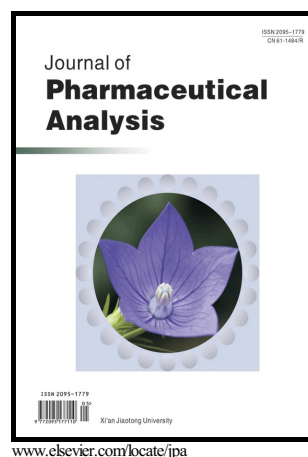


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Separation of Atropisomers by Chiral Liquid Chromatography and Thermodynamic Analysis of Separation Mechanism

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Abstract

In the pharmaceutical industry, the analysis of atropisomers is of considerable interest from a scientific and regulatory perspective. The compound of interest contains two stereogenic axes due to the hindered rotation around the single bonds connecting the aryl groups, which results in four potential configurational isomers (atropisomers). The separation of the four atropisomers is achieved on a derivatized β -cyclodextrin bonded stationary phase. Further investigation shows that low temperature conditions, including sample preparation (-70 °C), sample storage (-70 °C), and chromatographic separation (6 °C), were critical to preventing interconversion. LC-UV-Laser Polarimetric analysis identified peak 1/2 as a pair of enantiomers and peak 3/4 as another. Thermodynamic analysis of the retention data indicated that the separation of the pairs of enantiomers is primarily enthalpy controlled as indicated by the positive slope of the van't Hoff plot. The difference in absolute Δ (ΔH), ranged from 2.20 kJ/mol to 2.42 kJ/mol.

Keywords: Atropisomer separation, Chiral HPLC, Thermodynamic parameters, β -cyclodextrin stationary phase, Chiral separation mechanism

1. Introduction

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