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Enantiomeric separation of 1,4-dihydropyridines by liquid-phase microextraction with supercritical fluid chromatography

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ABSTRACT

Chiral separation of seven commonly used 1,4-dihydropyridines (1,4-DHP) was achieved by supercritical fluid chromatography (SFC) on a immobilised polysaccharide chiral selectors coated with cellulose-tris(3,5-dichlorophenylcarbamate) (Chiralpak IC). In this method, isopropanol was used as a modifier and a maximum resolution of 13.38 was resulted. Nimodipine content of actual samples was determined through two-phase hollow fibre-based liquid-phase microextraction (2*p*-HF-LPME). Under optimal conditions, the limits of detection of the two nimodipine enantiomers were 0.3 and 0.5 μg cm^{-3}. Recoveries of 80.0–99.8% were achieved. The developed SFC technique coupled with 2*p*-HF-LPME is a rapid, effective and environment-friendly method for separating and quantifying 1,4-DHP enantiomers.

1. Introduction

Calcium channel blockers play a significant role in vasodilatation [1] and are therefore effective in the treatment of essential hypertension and angina [2,3]. Three main groups of calcium channel blockers have been discovered, amongst which 1,4-dihydropyridines (1,4-DHPs) constitute an important class. 1,4-DHP drugs contain an asymmetric ester, and all of the compounds belonging to this class, except nifedipine, possess a chiral carbon atom at position 4 of the dihydropyridine ring. While most 1,4-DHP drugs are formulated as racemic mixtures, the pharmacological effects of the resulting enantiomers may vary [1,2]. For example, (*S*)-amlodipine is a more potent calcium channel blocker than (*R*)-amlodipine by about 2000-fold [4]. (*R*)-Azelnidipine exhibits calcium channel blocking activity, whereas (*S*)-azelnidipine does not. Therefore, development of stereoselective analytical methods is necessary. The structures of previously studied 1,4-DHPs and differences in the pharmacodynamic and pharmacokinetic properties of their enantiomers are shown in Table 1.

To date, enantioselective separation of chiral compounds remains a significant challenge. Many attempts have been made to develop an efficient chiral separation method for racemic analytes. Various studies and patents have reported the chiral separation of 1,4-DHP through high-performance liquid chromatography (HPLC) [5,6], capillary electrophoresis (CE) [7,8], capillary electrochromatography (CEC) [9] and hollow fibre-supported liquid membranes [10] and gas chromatograph (GC) [11]. Among these methods, chromatographic resolution procedures are the most effective.

Supercritical fluid chromatography (SFC) has attracted growing interest for its use in chiral separation [12–14]. SFC presents many advantages over traditional liquid chromatography (LC). In contrast to LC, SFC requires a shorter analysis time because of the use of supercritical fluid, which features low viscosity and high diffusivity, as the mobile phase [15,16]. The use of CO_2 also reduces the need for organic solvents, thereby rendering the process less hazardous to the environment.

Abbreviations: 1,4-DHP, 1,4-dihydropyridines; SFC, supercritical fluid chromatography; 2*p*-HF-LPME, two-phase hollow fibre-based liquid-phase microextraction; DAD, diode array detector; HPLC, high-performance liquid chromatography; CE, capillary electrophoresis; CEC, capillary electrochromatography; GC, gas chromatograph; LC, liquid chromatography; DEA, diethylamine; *k*, capacity factor; *R*, resolution; CSP, chiral stationary phase; LOD, limit of detection; RSD, relative standard deviation; MS, mass spectrometry; UV, ultraviolet.

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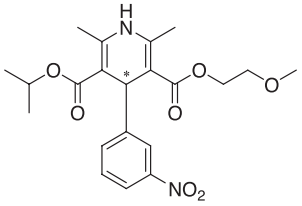
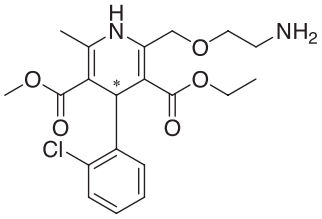
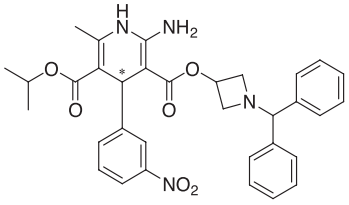
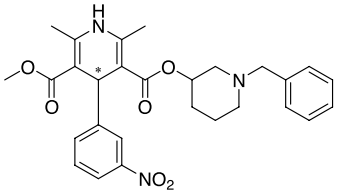
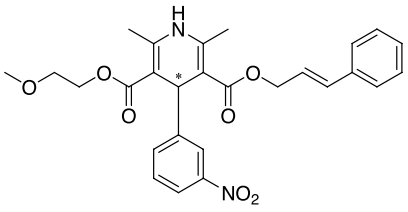
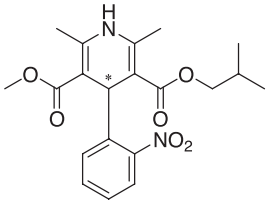
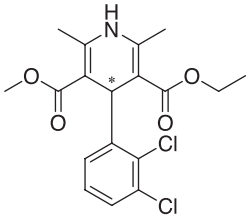
Table 1
Structure of selected 1,4-dihydropyridines and their pharmacodynamic and pharmacokinetic differences between enantiomers.

Names	Structures	Configuration	Pharmacological activity ratio (S/R or +/−)
Nimodipine		S(−), R(+)	5
Amlodipine		S(−), R(+)	1000
Azelnidipine		S(−), R(+)	Only R(+) has antihypertension activity
Benidipine		S(−), R(+)	30–100
Cilnidipine		S(−), R(+)	–
Nisoldipine		S(−), R(+)	12.8
Felodipine		S(−), R(+)	–