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A study of Fasoracetam's solid state forms: A potential anti-Alzheimer pharmaceutical

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Abstract

Different solid state forms of the research chemical fasoracetam, which counters the effects of Alzheimer's disease, have been subjected to a thermal and structural analysis. Single crystals were obtained from solution evaporation and from the melt. Single crystal x-ray analyses of the crystals show the existence of two hydrated and one non-hydrated crystalline form of fasoracetam. Under ambient conditions, the hydrate form I is found to be the most stable form, showing a melting point of 57℃. This low melting point, combined with possible water losses could cause problems when formulating the hydrated form and impact the storage conditions of the compound.

Keywords: Polymorphism, Crystal structure, Thermogravimetric analysis, Calorimetry (DSC), Solvent evaporation, Hydrate, Alzheimer's disease

1. Introduction

Fasoracetam (NS-105, 5-oxo-D-prolinepiperidinamide) is part of the racetam family, a drug of the pyrrolidone class and currently considered a research chemical[1]. The class is characterized by its nootropic (e.g. piracetam and fasoracetam), stimulating (e.g. oxiracetam) and anticonvulsant (e.g levetiracetam) properties[2–6]. Studies have shown promising results in its ability to counter and reverse the effect of Alzheimer's disease[7–9]. It is a known fact that the nature of a solid state form directly impacts bioavailability[10,11], solubility[12,13] and other pharmacokinetic parameters, which need to be controlled for maximum dosage effect and consistency. It is therefore important to exercise control over the solid phase form[14,15]. Screening for different solid phases of novel drugs has now become an integral part of the drug development process[16,17]. Additionally, legal instances still consider alternative solid forms as novel, hence a formulation with such a novel form would not infringe an existing patent[18]. Besides identifying different solid forms, an understanding of the thermodynamic relationships between these forms is also recommended, to avoid future issues related to phase transformations, as illustrated by the Ritonavir and Rotigotine cases, where a market withdrawal of the drug occurred due to phase transformations of the API[19,20].

Scheme 1: Chemical structure of Fasoracetam

Fasoracetam (scheme 1) is a promising research chemical and at ambient conditions available in solid form. However, no crystal structure was yet reported in literature, nor any solid screen performed for this compound. The chemical structure of Fasoracetam shows two amide functions which commonly take part in hydrogen bonding patterns, as the carbonyl can serve as a hydrogen acceptor, whereas the amide can act as a hydrogen donor. Having multiple hydrogen bonding sites available, this could possibly lead to different packing arrangements. Furthermore, other racetam compounds have already shown a propensity towards the formation of multiple solid state forms[21].

In this contribution, we therefore set out to identify different solid state forms of fasoracetam and describe these from a structural as well as a thermodynamical point of view. We identified a