Two Polymorphs – Which One is Stable at Ambient Conditions ?

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NN414 (6-chloro-3-(1-methylcyclopropyl)-amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide) is an opener of ATP sensitive potassium channels, which attenuates hyperinsulinemia. The compound prevents diabetes and improves glucose tolerance without affecting body weight or body composition in preclinical studies. Apart from its therapeutic effects it is also interesting because of its physico-chemical properties.

NN414 is a very weak acid with pK_a = 8.5, log P = 1.6, and molar weight M_w = 291.8 g/mol. Two true polymorphs, A and B, of this compound have been identified. Polymorph A crystallizes in needleshaped crystals with a triclinic unit cell by precipitation from a variety of solvents such as acetic acid, acetonitrile, diluted ammonia, methanol, N-methyl-pyrrolidone, 1-propanol, or 2-propanol [1]. Polymorph B forms prismatic crystals by precipitation from methanol or ethanol, and this unit cell is rhombohedral [1]. Mixtures of A and B can also be obtained. Both polymorphs are highly crystalline. Polymorph A melts at approximately 257°C whereas polymorph B melts at approximately 269°C [1].

To establish the thermodynamic relationship between A and B, different experiments concerning crystallization, density of mass, solubility and melting behaviour were carried out using hot stage microscopy, He-pycnometry, intrinsic solubility, and differential scanning calorimetry [2]. The results of these experiments unanimously point to an enantiotropic relationship between A and B, with A being thermodynamically stable at ambient conditions, and B being the stable polymorph at elevated temperatures. A transition point temperature between A and B has been estimated to T_{trans}= 215°C ± 15°C from the differences in melting enthalpies.

References

1 Jensen, A. F., Junager, F., Jessen, C. U., and Kornø, H. T. (2004) International Patent Application, WO2004005299.

2 Bernstein, J., Davey, R. J., and Henck, J.-O. (1999) Ang. Chem. Intl. Ed. **38**, 3440-3461.