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Giampiero Ventimiglia, Sonia Bellomi, Giuseppe Barreca, Lorella Giovannelli, Norberto Masciocchi

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Synthesis, Characterization and Crystal Chemistry of Tasimelteon, a Melatonin Agonist, in its Anhydrous and Hemihydrate Forms

GIAMPIERO VENTIMIGLIA,[1,*] SONIA BELLOMI,[1,*] GIUSEPPE BARRECA,[1] LORELLA GIOVANNELLI,[2] NORBERTO MASCIOCCHI[3]

[1] Chemessentia Srl, 28100 Novara, Italy

[2] Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale, 28100 Novara, Italy

[3] Dipartimento di Scienza e Alta Tecnologia, Università dell'Insubria, 22100 Como, Italy

ABSTRACT: Two crystalline forms of Tasimelteon, a drug approved by the US FDA for the treatment of non-24-hour sleep-wake disorder, have been studied by single crystal and powder diffraction analyses, TGA, DSC, spectroscopic and optical methods. The synthetic method forming Tasimelteon is described in detail, with its full analytical, spectroscopic and enantiopurity characterization. Solid Tasimelteon hemihydrate, $C_{15}H_{19}NO_2 \cdot 0.5H_2O$, is tetragonal with $a = b$ = 7.3573(2) Å, c = 52.062(2) Å, V = 2818.1(2) Å^3; Z = 8. Its crystal structure has been solved and refined in the $P4_32_12$ space group, showing the occurrence of polymeric (H-bonded) slabs, thanks to the presence of water molecule (O_W) tetrahedrally linked to four distinct Tasimelteon molecules in a $N_2(O_W)O_2$ fashion. The anhydrous form of Tasimelteon, $C_{15}H_{19}NO_2$, crystallizes in the monoclinic $P2_1$ space group, with a = 11.130(4), b = 4.907(2), c = 12.230(6) Å, β = 91.03(3)°, V = 667.8(5) Å^3; Z = 2. Thanks to the availability of good-quality specimens, the structure of the latter phase was solved by conventional single-crystal diffraction analysis, showing short intermolecular C=O···H-N interactions between (translationally related) Tasimelteon molecules, forming, in the crystal, well defined chains running along the **b** axis. The morphology of the two crystal forms has been analyzed by means of optical microscopy and particle size distribution analysis. Worthy of note, the newly determined crystal structures enable the successful usage of full-pattern matching X-ray-based quantitative analyses of batches of industrial interest, in search for contamination or phase stability issues.

Keywords: Crystal structure; X-ray powder diffractometry; thermal analysis; solid state; hydrates/solvates.

Additional Supporting Information may be found in the online version of this article.

Correspondence to: Giampiero Ventimiglia (Tel: +39 0321 650 255 Fax: +39 0321 479 200, E-mail: giampiero.ventimiglia@chemessentia.it)