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Review

Pharmaceutical and forensic drug applications of chiral supercritical fluid chromatography

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ABSTRACT

The supercritical fluid is an excellent choice as the chromatographic mobile phase because it allows rapid separation with high efficiency and applications involving enantioresolution are common. Supercritical fluid chromatography (SFC) is increasingly used for analytical, semi-preparative and preparative purification of chiral compounds, including production of enantiomers that are mainly encountered during drug development. SFC can be used as an alternative to HPLC for many drug substances, so it is gaining popularity in the pharmaceutical industry. The main advantages of SFC in separating chiral pharmaceuticals are: high speed, short analysis time, limited environmental impact and high efficiency. The reduction in the use of organic solvents has cost, health, and safety benefits. Due to these advantages, SFC fulfills all the requirements of Green Analytical Chemistry approaches.

In this article, we present application of SFC as a tool for chiral separation of pharmaceuticals and drugs of abuse.

Contents

Abbreviations: 2D SFC/SFC/MS, Two-dimensional supercritical fluid chromatography/mass spectrometry; ABZSO, Albendazole-sulfoxide enantiomers; ACN, Acetonitrile; CD, Cyclodextrin; CE, Capillary electrophoresis; CEC, Capillary electrochromatography; CHA, Cyclohexylamine; CHMP, Committee for Medicinal Products for Human Use; CSP, Chiral stationary phase; DEA, Diethylamine; DEABV, Polymeric trans-9,10-dihydro-9,10-ethanoanthracene-(11S,12S)-11,12-dicarboxylic acid bis-4-vinylphenylamide; DMOA, N,N-dimethyloctylamine; DM-β-CD, Dimethyl-β-CD; DPEVB, Polymeric N,N′-[(1R,2R)-1,2-diphenyl-1,2-ethanediyl]-bis-4-vinylbenzamide; EI, Electrospray ion; EtOH, Ethanol; FDA, Food and Drug Administration; GC, Gas chromatography; HPLC, High-performance liquid chromatography; IPA, Isopropylamine; k, Retention factor; l-PA, l-Phenylalanine anilide; MeOH, Methanol; MIP, Molecularly-imprinted polymer; NPLC, Normal-phase-liquid chromatography; P-CAP, Polymeric N,N′-(1S,2S)-1, 2-cyclohexanediyl-bis-2-propenamide; P-CAP-DP, Polymeric N,N′-[(1R,2R)]-1,2-diphenyl-1,2-ethanediyl]-bis-2-propenamide; PPAR, Peroxysome proliferator-activating receptor; RPLC, Reversed-phase-liquid chromatography; Rs, Enantiomeric selectivity; Rt, Retention time; SCF, Supercritical fluid; SFC, Supercritical fluid chromatography; TEA, Triethylamine; TFAA, Trifluoroacetic anhydride; TIC, Total ion current; TLC, Thin-layer chromatography.

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1. Introduction

A chiral compound is a type of molecule that lacks an internal plane of symmetry and therefore has a non-superimposable mirror image. These molecules exist in two distinct mirror image forms, termed enantiomers (or optical isomers). Although enantiomers have identical physical and chemical properties, such as melting and boiling point, density, solubility, and chemical reactivity, the direction in which they rotate plane-polarized light differs, so their optical activity is different [1].

Chirality was first observed in 1815 by French physicist Jean-Baptiste Biot [2], but the pharmaceutical implications of racemic drugs have only been extensively recognized since 1984 [3–5]. Chiral molecules are constituents of a large proportion of therapeutic agents [2]. The separation of enantiomers is of great interest to a number of scientific disciplines, including the pharmaceutical industry and forensic science laboratories [6]. Since more than half of pharmaceutically-active ingredients are optically active, the industry requires the separation of these isomers [7].

It is well known that the body is stereospecific, and enantiomers frequently exhibit very different biological activity because of interactions with active sites of enzymes [8] resulting in differences with pharmacological activity and pharmacodynamic and pharmacokinetic effects. In many cases, one enantiomer may produce the desired therapeutic action, while the other may be inactive or even toxic and produces unwanted effects [8]. An example of this is thalidomide, which was introduced as sedative drug and painkiller in the late of 1950s. It was often used by pregnant women. In the late 1950s and early 1960s, thousands of children in 46 countries were born with deformities as a consequence of thalidomide use. Now, it is well documented that S-(+)-thalidomide has a strong mutagenic effect on human fetuses [9]. Another example is amphetamine where the S-(+)-isomer is a few times more potent in central nervous system stimulation than R-(-)-amphetamine, which is slightly more potent in the peripheral system, for example in cardiovascular action [10]. The importance of separation and testing of single-enantiomer drugs is therefore clear and has become standard within the pharmaceutical industry [11].

The Food and Drug Administration (FDA, USA) and the Committee for Medicinal Products for Human Use (CHMP, European Union, EU) have issued guidance that recommends only the therapeutucally active enantiomer of a chiral drug be brought to market. The pharmacological properties and metabolic pathways of each enantiomer of the drug should therefore be studied separately before decisions are made [12,13]. This requires powerful means of chiral drug detection and separation.

Forensic science laboratories are also interested in the enantiomeric characterization and separation of drugs, because knowledge of stereochemical composition is useful in investigations of crime to establish manufacturing sources, and to provide information for sentencing guidance for drug-related offences. Moreover, this knowledge is important to determine whether the drug of concern is derived from a controlled substance. Both impurity and chirality profile provide a link between starting materials and the illicit drug synthesized by the clandestine chemist [14]. A good example of this is methylamphetamine, one of the most popular drugs of abuse, often manufactured from ephedrine stereoisomers as precursors. The enantiomeric composition may suggest which method of synthesis has been used and thereafter how the starting materials were extracted from pharmaceutical product (single enantiomers), the plant ephedra (mixture of enantiomers) or illicit ephedrine synthesized by fermentation processes [15]. For intelligence purposes, it is important to identify and to separate the enantiomers of the drug of abuse in order to recognize its possible provenance. It is therefore vital to focus on this problem and to develop appropriate analytical techniques as tools to obtain reliable, detailed information, and to provide results and methods of analysis of interest to end users, such as law-enforcement organizations.

After administration, pharmaceutical compounds can be partly metabolized within the human or animal body, so parent compounds and their metabolites may be released from the body into the environment. Many of these pharmaceutical pollutants are chiral, existing in the environment as a single enantiomer as well as

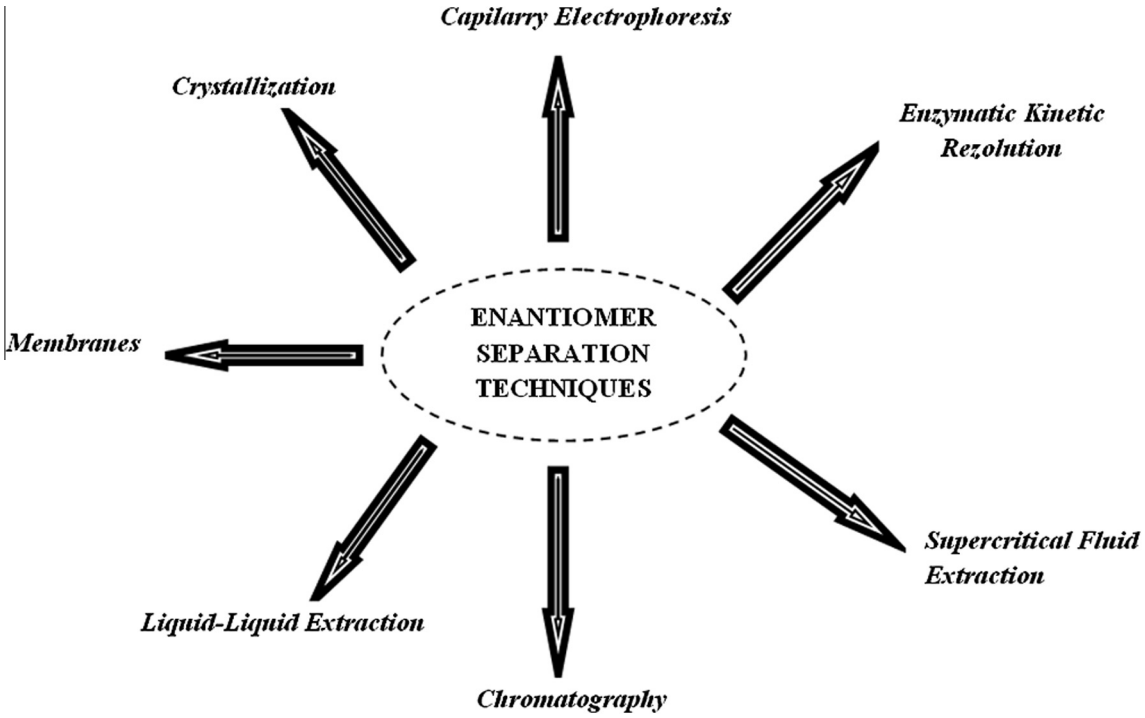

Fig. 1. Enantiomer separation techniques.