Structure and stability of δ-indomethacin

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Polymorphism is a common aspect of most commercially relevant drugs. One-third of crystalline organic molecules and about half of marketed active pharmaceutical ingredients (APIs) are known to form polymorphs [1, 2]. The characterization of all polymorphic species and the understanding of the overall polymorphic energy landscape represents a prominent aspect of drug development and is crucial to establish efficacy, formulation, and shelf life. Moreover, the discovery of new polymorphs with different chemical and physical properties may result in treatments that are more effective and with reduced side effects [3].

Here, we report the crystallization, structure determination and dissolution behaviour of the δ-polymorph of the non-steroidal anti-inflammatory drug indomethacin (IMC), a poorly studied polymorph first mentioned almost 50 years ago [4] and whose structure has remained hitherto unknown. δ-IMC shows a significantly enhanced dissolution rate compared with the more common and thoroughly studied α- and γ-polymorphs, potentially connected with an increased bioavailability.

Pure δ-IMC was obtained via desolvation of the methanol solvate form. Its crystallisation results in fibrous crystals that are too tiny for conventional single-crystal X-ray diffraction (XRD). Structure determination was therefore obtained based on continuous three-dimensional electron diffraction (3D ED) [5], recorded by a single-electron detector [6]. The structural model obtained from 3D ED was refined using the Rietveld method against powder XRD data, following the protocol used for other pharmaceutical compounds [7, 8] and allowing the accurate determination of free torsion angles and intermolecular bonding.

The structure solution provides a solid clarification of δ-IMC spectroscopic IR and Raman data and a tentative interpretation for still unsolved indomethacin metastable polymorphs. Moreover, it explains the observed solid-solid transition from the δ-polymorph to the α-polymorph, which is likely driven by similarities in molecular conformation.

The applied procedure for structure determination may be implemented as a standard protocol for the R&D department of a pharmaceutical company.

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