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Review

Enantioseparations in super- and subcritical fluid chromatography

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Abstract

The separation of chiral compounds by sub- and supercritical fluid chromatography has been a field of great progress since the first demonstration of a chiral separation by SFC in 1985. Almost all of the chiral selectors used in gas or liquid chromatography have been successfully applied to sub-/supercritical chromatography. Easier and faster method development, high efficiency, superior and rapid separations of a wide variety of analytes, extended-temperature capability, analytical and preparative-scale equipment improvements and a selection of detection options have been reported.

Keywords: Reviews; Enantiomer separation; Supercritical fluid chromatography; Subcritical fluid chromatography; Chiral stationary phases, SFC

Contents

1. Introduction

Chiral separations using sub- and supercritical fluid chromatography (subFC and SFC) have been a field of growing interest and success since the first report by Mourier, Eliot, Caude, Rosset, and Tambute in 1985 [1]. The interest in subFC and SFC is based on the theoretical and demonstrated advantages when compared with HPLC and fueled further by the regulatory requirements regarding the chiral purity of drugs. Chiral subFC and SFC methods, applications and new developments have been extensively reviewed in journals and books [2–21]. SubFC, SFC, and enhanced fluidity chromatography are commonly used terms to describe the use of mobile phases operated near or above the critical parameters. A discussion of chromatography from

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the mobile phase perspective providing physicochemical background and associated terminology was published by Chester [22]. Chiral subFC/SFC has been reported in packed column [1,16], open-tubular column [23], packed capillary [24], and ion-pair [20] modes. Operating conditions typically are mild, at temperatures below 40°C, affording long column lifetime (>2 years) and highly reproducible separations [25].

2. Applications

Historically, chiral subFC/SFC has been performed using capillary columns (cSFC) or packed columns (pSFC). Currently, commercial equipment is available for analytical cSFC, analytical and preparative pSFC, and packed column supercritical fluid simulated moving bed chromatography (SF-SMB). The choice of operating mode, cSFC or pSFC, is primarily an attempt to exploit different aspects of the physicochemical properties of near- and supercritical fluids and is reflected in the instrument design. Virtually all chiral separations by subFC/SFC published have used carbon dioxide as the primary mobile phase component. The advantages of using carbon dioxide as a mobile phase component have long been recognized and are very briefly summarized in the following.

Carbon dioxide, when compared with most commonly used organic solvents, is environmentally friendly, has a viscosity that is about one order of magnitude less than that of water (0.93 cP at 20°C), allowing for high flow-rates and low pressure drop. In addition, diffusion coefficients of dissolved compounds are increased by one order of magnitude (D_M(naphthalene): 0.97×10^{-4} cm^2 s^{-1} in CO_2 at 25°C, 171 bar, 0.90 g cm^{-3}), resulting in high efficiency separations due to improved mass transfer. The eluent strength can be varied by controlling the density of the mobile phase through adjusting pressure and temperature. A wider polarity range becomes available by adding organic modifiers, such as alcohols, and additives, such as acids and bases. Binary or ternary mobile phases are commonly used. More than 100 chiral stationary phases have been reported in the literature to date [26] and almost all chiral selectors used in gas or liquid chromatography have been successfully applied to sub-/supercritical chromatography. Chiral separations performed under subFC/SFC conditions reported from 1997 to 1999 are summarized in Table 1 and provide an overview of the molecular diversity of the analytes as well as the CSPs most commonly used.

2.1. Packed column SFC

pSFC is best carried out using pumps in a flow-control mode. Modern instruments have a back-pressure regulator mounted downstream of the column and the detector, allowing the user to control the pressure drop in the chromatographic system independent of the flow-rate and composition [27]. Fixed restrictors and their use with packed capillary columns/capillary columns is discussed below (Section 2.2). Detection options comprise FID, FT-IR, evaporative light scattering, UV–Vis, or hyphenated techniques such as pSFC-MS and pSFC-NMR [28]. Temperature control of column and mobile phase is achieved in a column oven allowing for operation from ambient temperature to 150°C. The analysis of thermally interconverting enantiomers under cryogenic conditions using a cooling bath has been reported [14].

Finding the best chiral stationary phase/mobile phase combination can be time-consuming. Chirbase (http://chirbase.u-3mrs.fr/chirbase/) [29], a database specializing in chiral chromatographic separations including subFC/SFC, can often aid in reducing the development effort. Guidelines for initial experimental subFC/SFC parameters have been published [12,25] and generally accepted conditions are summarized in Table 2.

The scouting process can be automated using solvent and column switching valves. Villeneuve and Anderegg [30] described the modification of a commercial instrument to incorporate a six-way selection valve and a four-way modifier selection valve to allow for the automated screening of multiple chiral columns and modifiers. Using their automated system, the authors successfully developed the optimal separation conditions for several compounds unattended within 24 h. Several authors have used as many as five different CSPs connected in series in an attempt to provide a versatile chiral separation system [10,24,31,32]. While this approach

Table 1
Chiral separations using sub-/supercritical fluid chromatography reported from 1997 to 1999

Analyte	Chromatography mode	CSP/Selector [Ref.]
Alkane	Open tubular column	Cyclodextrin containing polymer [23,24]
Amide	Open tubular column, packed capillary column	Cyclodextrin containing polymer [24], Vancomycin [58]
Amidotetralin	Packed column	Whelk-O [66]
Amine	Packed column	Whelk-O [19]
Anticoagulant	Packed column, packed capillary column	Whelk-O [19], Vancomycin [66]
Arylalkanol	Packed column	Chiralcel OB, Chiralcel OD [18], Whelk-O, Poly Whelk-O [19]
Aryloxypropionic acid	Packed column, packed capillary column	Chirobiotic V, Chirobiotic T [12], Whelk-O, Poly Whelk-O [19], Vancomycin [66]
Arylpropionic acid	Packed column, packed capillary column	Chirobiotic T, Chirobiotic V [12], Whelk-O, Poly Whelk-O [19], Vancomycin [66]
Arylsulfoxide	Packed column	Whelk-O, Poly Whelk-O [19]
Barbiturate	Packed column	Chirobiotic T, Chirobiotic V [12]
Benzodiazepine	Packed column	Chirobiotic T, Chirobiotic V [12], Chiralpak AD [36], Chiralcel OD [12,36], Chiralcel OD-H [27]
Benzothiazepine	Packed column	Chiralcel OC, Chrialcel OJ [13]
Calcium channel blocker	Packed column	Chiralcel OD [20]
Chlorohydrin	Packed column	Whelk-O, Poly Whelk-O [19]
Dinitrobenzamide	Packed column	Whelk-O, Poly Whelk-O [19]
β-Blocker	Packed column, packed capillary column	Chirapak AD, Chiralcel OD [12,36], Vancomycin [58]
Epoxide	Packed column	Whelk-O, Poly Whelk-O [19]
Hydantoin	Packed column	Whelk-O, Poly Whelk-O [19]
Imidazole	Packed column	Chiralcel OD, Chiralcel OJ, Chiralpak AD, Chiralpak AS [30]
Isoxazoline	Packed column	Chiralcel OD-H [64]
Ketone	Packed capillary column	Cyclodextrin containing polymer [24]
Lactone	Open tubular column, packed capillary column	Cyclodextrin containing polymer [23,24]
Local anesthetic	Packed capillary column	Vancomycin [58]
N-Protected amino acid/ester	Packed column	Chiralpak AD [25]
Proton pump inhibitor	Packed column	Dinitrobenzoylphenylglycine [20]

can reduce the number of experiments on individual CSPs, it also has disadvantages such as decreased enantioselectivity when compared with a single selector operated under optimum conditions [33–35]. Also, the coupling of achiral columns with chiral stationary phases was developed to address the limited achiral selectivity of chiral stationary phases [36]. Short equilibration times and rapid chromatographic separations typically are observed on cellulose- and amylose-based as well as Pirkle-type CSPs (Fig. 1) [6,7,37–40]. Sandra et al., however, report the need for 6 h equilibration time when using Chirobiotic V and Chirobiotic T as the stationary phase [12] whereas Sun and Olesik [31] obtained favorable results more recently.

2.1.1. Preparative packed column SFC

Preparative scale supercritical fluid chromatography with eluent recycling was patented by Perrut in 1982 [41–43]. A review and detailed description of a preparative SFC system, specific design and construction of the sample introduction and fraction

Table 2
Initial conditions for chiral method development on packed columns (250×4.6 mm) using modified carbon dioxide as the mobile phase [12,26]

Chromatographic Parameter	Value
Flow-rate	2.0 ml/min
Temperature	30°C
Modifier	methanol, containing 0.1% trifluoroacetic acid and/or 0.1% triethylamine depending on analyte
Modifier concentration	isocratic: 10% gradient: 5% (5 min) to 30% at 5%/min
Injection volume	5 μl
Sample concentration	1 mg/ml
Detection	UV, Diode Array

collection technology can be found in [44]. The scale-up of the analytical separation of racemic Propranolol using a Pirkle-type CSP (ChyRoSine A) and modified carbon dioxide as the mobile phase afforded a specific throughput of better than 1 g/g L h (one gram of sample per gram of stationary phase, per liter of mobile phase, per h) [27]. Other applications reported are the analytical and preparative separation of DL-flavanone by pSFC on Chiralcel OD [45] and the separation of the four optical isomers of the antidiabetic drug Troglitazone on cellulose-derived CSPs [46]. Blum et al. [47] published a comparison of cellulose-based (Chiralcel) and Pirkle-type (Whelk-O) CSPs in preparative pSFC and HPLC. The authors observed selectivity advantages for Verapamil under SFC conditions and used a 1 inch I.D. column packed with a Pirkle-type selector (Whelk-O) for the separation of a number of racemic mixtures.

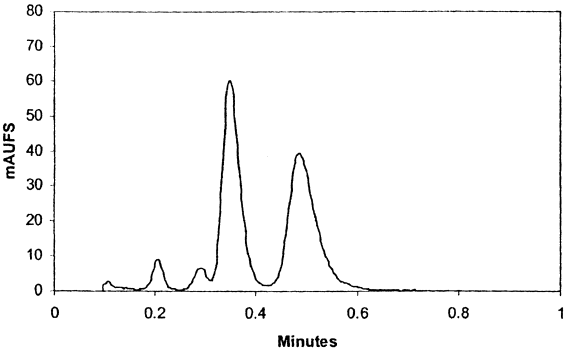

Fig. 1. Chiral separation of a development compound by subcritical fluid chromatography. Conditions: 2.0 ml/min, Carbon Dioxide modified with 10% Methanol, 200 bar, 30°C, UV detection at 228 nm, Chiralpak AD (50×3 mm) [26].

2.1.2. Supercritical fluid simulated moving bed chromatography

While preparative liquid chromatography traditionally has been carried out in batch mode, i.e. repeated cycles of injection, elution, and fraction collection, Blehaut and Nicoud reported the installation of the first industrial simulated moving bed system (SMB) for a chiral application [48], allowing the user to continually inject and collect [49–52]. It should be noted that SMB chromatography using classical mobile phases is an isocratic process. However, the use of sub-/supercritical fluids such as carbon dioxide provides an opportunity to change the solvent strength by modifying pressure and temperature. More recently, the separation of the non-steroidal anti-inflammatory drug Naproxen using a supercritical fluid simulated moving bed chromatography system (SF-SMB) was published [53]. The authors described the experimental procedures for measuring adsorption isotherms and hydrodynamics needed for the computer-aided simulation of the separation process. The computer model showed that eluent consumption could be reduced and productivity increased by applying a pressure gradient, effectively making the transition from an isocratic to a gradient operating mode [54]. A publication including experimental details is expected for the year 2000 [55].

2.2. Capillary SFC

In contrast to pSFC equipment, commercial cSFC systems appear to be gas chromatographs operated at high pressures, with the pressure/density programming taking the place of temperature programming in the GC. The major difference in cSFC instrument design, when compared with pSFC, is the use of a fixed restrictor downstream of the column. The restrictor, typically a length of silica tubing, a frit or a pinhole, restricts the massflow through the system at the pressure given by the pump. The flow-rate cannot be adjusted independently of pressure, temperature and composition without changing the restrictor. In addition, fixed restrictors have the tendency to plug, resulting in an uncontrollably changing flow-rate. Detection options are similar to pSFC and comprise FID, and other GC detectors, FT-IR spectrometer, evaporative light scattering detector, UV–Vis, or hyphenated techniques such as cSFC-MS [27]. As in pSFC, temperature control of column and mobile phase is achieved in a column oven allowing for operation from ambient temperature to 150°C.

Open-tubular columns (ot) and packed columns (pc) find application in capillary SFC. The first chiral separation performed by otSFC was published by Röder, Ruffing, Schomburg and Pirkle in 1987 [56]. Lee and coworkers [57] carried out a detailed comparison of the performance of pcSFC and otSFC columns containing the same cyclodextrin-modified polymer and observed that capacity factors can differ 10-fold within a certain range of pressure, with no significant change in chiral selectivity. Schurig and coworkers [23] linked permethylated β-cyclodextrin via an octamethylene bridge to polydimethylsiloxane resulting in the chiral polymer Chiralsil-Dex. The polymer was immobilized onto the inner surface of fused-silica capillaries or on silica particles by crosslinking or bonding. The resulting CSPs were investigated for use in GLC, open-tubular and packed column LC and SFC, and capillary electrochromatography (CEC). Other CSPs based on metal complexes, amides, amino acids, or polysaccharides were successfully used in otSFC and have been reviewed previously [6].

The on-column immobilization of the macrocyclic antibiotic Vancomycin to afford a CSP for pcSFC was published by Svensson and coworkers [58]. The authors demonstrated the impact of modifiers, additives and temperature on the enantioseparation of a variety of compounds (see Table 1 for details) and observed a complex temperature behavior resulting in nonlinear van't Hoff plots.

3. Thermodynamics and modeling

As stated by Blackwell and Stringham [59], conclusions regarding the superiority of one technique over another (SFC and normal-phase HPLC) often were limited to the model compounds used for the comparison or limitations in the experimental space investigated. In an effort to be able to make a rational choice of operating mode, the authors investigated the applicability of linear solvation energy relationships (LSERS) to the modeling of selectivity in near-critical solvent systems and studied the cumulative effects of controlling pressure, temperature, or state of the mobile phase [60]. Assuming that capacity factors can be altered without affecting chiral selectivity or efficiency [61], the experimental data suggest that optimal resolution may be obtained at low temperature and high pressure, i.e. at pressures above the critical pressure and temperatures below the critical temperature. Recently, results from the same laboratory provided an empirical relation of mobile phase modifier to chiral selectivity for a given analyte/chiral selector combination [62,63]. The authors demonstrated the predictive ability of the modeling approach using novel modifiers and chiral analytes. In a further study, Blackwell [64] reports the ''fine tuning'' of chiral resolution by using low-volatile additives at levels of 0.1–2.0 volume percent in the mobile phase. The observed effect of several acidic, basic and neutral additives on resolution was profound. Neutral compounds were affected least but the use of an additive often resulted in improved resolution. Ionizable chiral analytes were most efficiently resolved when an additive was chosen that could compete for polar sites on the CSP.

Stringham and Blackwell for the first time in SFC reported the reversal of elution order when operating the instrument at a temperature higher than the isoelution temperature [65]. At the isoelution tem-

perature, T_{iso}, the entropic and enthalpic contributions to the separation are equal. Chiral separations carried out at $T>T_{iso}$ are said to be ''entropically driven''. This approach could be helpful for the determination of optical purity in instances where the CSP is available only as one enantiomer, as it is favorable to elute the minor component first, and was successfully demonstrated for twenty six out of thirty racemic 2-amidotetralins by De Zeeuw and coworkers [66].

4. Conclusions

The majority of publications until 1994 was focused on cSFC. In recent years though, a shift to pSFC has occurred due to its applicability to a wide range of medium-polar and polar chiral compounds, especially pharmaceuticals. The ability to perform automated and unattended method development and operation coupled with short analysis time make chiral pSFC the method of choice for many practitioners working under time constraints. Its environmental friendliness is especially of interest in preparative applications. It is interesting to note that not many preparative chiral applications have been published. With the development and publication of applications, preparative SFC and SF-SMB have the potential to become an important alternative for large-scale achiral and chiral separations.

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