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Baclofen (4-amino-3-p-chlorophenylbutyric acid), a p-chlorophenyl analogue of γ -aminobutyric acid, is widely used in the treatment of spastic disorders as a skeletal muscle relaxant. The enantiomers of baclofen differ in their pharmacodynamic and toxicological properties: the R-(-)-enantiomer is much more active but also more toxic than the S-(+)-enantiomer. Besides, the "ineffective" S-(+)-enantiomer antagonizes the action of the effective R-(-)-enantiomer, so that the R-(-)-enantiomer is also substantially more effective than racemic baclofen. Because the kinetic disposition of the two enantiomers may be different, the investigation of the pharmacokinetic behavior of both enantiomers is often desirable. In this study, the optimal enantiomeric separation of baclofen and the validation of the method for its accurate and precise assay in human plasma will be discussed by capillary electrophoresis using highly sulfated γ -cyclodextrins as chiral additives.

[PD4-13] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

New reagent for the enantiospecific analysis of primary or secondary amino group via High-Performance Liquid Chromatography

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The synthesis and analytical testing of new ultraviolet active chiral derivatizing agent, (S)-[3-(3-Fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-2,5-dioxo-pyrrolidin-1-yl ester were investigated. In a rapid, one-step procedure, the compound reacts with primary or secondary amino group of β -blockers(acebutolol, arotinolol, betaxolol, bisoprolol, celiprolol, metoprolol, pindolol and propranolol) to form stable asymmetric urea derivatives. Studies on derivatization conditions demonstrate excellent derivative yield in mild organic base solutions. With excess of 20 times molar or more of chiral derivatizing agent, chiral derivatization reactions were completed within one hour at room temperature. Diastereomeric derivatives of β -blockers were well resolved in the ODS-C8 column using acetonitrile-methanol-water as mobile phase.

A reversed-phase high performance liquid chromatographic method was developed to determine the optical purity of propranolol enantiomers. The enantiomers were converted to diastereomeric derivatives using this new chiral derivatizing agent. Separation of the enantiomers as diastereomers was achieved by reversed phase HPLC within 35 min using Develosil C8 column. This method allowed determination of 0.05% of either of the enantiomers in the presence of its stereoisomer and method validation showed adequate linearity over the required range. Owing to the reaction condition during the derivatization with (S)-[3-(3-Fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-2,5-dioxo-pyrrolidin-1-yl ester, the possibility of racemization had to be established. Different ratios of (R)-(+)-propranolol and (S)-(-)-propranolol were prepared. Enantiomeric separation of these mixtures took place on a Chiracel OD column or, after derivatization with (S)-[3-(3-Fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-2,5-dioxo-pyrrolidin-1-yl ester, on a Develosil C8 column. The results from these two independent separation systems were compared with trace racemization and were in very good agreement. No racemization was found during the experiment.

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Influence of temperature and time differences on contents of cefaclor in dried-syrup.

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