioavailability which directly impact drug performance. Consequently, understanding polymorphism is essential for the design, development, and quality control of pharmaceutical products.

Oxytetracycline hydrochloride (OxyCl), a widely prescribed antibiotic from the tetracycline family, has been believed to exhibit polymorphic forms for years. Its therapeutic efficacy, stability, and absorption in the body can vary depending on the specific form present. While recent publications describe four polymorphic variants of OxyCl identified using, i.a., PXRD and DSC [1], the Cambridge Structural Database (CSD) contains only one resolved crystal structure (OxyCl-II), published in 1965 [2].

In our investigation, we explored the solid-state forms of OxyCl using single-crystal X-ray diffraction. In addition to reproducing the four previously reported forms, we identified three novel structures. Among these seven forms, only one corresponds to a true anhydrous form (OxyCl-II). The remaining six comprise four hydrates, which all differ in the amount of water molecules in the unit cell, and two alcohol solvates. Interestingly, even the commercially available compound was found to be a hydrate.

Our study also uncovered significant structural disorder, particularly within the hydrated forms. These typically exhibit arrangements of oxytetracycline cations (organic layers) interspersed with chlorine anions and water-filled voids (inorganic layers). These observations have led to a potential explanation for the differences in solubility among the structures, which was never truly addressed. Additionally, it opened a new door for experiments in changing humidity conditions, which indicate a dynamic uptake or release of the water molecules by some forms and changes in their cell parameters. Nevertheless, our current results represent only the tip of the iceberg in terms of understanding the true nature of solvated crystals, and further research is certain to follow.

[1] Bueno, M.S. et al. (2020). *International Journal of Pharmaceutics*, **585**, 119496.

[2] Cid-Dresdner, H. et al. (1965) Z. Kristallogr. Kristallgeom. Kristallphys. Kristallchem., **121**, 170.

Financial support from the Polish National Science Centre (SONATA17 grant 2021/43/D/ST4/03136) is kindly acknowledged.