Poster Presentations

[MS45-P08] Trospium chloride: Polymorphism vs. Molecular Disorder.

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The characterization of the solid state properties of an active pharmaceutical ingredient is a necessary step in drug development[1]. One such API is trospium chloride (TCl), an anticholinergic drug used to treat incontinence and overactive bladder syndrome[2], [3]. One crystal form was known up to now, but from the crystallographic point of view it has only been described by X-ray powder diffraction pattern[4]. To the best of our knowledge, no crystal structures of trospium chloride have been published, so we decided to prepare and describe different possible crystal forms. Using single-crystal X-ray diffraction, the structures of two new polymorphs were solved (both monoclinic): FormI (a = 9.1551(10) Å, b = 10.9184(13) Å, c = 11.0126(12) Å, β = 101.042(11) °, V = 1080.4(2) Å3); Form II (a = 10.9483(3) Å, b = 10.9241(3) Å, c = 18.0149(5) Å, β = 100.685(3) °, V = 2117.23(10) Å3).
The two polymorphs were obtained from ethanol mother liquor and they both exhibited a significant pseudo-symmetrical disorder. The crystal structures of these polymorphs were very similar and exhibited pseudo-symmetrical disorder, making them even more similar. The high degree of similarity between the crystal arrangements of both TCl polymorphs makes the study of this system more complex. In almost all cases, XRPD is able to easily identify different polymorphs. However, the powder X-ray patterns of the polymorphs of trospium chloride were similar to the point that XRPD from laboratory source was not able to distinguish between them.

Were the polymorphs we discovered real or just the result of different growth conditions? The answer lay in the observed crystal symmetry[5] and reflections visible on the single-crystal area detector. With the use of the single-crystal X-ray diffraction patterns, we showed that polymorphs of trospium chloride truly exhibit different overall symmetry. Form I crystallized in the space group $P21$ while Form II had the higher symmetry of $P21/c$. Observed reflections on area detector were in agreement with this space group assignment. A detailed inspection of the molecular packing revealed that variations in the short range disorder most likely gave rise to these two sibling polymorphs, virtually undistinguishable by X-ray powder diffraction from laboratory source. Powder data measured on the synchrotron source demonstrated clearly the presence of only Form I. The reason of this effect can be pressure inducted transformation of Form II to Form I. By extending the knowledge of crystal forms of trospium chloride, we have simultaneously increased understanding of the solid state of the API and reduced the danger of an unexpected phase transition occurring during the production of a final drug product.

[1] *Polymorphism in pharmaceutical solids*, 2nd ed. New York: Informa Healthcare, 2009. [2] A. K. G. Aberg, "Methods for relaxation of smooth muscle contractions using Trospium, [3] D. Singh-Franco, C. Machado, S. Tuteja, and A. Zapantis, "Trospium chloride for the treatment of overactive bladder with urge incontinence," *Clin. Ther.*, vol. 27, no. 5, pp. 511–530, May 2005. [4] D. Scher, R. Ryznal, and C. Blizzard, "Complex of Trospium and Pharmaceutical Compositions Thereof," WO/2010/01181329-Jan-2010. [5] A. Gavezzotti, "A solid-state chemist's view of the crystal polymorphism of organic compounds," *J. Pharm. Sci.*, vol. 96, no. 9, pp. 2232–2241, 2007.

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