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Supercritical fluid chromatography *versus* high performance liquid chromatography for enantiomeric and diastereoisomeric separations on coated polysaccharides-based stationary phases: Application to dihydropyridone derivatives

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ABSTRACT

For analytical applications, SFC has always remained in the shadow of LC. Analytical enantioseparation of eight dihydropyridone derivatives, was run in both High Performance Liquid Chromatography and Supercritical Fluid Chromatography. Four polysaccharide based chiral stationary phases namely amylose and cellulose tris(3, 5-dimethylphenylcarbamate), amylose tris((S)-α-phenylethylcarbamate) and cellulose tris(4-methylbenzoate) with four mobile phases consisted of either *n*-hexane/ethanol or propan-2-ol (80:20 v:v) or carbon dioxide/ethanol or propan-2-ol (80:20 v:v) mixtures were investigated under same operatory conditions (temperature and flow-rate). The elution strength, enantioselectivity and resolution were compared in the two methodologies. For these compounds, for most of the conditions, HPLC afforded shorter retention times and a higher resolution than SFC. HPLC appears particularly suitable for the separation of the compounds bearing two chiral centers. For instance compound **7** was baseline resolved on OD-H CSP under *n*-Hex/EtOH 80/20, with resolution values equal to 2.98, 1.55, 4.52, between the four stereoisomers in less than 17 min, whereas in SFC, this latter is not fully separated in 23 min under similar eluting conditions. After analytical screenings, the best conditions were transposed to semi-preparative scale.

1. Introduction

More and more drug candidates which are developed in the 21 st century's pharmaceutical industry, are chiral. It was proved that specific stereochemistry of these substances affects the biological activity and affects as well the commercial viability of the drug candidate. Therefore, enantioselective separation techniques are vital in the development of new pharmaceutical products. The Thalidomide (Contergan©) disaster led to the story of success of the chiral chromatography methodologies, despite the fact that sometimes asymmetric synthesis is firstly considered, however is neither time nor cost effective. The need to obtain the two pure enantiomers simultaneously and/or to verify optical purity has incredibly favored Liquid Chromatography which has predominated in the last 40 years. HPLC using polysaccharide based chiral stationary phases (CSPs) has been extensively used for chiral drugs [1,2], mainly because of its wide range of applications due to numerous available CSPs, its sensibility and its low limit of detection. Taking advantage of improved instrumentation performance and of the transposition of these HPLC polysaccharide CSPs to SFC, the latter one knows a renewal of interest [3,4] and a technological extension into Ultra High Performance SFC (UHPSFC) [5,6]. SFC started to carve out a niche also because of health, environment and safety issues [7,8]. Moreover in SFC, analysis times (because of the allowed high flow-rate) and column equilibration are faster than in HPLC and it allows column coupling. In many laboratories SFC has become the technique of choice for both achiral [9] and chiral [10] analyses, but its principal application is undoubtedly the chiral preparative purification [11,12]. Considering the preparative scale, same particle sizes can be used at analytical and preparative scales as the operational pressure in SFC is much lower than in HPLC. But the major advantage of SFC *versus* HPLC is the lower fraction volumes, reducing solvent consumption and thus time for solvent removal, minimizing global cost of enantiomer isolation.

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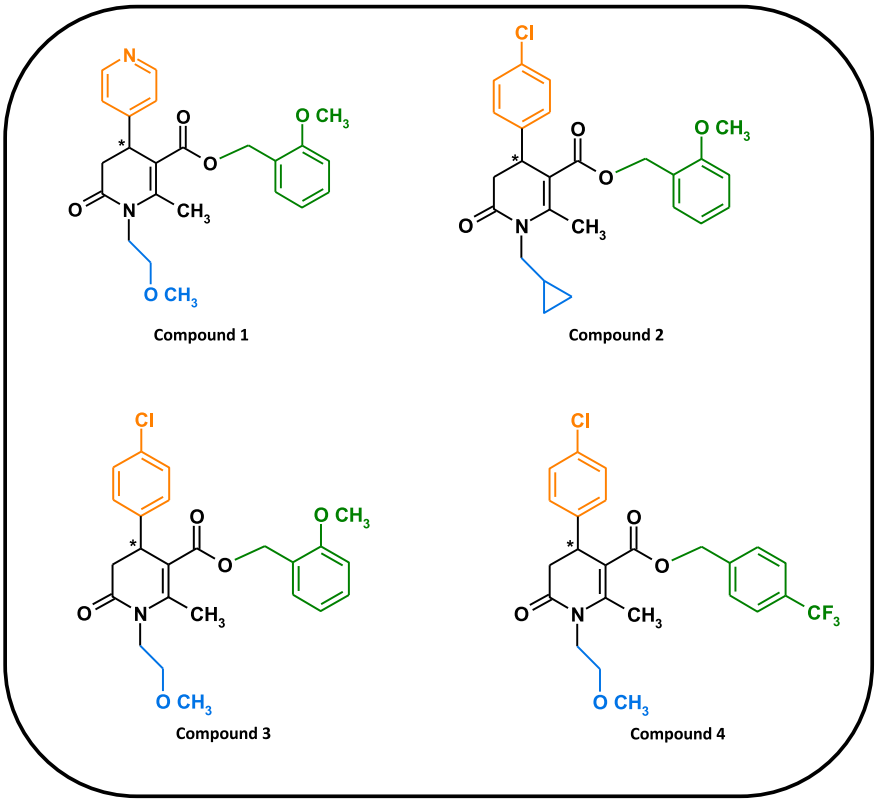

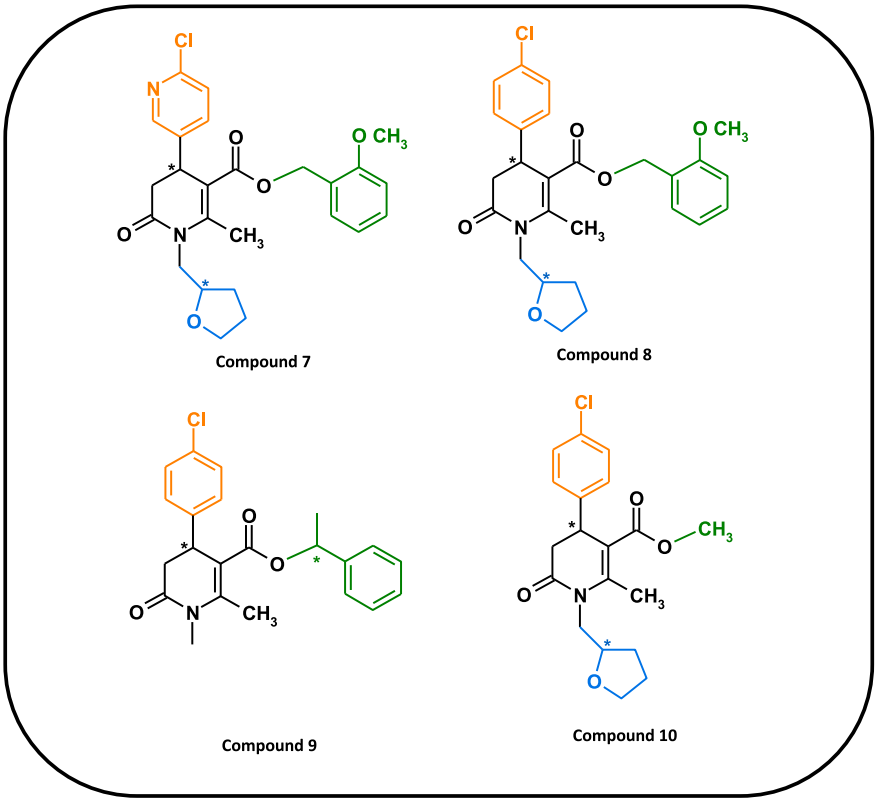

Fig. 1. Structures of dihydropyridone derivatives.

Therefore, these two techniques were employed to carry out the enantioseparation of four compounds (**1**–**4**) bearing one asymmetric carbon and four compounds (**7**–**10**) bearing two asymmetric carbons (Fig. 1) of a patented series entrusted to our laboratory. Worldwide, more than 415 million subjects have diabetes and the International Diabetes Federation predicts that the number will rise

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