MS28-1-14 Polymorphism in lithium ionic cocrystals
#MS28-1-14

Y. Hjiej Andaloussi [1], M. Zaworotko [1]
[1]University of Limerick - Limerick (Ireland)

Abstract
The use of lithium as a highly effective therapeutic for the treatment of bipolar disorder and major depressive disorder has been historically hindered by a narrow therapeutic window between efficacy and toxicity. In 2013, lithium was modified to have improved pharmacokinetic properties through the use of an ionic cocrystal with salicylate and L-Proline, known as LISPRO, that has since been taken through to phase 2 clinical trials for the treatment of Alzheimer's disease. But did we get the right crystal form? Polymorphism in ionic cocrystals is an understudied phenomenon. As such this was investigated in LISPRO which found that the previously reported cocrystal polymorph of LISPRO, LISPRO(α), is in fact metastable. LISPRO(α) was found to transform under slurry conditions to the more thermodynamically stable polymorph, LISPRO(β), which possesses a highly similar Powder X-ray diffraction (PXRD) pattern. We assessed the polymorphism of a similar lithium L-Proline cocrystal with 4-methoxybenzoate (L4MPRO) which was shown to form the kinetically hindered but thermodynamically more stable L4MPRO(α) form, and the metastable L4MPRO(β) and (γ) forms. These case studies in the polymorphism of pharmaceutically-relevant agents offer cautionary tales and lessons on the mechanochemical and solution-based methods to study polymorphism in ionic cocrystals.

References
Sanii, R.; Andaloussi, Y. H.; Patyk-Kaźmierczak, E.; Zaworotko, M. J., Polymorphism in Ionic Cocrystals Comprising Lithium Salts and l-Proline. Crystal Growth & Design 2022.

Smith, A. J.; Kim, S.-H.; Duggirala, N. K.; Jin, J.; Wojtas, L.; Ehrhart, J.; Giunta, B.; Tan, J.; Zaworotko, M. J.; Shytle, R. D. Improving Lithium Therapeutics by Crystal Engineering of Novel Ionic Cocrystals. Mol. Pharm. 2013, 10, 4728– 4738

Schou, M.; Baastrup, P. C.; Grof, P.; Weis, P.; Angst, J. Pharmacological and Clinical Problems of Lithium Prophylaxis. Br. J. Psychiatry 1970, 116, 615– 619

Habib, A.; Sawmiller, D.; Li, S.; Xiang, Y.; Rongo, D.; Tian, J.; Hou, H. Y.; Zeng, J.; Smith, A.; Fan, S. N.; Giunta, B.; Mori, T.; Currier, G.; Shytle, D. R.; Tan, J. LISPRO mitigates beta-amyloid and associated pathologies in Alzheimer's mice. Cell Death Dis. 2017, 8, e2880