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REVIEW

History of supercritical fluid chromatography: Instrumental development

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In the early days of supercritical fluid chromatography (SFC), it was categorized as high-pressure or dense gas chromatography (HPGC or DGC) and low boiling point hydrocarbons were used as supercritical mobile phase. Various liquids and gases were examined, however, by the late 1970s, carbon dioxide (CO_2) became the most preferred fluid because it has low critical temperature (31.1°C) and relatively low critical pressure (7.38 MPa); in addition, it is non-toxic, non-flammable and inexpensive. A prototype of a modern packed-column SFC instrument appeared in the late 1970s. However, in the 1980s, as open tubular capillary columns appeared and there was keen competition with packed columns. And packed-column SFC at once became less popular, but it regained popularity in the early 1990s. The history of SFC was of "the rise and fall." Advances in chiral stationary phase took place in the early 1990s made packed-column SFC truly useful chiral separation method and SFC is now regarded as an inevitable separation tool both in analytical and preparative separation.

[**Key words:** Supercritical fluid; Chromatography; Open tubular capillary column; Packed column; Preparative supercritical fluid chromatography; Chiral separation]

What is a supercritical fluid? It is a highly compressed gas that has a density similar to that of a liquid. Fig. 1 shows the phase diagram of a pure substance.

At the triple point (*TP*) the three phases (gas, liquid, and solid) of the substance coexist in thermodynamic equilibrium. As the temperature goes high, the substance coexists in two phases, i.e., gas and liquid. At the critical point (*CP*) and in the region the temperature and the pressure are above the critical temperature and pressure, the substance exists in a single gaseous phase. The substance in this region is defined as in the supercritical state where the density is liquid-like while the viscosity is gas-like, and the diffusivity is in between those of a liquid and a gas as shown in Table 1 (1). It is expected that a supercritical fluid, which has the higher diffusivity and the lower viscosity than a liquid solvent, will function much better than a liquid solvent as an extractant and a mobile phase in extraction and chromatography.

Chromatography that uses a supercritical fluid as the mobile phase, i.e., supercritical fluid chromatography (SFC), was first reported by Klesper et al. (2) as high-pressure gas chromatography (HPGC) in 1962, a little before the advent of high-performance liquid chromatography (HPLC). Although SFC has a history as long as or even a little longer than that of HPLC, it was not so long ago, probably in the latter half of the 1990s, when SFC was recognized as a truly useful separation method. There are a few reasons why it took such a long time. The greatest reason is the advent of HPLC. At the time of the first report on SFC, gas chromatography (GC) was already a well established method and its instrumentation was readily available from several commercial sources and researchers' interest was shifted to an analytical method that could analyze thermally labile, non-volatile or polar compounds that could not be separated by GC. Liquid chromatography (LC) has the potential to realize these requirements, however, stationary phases and instrumentation available at the time did not allow high-speed and high-efficiency analysis comparable to that of GC. And tremendous efforts were paid to the development of HPLC. Although SFC is not as versatile as LC, it too has good potential. The development of SFC was unfortunately shaded by the rapid development of HPLC that took place in the latter half of the 1960s and the 1970s.

There are two important review articles on SFC, one published in 2009 by Taylor (3) and the other in 2011 by Guiochon and Tarafder (4). Taylor (3) overviewed various techniques in SFC and put them into a compact and comprehensive article. Guiochon and Tarafder (4) covered every aspect of SFC including theoretical and empirical treatments of physicochemical properties of high temperature and high-pressure fluids, even including thermodynamics and the equations of state. Their article is roughly 77 pages and could be a small monograph. The author recommends the readers to read these review articles for an in-depth understanding of SFC. In this article, the author covers mainly a history of instrumental development that was partially discussed in the above reviews.

Fig. 2 shows the number of articles on SFC published each year from 1962 to 2012. In the 1960s, the number is very small and does not chart as well relative to the later years. In the 1970s, the number varies but not more than 30 per year. However, in the 1980s, the number exponentially increases from 15 to over 400 in a decade. In

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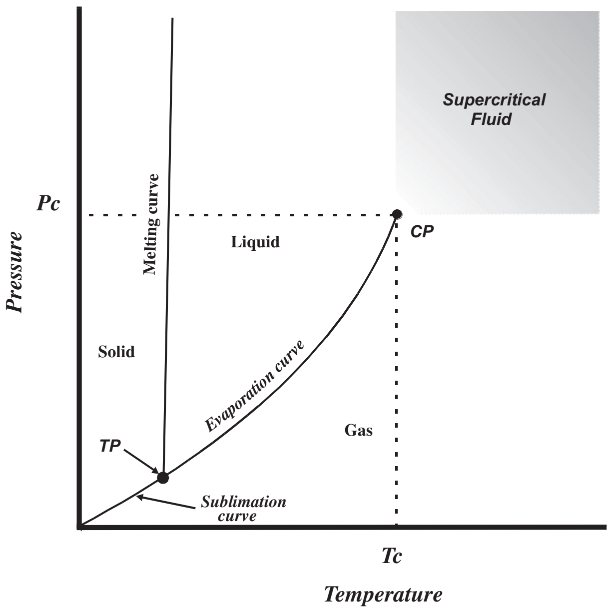

FIG. 1. Phase diagram of pure substance. *TP*: triple point; *CP*: critical point; P_c: critical pressure; and T_c: critical temperature. These parameters are specific to each substance. Reproduced from Saito et al. (47) with permission of John Wiley & Sons, Inc.

the 1990s, the number is somehow saturated at around 500–600. Then, it rapidly increased again in the first decade of the 21st century.

EARLY WORKS IN HIGH-PRESSURE GAS CHROMATOGRAPHY (HPGC) OR DENSE GAS CHROMATOGRAPHY (DGC)

Works of early pioneers In the early days, presently accepted terminology “supercritical fluid chromatography (SFC)” for the method was not established, and various terms were used such as (ultra) HPGC and dense gas chromatography (DGC).

The first report on SFC by Klesper et al. (2) appeared in the Communications to the editor section of Journal of Organic Chemistry in 1962. It is a brief report, less than 2 pages. They indicated thermally labile porphyrin mixtures were separated on polyethylene glycol stationary phase with two mobile phase gases such as dichlorodifluoromethane ($T_c = 112°C$) and monochlorodifluoromethane ($T_c = 96°C$) at temperatures of 150–170°C. They also stated “above 1000 psi (7 MPa) with the first and 1400 psi (9.8 MPa) with the second, vaporization increased with increasing gas pressure”, indicating that porphyrins were dissolved in the supercritical mobile phase. In addition, they foresaw the possibility of preparative SFC by stating “the porphyrins could be recovered at the outlet valve.”

Sie et al. (5–8) published a series of articles on HPGC in 1966 and 1967. They used supercritical carbon dioxide as the mobile phase and discussed fluid–solid and fluid–liquid separation modes. It should be noted that they developed a sophisticated pneumatically operated injector in order to inject a sample under high-pressure and high-temperature conditions. It is also unique that they used a UV absorption detector with a quartz cell that was equipped with a gas–liquid separator and detection was carried out under atmospheric pressure. Both devices did not survive, however, the author thinks it is worth mentioning these pioneering works.

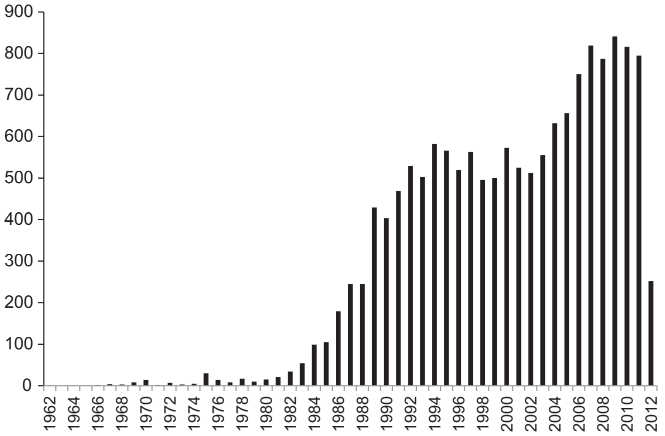

FIG. 2. Numbers of publications on supercritical fluid chromatography. Based on a Google Scholar search performed on July 2, 2012.

Sophisticated instrumentation developed in the late 1960s In 1968, Klesper’s group reported a new SFC system (9). The system was equipped with a mechanical backpressure regulator that could control the pressure independent of the flow rate. The detector was a filter photometer with a high-pressure flow cell. It should be noted that the detector used in HPLC at that time was a simple single-wavelength photometer with a low-pressure Hg discharge lamp as the light source which emits UV light at 254 nm (10). In 1968, vacuum tubes were still in use and the transition to transistors had just begun. Therefore, the author believes that the system consisted of a sophisticated analog servo system with vacuum tubes. It is remarkable that a prototype of a modern packed-column SFC appeared more than 40 years ago.

In 1969, Giddings et al. (11) reported DGC. In the article they stated “One of the most interesting features of ultra-high-pressure gas chromatography would be its convergence with classical liquid chromatography. A liquid is ordinarily about 1000 times denser than a gas; at 1000 atm, however, gas molecules crowd together with a liquid-like density. At such densities intermolecular forces become very large, and are undoubtedly capable of extracting big molecules from the stationary phase. Thus in effect, non-volatile components are made volatile.”

The first sentence seems to imply the unified chromatography that was later realized and reported by Ishii et al. (12) in 1988 and more recently by Chester and Pinkston (13). The latter part of the paragraph describes solvation of a solute in a supercritical fluid. This phenomenon was investigated and well elucidated by Kim and Johnston (14) in 1987 and Kajimoto et al. (15) in 1988. Their works will be explained later.

TABLE 1. Properties of gas, liquid and supercritical fluid.[a]

Property	Units	Gas 1 atm, 25°C	Liquid 1 atm, 25°C	Supercritical fluid	
				Tc, Pc	*Tc, 4Pc*
Density	ρ (g cm^{-3})	$0.6–2 \times 10^{-3}$	0.6–1.6	0.2–0.5	0.4–0.9
Diffusivity	D_m (cm^2 s^{-1})	$1–4 \times 10^{-1}$	$0.2–2 \times 10^{-5}$	$0.5–4 \times 10^{-3}$	$0.1–1 \times 10^{-3}$
Viscosity	η (g cm^{-1} s^{-1})	$1–3 \times 10^{-4}$	$0.2–3 \times 10^{-2}$	$1–3 \times 10^{-4}$	$3–9 \times 10^{-4}$

[a] After Takishima and Masuoka (1).