J. of Supercritical Fluids 47 (2009) 566–573

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

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

Review

Supercritical fluid chromatography for the 21st century

Larry T. Taylor*

Department of Chemistry, Virginia Tech, Blacksburg, VA 24061-0212, United States

ARTICLE INFO

Article history:
Received 12 July 2008
Received in revised form
11 September 2008
Accepted 12 September 2008

Keywords:
Supercritical fluid chromatography
Packed columns
Capillary columns
Mass spectrometry
Preparative scale separations
Simulated moving bed
Chiral separations

ABSTRACT

A brief historical review of supercritical fluid chromatography (SFC) as it pertains to open tubular (i.e. capillary) column SFC and packed column SFC is presented. Specific sections include (1) early emphasis on open tubular columns and non-polar analytes; (2) packed column SFC for separation of more polar analytes; (3) preparative scale packed column SFC. The review is completed by discussing current trends in SFC such as (a) chiral separations, (b) achiral separations, (c) simulated moving bed SFC, and (d) SFC coupled to mass spectrometry.

Contents

1. Introduction

Supercritical fluids (SF) have densities and dissolving capacities similar to those of certain liquids, but lower viscosities and better diffusion properties. Accordingly, SF used as mobile phases in chromatography should act both as substance carriers like the mobile phases in gas chromatography (GC) and also dissolve these substances like the solvents in liquid chromatography (HPLC). This chromatographic variant is known as supercritical fluid chromatography (SFC). Klesper et al. are considered to be the discoverers of SFC [1]. They described in 1962 the separation of thermo-labile porphyrin derivatives using supercritical chlorofluoromethanes at pressures up to 140 bar and temperatures from 150 to 170 °C. This method was further developed both theoretically and experimentally later by other workers in the 1960s [2,3]. Unfortunately, the development of SFC during this period was not comparable with the tempestuous growth of HPLC which occurred at about the same time. The initial major growth period

* Tel.: +1 540 231 6680; fax: +1 540 231 3255.
E-mail address: ltaylor@vt.edu.

0896-8446/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.supflu.2008.09.012

for SFC, thus, occurred approximately 20-year later in the 1980s [4].

The renaissance of SFC is generally recognized to have come in 1981–1982 with Hewlett-Packard's introduction of SFC instrumentation for packed column SFC at the Pittsburgh Conference and numerous subsequent studies by Berger [5] and Gere [6]. Concurrent with this event was the first report on the use of open tubular wall-coated capillary columns in SFC by Novotny et al. [7]. Capillary SFC, as popularized in the 1980s to almost the exclusion of packed column SFC, was practiced during this time using (1) capillary columns (50 μm i.d.), (2) a GC-like oven, (3) pure carbon dioxide, (4) a pump used as a pressure source to perform either pressure or density programming, (5) a fixed restrictor to maintain pressure in the column and to serve as an interface between the column outlet and the laboratory atmosphere, and (6) a flame ionization detector [8–10]. Historically, capillaries tended to be operated at temperatures well above the critical temperature of the fluid. Thus, this type of SFC was viewed as an extension of GC (but with a greater sample base) where some of the thermal energy required for mobilizing solutes was replaced with solvation energy. In contrast to conventional GC, capillary columns had significantly smaller inner diameters and stationary phases were more highly cross-linked. The most appropriate solutes tended to be homologous series of polymers and surfactants with moderate molecular weights up to approximately 10,000.

The reemergence of more user friendly packed column instrumentation and a switch in emphasis to more polar solutes such as pharmaceuticals and agrochemicals was delayed until the 1990s, and even then users largely relied on concepts developed in either GC or HPLC which were often inappropriate and misleading. Berger noted many times that "there are differences between supercritical fluids, gases, and liquids but they are not as dramatic as often supposed. In the final analysis, packed column SFC can be thought of as an odd form of HPLC, and furthermore, it has little in common with capillary SFC" [11]. The reader is referred to several reviews that discuss the progress of packed column SFC development during this period [12,13]. The goal of this review, however, is to briefly trace the historical development of SFC in general and to describe the current state of the art.

2. Early emphasis on capillary columns

In 1984 a patent was surprisingly issued to Brigham Young University for a technique called "open tubular supercritical fluid chromatography" although several vendors argued at the time that the work was based primarily on prior art and the patent should be declared invalid [14]. Two years later, instrumentation for capillary SFC was introduced by several vendors at the Pittsburgh Conference. The primary thrusts during the 1980s came naturally from workers in the GC field rather than the HPLC field. Thus, greater emphasis was placed on open tubular columns during that time than on packed columns. Capillary SFC experienced an explosive growth mainly due to the novel combination of supercritical mobile phases and open tubular fused silica column technology. A lengthy text was published during the period which discussed various aspects of the technology and greatly aided new workers in the field [15]. A less extensive monograph also appeared in this time frame [16]. Initially, the ability to work with longer columns which yielded greater numbers of theoretical plates was deemed to be a great advantage. In addition, GC detectors such as flame ionization, electron capture, nitrogen phosphorus, and sulfur chemiluminescence were popular with SFC. Alternatively, the flame ionization detector block (which was the most popular detector at the time) was run at 400 °C. The wide acceptance of open tubular column SFC at this point, unfortunately, did not lessen the heated exchanges between open tubular SFC users and packed column SFC users. For example, during this period, the first SFC user's meeting (SFC 1987 or the First International Conference on SFC) was held, and it focused on packed columns. The meeting was sponsored by the Chromatography Forum of the Society for Analytical Chemists of Pittsburgh. This initial meeting was followed a few months later by the 1988 Workshop on Supercritical Fluid Chromatography which was organized by Milton Lee and Karin Markides, and it focused on open tubular columns. It was anticipated by many in the audience that in the near future SFC would fully take its place in between GC and HPLC and "would prove to be a widely applicable and useful addition to chromatographic techniques" [17]. A prime issue at the time dealt with the now inaccurate notion that higher pressure drops across packed columns relative to open tubular columns would drastically worsen chromatographic resolution even at high mobile phase densities. In retrospect, the single most important factor accounting for the early emphasis on open tubular columns was probably their lack of surface activity compared to bonded silica-based packed columns with pure carbon dioxide as the mobile phase [4]. Although in some laboratories, the possibility of universal detection afforded by flame ionization was a compelling factor.

The conviction that open tubular columns were preferred over packed columns was popularly held during the 1980s even though linear velocities 10–20 times the optimum were required to achieve reasonable analysis times. Column efficiency was noted to markedly decrease with carbon dioxide density programming because flow varied with pressure and temperature using fixed restrictors which continues to be the norm even today. Nevertheless, many fantastic separations were reported employing capillary columns. Many such applications were unique, with no other viable solution. Concurrent with these experimental developments was a strong manufacturer push behind capillary methods. The initial publicity talked of SFC having all the advantages of GC and HPLC but none of the disadvantages [18]. Unfortunately, a disregard of the physical properties of the fluids and the resulting problems associated with them were rapidly discovered when attempts were made to apply the method. Furthermore, it was observed that the polarity and the solvating power of carbon dioxide are low and many analytes of interest were simply not soluble although earlier reports had postulated that dense carbon dioxide should be as polar as isopropyl alcohol [19]! In the early days (and even today), the targeted application areas of open tubular SFC are primarily in the petrochemical industry. Most pioneers from the pharmaceutical industry who tested the available instrumentation in the 1980s found the technology was very limited, if not almost useless because of its poor reproducibility and limited application range. In other words, SFC became known as a separations technique that was considered revolutionary when first introduced but whose reputation had slowly ebbed over the years. Thus, in the early 1990s the technology almost died through lack of application to more polar analytes in the pharmaceutical market [20,21].

3. Packed columns rescue SFC

The other form of SFC uses packed columns, usually binary or ternary fluids, composition programming, and a UV detector. Stationary phases have much higher surface area to void volume ratios than capillaries and are thus much more retentive. Polar modifiers (which are usually incompatible with flame ionization detection) mixed with the main fluid (CO_2) increase the solvating tendency and decrease the retention time of solutes. Once modifiers are added, mobile phase composition becomes more important than carbon dioxide pressure or density in determining retention unlike