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Polymorphism in the Binary System of Enantiomeric Dihydropyridines

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Dihydropyridine channel blockers are widely used in the treatment of hypertension and angina pectoris. They are predominantly chiral molecules and commercially used as racemates. Furthermore, polymorphism is a very common phenomenon among this group of drug substances and may additionally complicate the analytic and standardization of these compounds.

The aim of this study was to characterize and identify the crystal forms of enantiomers, and racemic mixtures of three chiral dihydropyridines, namely nitrendipine [1], arnlodipine besylate, and felodipine [2, 3]. They were investigated by thermoanalytical, spectroscopical and X-ray diffraction methods. The binary melting phase diagrams of nitrendipine and felodipine were established by DSC and hot stage microscopy, allowing determination of the racemic species and an understanding of the complex thermal behavior.

Three monotropically related modifications of racemic nitrendipine were characterized and identified as a racemic compound (mod. I, mp. ~158°C) and two conglomerates (mod. II, mp. ~134°C, and mod. Ill, mp. ~126°C). In the racemic mixture, arnlodipine besylate crystallizes as anhydrate (mod. I, mp. ~198°C) and stable monohydrate. Dimorphism was found in the case of felodipine enantiomers (En-mod. I, mp. ~144°C; En-mod. II, mp. ~133°C), as well as in the racemic mixture (mod. I, mp. ~145°C; mod. II, mp. ~135°C). An unusual continuous series of solid solutions is manifested between their higher melting crystal forms which defines felodipine mod. I as pseudoracemate.

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