Journal of Chromatography A, 1250 (2012) 227–249

Contents lists available at SciVerse ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Review

Design of preparative-supercritical fluid chromatography

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ARTICLE INFO

Article history:
Available online 16 May 2012

Keywords:
Supercritical fluid chromatography
High pressure chromatography
Carbon dioxide
Design and optimization
Isotherm determination
Preparative separations

ABSTRACT

Preparative supercritical fluid chromatography (prep-SFC) is an important separation process in the chromatographers toolbox. Owing to the unique properties of the mobile phase, which is predominantly CO_2, the behavior of SFC is markedly different from high performance liquid chromatography (HPLC). This review article focuses on the scale-up of preparative chromatography. The basics of SFC, with particular focus on highlighting the key differences between SFC and HPLC, are introduced. Then, a framework for rational design of prep-SFC is proposed. This framework is based on obtaining basic system parameters from analytical scale equipment, i.e., with very small amount of material, and performing design and optimization in silico to evaluate process performance and to identify operating conditions for scale-up. The tools required to obtain the input parameters such as adsorption isotherms are discussed and the development of the design and optimization framework is elaborated. Examples from the literature which use this approach for successful scale-up are provided. Finally the design of multi-column SFC systems is discussed.

Contents

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http://dx.doi.org/10.1016/j.chroma.2012.05.037

1. Introduction

Preparative chromatography (prep-chromatography) is an important separation method that has had significant impact in several industries including pharmaceutical, food, fragrance, agrochemicals, etc. [1–5]. The particular advantage of prep-chromatography arises from the ease of scalability, robustness of the equipment and the possibility to separate a diverse set of mixtures, both binary and multicomponent. Further prep-chromatography is an example of a separation process that finds applications from scales ranging from a few micrograms to tonnes [6]. The impact of chromatography on enantiomer separation is well known [1,4]. This has been possible due to simultaneous developments in the synthesis of chiral stationary phases [7–11] and process technologies [2,12]. Several blockbuster drugs contain active pharmaceutical ingredients (APIs) that were purified using at least one chromatographic step [13–16]. In recent years prep-chromatography is starting to make impact on the separation of biomolecules, e.g., peptides, mono-clonal antibodies, etc. [17].

Prep-chromatography is routinely used for the purification from a few grams to tons/day scale. For small scales (typically up to 10 s of kg/day) single column processes and their variations are used. For larger scales, complex multi-column processes such as the simulated moving bed (SMB) and its variants are employed [1,4,18]. The choice of a process for preparative scale separations depends on several aspects, viz., as productivity, solvent consumption, complexity of design and certainly the cost of separation. A key shortcoming of chromatography is that the solutes that need to be separated are often dissolved in a solvent and injected into the column. The maximum allowable injection concentration is dictated by the solubility of the solute mixture in the solvent. Owing to the inherent nature of elution chromatography, the products are usually collected at dilute conditions compared to the feed. Hence, concentrating the solute from the product requires the evaporation of significant quantities of the solvent. This process requires energy and increases the operating costs [19–22]. While the solvent can be reused for a certain number of times, they have to be eventually disposed. They are either treated by a suitable waste-treatment process or incinerated to recover heat [23].

Reducing solvent consumption in order to make chromatographic separations more environmentally friendly and to reduce the cost of separations is the key driver in today's industrial operations [23–25]. Further, increasing cost of solvents, either owing to the increasing costs of crude oil or owing to supply shortages, e.g., the acetonitrile shortage of 2008 have pushed separation scientists to look for viable alternatives for organic solvents [26].

Supercritical fluid chromatography (SFC) which employs a compressed gas as a mobile phase has been studied since the 1960s when Klesper reported the separation of porphyrin derivatives using supercritical dichlorodifluromethane as a mobile phase [27]. While several fluids including NH_3, SF_6, etc., have been used, supercritical CO_2 (sc-CO_2) has been the most popular choice for the mobile phase. 'The advantages of using supercritical fluids can be readily appreciated by considering their physical properties. The viscosity of sc-CO_2 is in the range of ≈0.02–0.1 cP (temperature range of 30–75 °C) which is still lower than most commonly used mobile phases in high performance liquid chromatography (HPLC). This allows for higher mobile phase flow rates with moderate pressure drops. Further, the diffusion coefficients of solutes in sc-CO_2 is larger than that in organic solvents and it is possible to obtain higher efficiencies [28–32]. These properties make sc-CO_2 as a strong contender for a choice as a mobile phase. The non-toxic and non-flammable nature of CO_2 makes it an ideal choice for use in food and pharmaceutical processes.

Over the years, SFC has been developed into a mature technology both for analytical and preparative separations [5,28,30,33–36]. During the early days of the technology SFC was widely expected to replace HPLC. However, in the years that followed, it became increasingly clear that SFC, while not capable of replacing HPLC has an important role in separation sciences. The demand for chiral separations in the pharmaceutical industry, improved understanding of the fundamentals, availability of reliable instrumentation and the need to reduce operating costs and the emphasis on green sustainable chemistry in the mid-late 1990s have made SFC an attractive separation alternative.

The advantages of SFC is now well-documented and several excellent review articles and monographs have been published [5,32,33,35–37]. There are also interesting case studies that have documented the advantages of SFC over HPLC, in terms of speed, cost of operation, etc. [38]. The reader is suggested to refer to these works to obtain a background of this technology. The focus of this review is on the design aspects of preparative SFC (prep-SFC). The basics of prep-SFC are introduced and the methods of measuring fundamental properties required for the design are discussed. Advancements in numerical techniques and optimization algorithms have provided tools that can have significant impact on the design of chromatographic separations. The case for using these techniques in routine separations is made and the steps involved therein are discussed. Examples of successful applications are provided.

2. Review of SFC fundamentals

2.1. Overview of SFC

The schematic of a typical prep-SFC unit is shown in Fig. 1. The system consists of the chromatographic separation and fraction-collection modules. The CO_2 from the tank is liquified and pumped using high pressure pumps to which the modifier is added. The mixed stream is then heated to the required temperature. The sample to be separated is injected into the mobile phase and the column separates the mixture into its constituents. A back pressure regulator (BPR) is used to control the pressure in the system.