Poster

# Pushing Technique Boundaries to Probe Conformational Polymorphism

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In this study, we present an integrated experimental-computational approach to explore the solid-form landscape of the highly conformationally flexible molecule, chlorpropamide (CPA) [1]. CPA is unusual in the sense that in that it has been subject to significant solid form screening experiments utilising a range of non-traditional approaches that include high pressure [2, 3] and mechanochemistry [4, 5, 6]. However CPA demonstrates significant conformational flexibility and therefore the question was asked – should we expect more polymorphs of CPA?

In this comprehensive solid state study, non-traditional crystallization methods such as spray drying, impurity-assisted crystallization, and gel-phase crystallizations were applied. The work allowed for the successful identification of new polymorphic forms of CPA, including a metastable ζ-polymorph and resolved the structure of the η-form previously identified in 2019.

The newly identified structures were contextualised through the generation of a crystal energy landscape via CSP. The discovery of the ζ-polymorph, approximately 14 kJ/mol higher in energy than the most stable α-form according to density functional theory (DFT), highlights the critical need for CSP workflows to include a wider range of energetic states. This approach allows for the exploration of highly metastable phases that traditional methods might overlook.

The CSP approach not only identified the new forms but also achieved significant success in locating five of six previously known forms of CPA. However, the study highlighted the challenges that remain in modelling molecules outside the calibrated energy and conformational range, underscoring a fundamental limitation in current CSP methodologies, particularly when dealing with flexible molecules.

Furthermore, we demonstrate how the presence of degradation products in CPA solutions can significantly influence the crystallization outcomes, promoting the nucleation of otherwise difficult to obtain metastable polymorphs of CPA. This work emphasizes the importance of combining computational predictions with diverse experimental techniques to fully explore and understand the solid-state landscape of pharmaceutical materials. The findings not only advance our understanding of CPA but also provide a robust framework for exploring other polymorphic and conformationally flexible pharmaceuticals..

[1] Ward, M. R.; Taylor, C. R.; Mulvee, M. T.; Lampronti, G. I.; Belenguer, A. M.;, Steed, J. W.; Day, G. M; Oswald, I. D. H. Cryst. Growth Des. 2023, 23, 7217−7230

[2] Belenguer, A. M.; Cruz-Cabeza, A. J.; Lampronti, G. I.; Sanders, J. K. M. On the Prevalence of Smooth Polymorphs at the Nanoscale:
Implications for Pharmaceuticals. CrystEngComm 2019, 21, 2203− 2211

[3] Bouvart, N.; Palix, R. M.; Arkhipov, S. G.; Tumanov, I. A.; Michalchuk, A. A. L.; Boldyreva, E. V. Polymorphism of Chlorpropamide on Liquid-Assisted Mechanical Treatment: Choice of Liquid and Type of Mechanical Treatment Matter. CrystEngComm 2018, 20, 1797−1803.

[4] Seryotkin, Y.; Drebushchak, T. N.; Boldyreva, E. A highpressure polymorph of chlorpropamide formed on hydrostatic compression of the α-form in saturated ethanol solution. Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater. 2013, 69, 77−85

[5] Zakharov, B. A.; Seryotkin, Y. V.; Tumanov, N. A.; Paliwoda, D. D.; Hanfland, M.; Kurnosov, A. V.; Boldyreva, E. V. The role of fluids in high- pressure polymorphism of drugs: different behaviour of βchlorpropamide in different inert gas and liquid media. RSC Adv. 2016, 6, 92629−92637.

[6] Zakharov, B. A.; Goryainov, S. V.; Boldyreva, E. V. Unusual Seeding Effect in the Liquid-Assisted High-Pressure Polymorphism of Chlorpropamide. CrystEngComm 2016, 18, 5423−5428.