

Thermoanalytical investigation of the complex binary system of (+)- and (-)-diprophylline

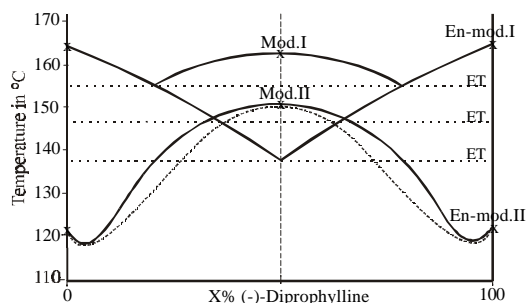
Judith M. Rollinger¹, Ulrich J. Griesser¹, Martin Szelagiewicz² and Urs Hofmeier²

¹Institute of Pharmacy, University of Innsbruck, Innsbruck, Austria

²Solvias AG, Basel, Switzerland

In the development of separation methods of racemic substances, it is essential to have knowledge of the mixing behavior of enantiomers. When polymorphism is involved, the analysis of binary systems is particularly challenging. The theophylline-derivative, (\pm)-diprophylline, which is used as a bronchodilator is known to exist in two monotropically related forms [1]. The pure enantiomers which enabled the characterization of the binary system were separated and provided by Solvias AG. Mainly thermoanalytical methods - differential scanning calorimetry (DSC) and hot stage microscopy (TM) - were applied for the construction of the phase diagram. The different crystal forms were additionally characterized by FTIR and X-ray powder diffractometry (XRPD).

The diprophylline enantiomers were also found to crystallize in two monotropically related polymorphic forms (En-mod.I, mp. 164°C and En-mod.II, mp.122°C). The data obtained from various DSC and TM-experiments are depicted in a binary melting phase diagram (see scheme). The resulting curve shapes obviously show that mod.I crystallizes as a racemic compound forming an eutectic mixture at about 23% (+)- and (-)-diprophylline En-mod.I with an eutectic melting (ET) at 155°C. A further ET lies between racemic mod.II and En-mod.I at 147°C. A third ET was observed by TM at 138°C on the 50%-axis corresponding to a hypothetical, unstable conglomerate. The most striking result however was the crystallization of racemic mod.II as a solid solution (pseudoracemate), with an unusual continuous curve shape, as recently described in the binary system of (+)- and (-)-felodipine [2], termed Roozeboom Type 2 b [3]. Due to this behavior, isomorphism between En-mod.II and racemic mod.II was expected and confirmed by FTIR and XRPD.



To our knowledge this is the first case where all basic types of racemates have been observed in one binary system, although the conglomerate is kinetically unstable.

- [1] U. J. Griesser, M. E. Auer and A. Burger, *Sci. Pharm.* 67, 319-330 (1999).
- [2] J. M. Rollinger and A. Burger, *J. Pharm. Sci.* 90, 949-959 (2001).
- [3] M. Brandstätter-Kuhnert and M. Aepkers, *Mikrochim. Acta*, 1041-1054 (1962).