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REVIEW

Current trends in supercritical fluid chromatography

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Abstract

Supercritical fluid chromatography (SFC), which employs pressurized carbon dioxide as the major component of the mobile phase, has been known for several decades but has faced a significant resurgence of interest in the recent years, thanks to the development of modern instruments to comply with current expectations in terms of robustness and sensitivity. This review is focused on the recent literature, specifically since the introduction of modern systems but in relation to older literature, to identify the changing trends in application domains. Typically, natural products, bioanalysis, food science, and environmental analyses are all strongly increasing. Together with reduced extra-column volumes in the instruments, the advent of sub-2-μm particles and superficially porous particles in the stationary phases is favoring ultra-high-performance SFC (UHPSFC) allowing for improved resolution and faster analyses, but without the constraints of viscous liquids encountered in ultra-high-performance liquid chromatography (UHPLC). Hyphenation to mass spectrometry is also more frequent and opened the way to new application domains, and raises different issues from liquid chromatography mobile phases, especially due to decompression of carbon dioxide. It is also shown that the frontiers between SFC and HPLC are fading, as switching from one method to the other, even within the course of a single analysis, is facilitated my modern instruments. The present review is not intended to be exhaustive but rather giving a snapshot of recent trends in supercritical fluid chromatography, based on the observation of about 500 papers published in English-written peer-reviewed journals from 2014 to 2018.

Keywords Convergence chromatography · Hyphenation to mass spectrometry · Supercritical fluid chromatography · Ultra-high-performance supercritical fluid chromatography

Introduction

As names may be deceiving, modern supercritical fluid chromatography (SFC) does not necessarily employ a supercritical fluid as mobile phase [1]. Early developments in the technique employed several different fluids in their supercritical state (with both pressure and temperature above the critical values) [2], namely, fluorocarbons, ammonia, or carbon dioxide were most often employed. Among all possible fluids, carbon dioxide is the only one to have survived significantly through the ages, for several excellent reasons:

(i) the critical values of pressure and temperature are moderate (7.3 MPa and 31 °C);
(ii) it has interesting features for health and safety, being non-flammable, non-corrosive, and with limited toxicity;
(iii) it is cheap as is obtained as a side-product from many industries; it can be recycled when large amounts are necessary (at preparative scales);
(iv) it is miscible to most organic solvents, allowing for wide possibilities to optimize chromatographic separations and dissolve a wide array of analytes.

Indeed, while early developments principally reported one pure fluid in the supercritical state, modern SFC employs mixtures of carbon dioxide and co-solvents as mobile phase. This mixture is not necessarily a supercritical fluid, as pressure may be above the critical pressure while temperature is often below the critical temperature [3]. This is not causing any issues to the chromatographers, as the advantages of supercritical fluids are retained: the mixed fluid has a lower viscosity than usual liquids employed in high-performance liquid chromatography, which has a number of interesting consequences: high flow rates may be employed as pressure restrictions are

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less significant than with liquids, and analyte diffusivity is high. These features combined together allow for fast and highly efficient separations.

While most people practicing this technique wish to retain the name of supercritical fluid chromatography, some publications may refer to the same technique with other names (subcritical fluid chromatography, convergence chromatography, etc.). In this review, no distinction will be made among them as there is no fundament to distinguish them.

Recent instrumental developments

The recent resurgence of SFC is majorly due to the introduction of modern instruments. Prior to the years 2010s, most systems available had significant defects that rendered them unfit for current expectations of the analytical scientists. Most importantly, they had limited robustness causing poor reproducibility of the analyses, extra-column volumes were high, yielding significant extra-column band broadening, and baseline noise with UV detectors (most frequently used at that time for all sorts of applications) was too high to reach the low detection limits that are desired for pharmaceutical, clinical, or environmental applications. In chromatography laboratories, where ultra-high-performance liquid chromatography (UHPLC) had rapidly developed in the years 2000s, such defects were strongly felt. Then, a number of major chromatography manufacturers (Agilent, Waters, Jasco, and Shimadzu) released improved systems addressing the abovementioned defects [4, 5], so much so that the performance of modern SFC is now very near that of UHPLC.

Hyphenation to mass spectrometry (MS) has been largely facilitated (as will be further discussed in the fundamental research section below), so much so that MS is now by far the most employed detection mode, appearing in two thirds of the papers published in the years 2014–2018.

An interesting recent development is the on-line coupling of supercritical fluid extraction (SFE) to SFC. SFE has long been a favorite in the field of natural products [6] but most of the time, the extracts were analyzed with gas chromatography (GC) or UHPLC. However, when a fluid is good for extraction, it seems logical that it should also be good for the separation of the extracted analytes as solubility is ensured. Shimadzu has thus recently released a system allowing for on-line SFE-SFC-MS. Transferring the extracted analytes from the SFE cell to the SFC chromatographic column is achieved with a trap column so as to re-focus the analyte band prior to elution through the chromatographic column. The stationary phase employed in the trap column must be adapted depending on the target analytes. Another possible interface could be based on a split-flow introduction system proposed by Bamba and co-workers [7]. A few papers have been published to illustrate the benefits of the SFE-SFC-MS system in the field of natural products analysis to extract interesting bioactive components from food products [8, 9] or to extract contaminants from soil [10]. Other applications have appeared for bioanalysis, where lyophilized bacteria, dried urine, or dried serum spots were extracted to analyze metabolites or biomarkers [11–13]. This original hyphenated system should thus find use in many different application areas in the future.

Besides, the combined use of conventional liquids and carbon dioxide-based mobile phases is especially interesting as reversed-phase HPLC and SFC conducted on polar stationary phases are often found to be highly orthogonal. While several examples exist to illustrate the interest of off-line combination of LC and SFC separations [14, 15], commercial hyphenated systems are desirable that would allow for improved quality of separation. No commercial solution is available yet but a few examples have appeared in the literature to illustrate the benefits and difficulties of such combinations [16–20]. Two-dimensional SFC × SFC would be equally desirable, as changing stationary phases polarity in SFC allows for tremendous changes in separation selectivity; thus, SFC can be said to be orthogonal to itself. However, while neat carbon dioxide offers facilitated solutions (comparable to those employed in GC × GC) [21], practical solutions offering the possibility to use more complex mobile phases would be desirable to extend the application range of such devices [22].

Recent developments in stationary phases

Concomitantly to the development of modern instruments, several column manufacturers producing stationary phases for liquid-phase chromatography started to develop novel stationary phase chemistries designed for SFC use and sometimes improved packing procedures to take account of operating pressures and of the chemical nature of the SFC mobile phase. For instance, in addition to hybrid silica previously developed to sustain ultra-high pressures in liquid chromatography, special bonding chemistry on silica particles was developed by Waters to ensure that retention would not degrade over time with the formation of silyl ethers [23, 24]. Regarding stationary phase chemistries, a large variety of stationary phases, from the most polar silica to the least polar well-endcapped or densely bonded alkyl-bonded silica, is now available [25] allowing for a diversity of selectivities. In the most recent papers (2016–2018), it appears in Fig. 1a that the most frequently cited stationary phase in achiral analytical applications (nearly a quarter of them) is a 2-ethylpyridine-bonded silica phase (2-EP). This stationary phase chemistry was first introduced by Princeton Chromatography in the years 2000s and was always very successful, especially for applications involving the analysis of basic compounds. It was later imitated by other manufacturers. The second most frequently used phase is bare silica (or hybrid silica) in 20%

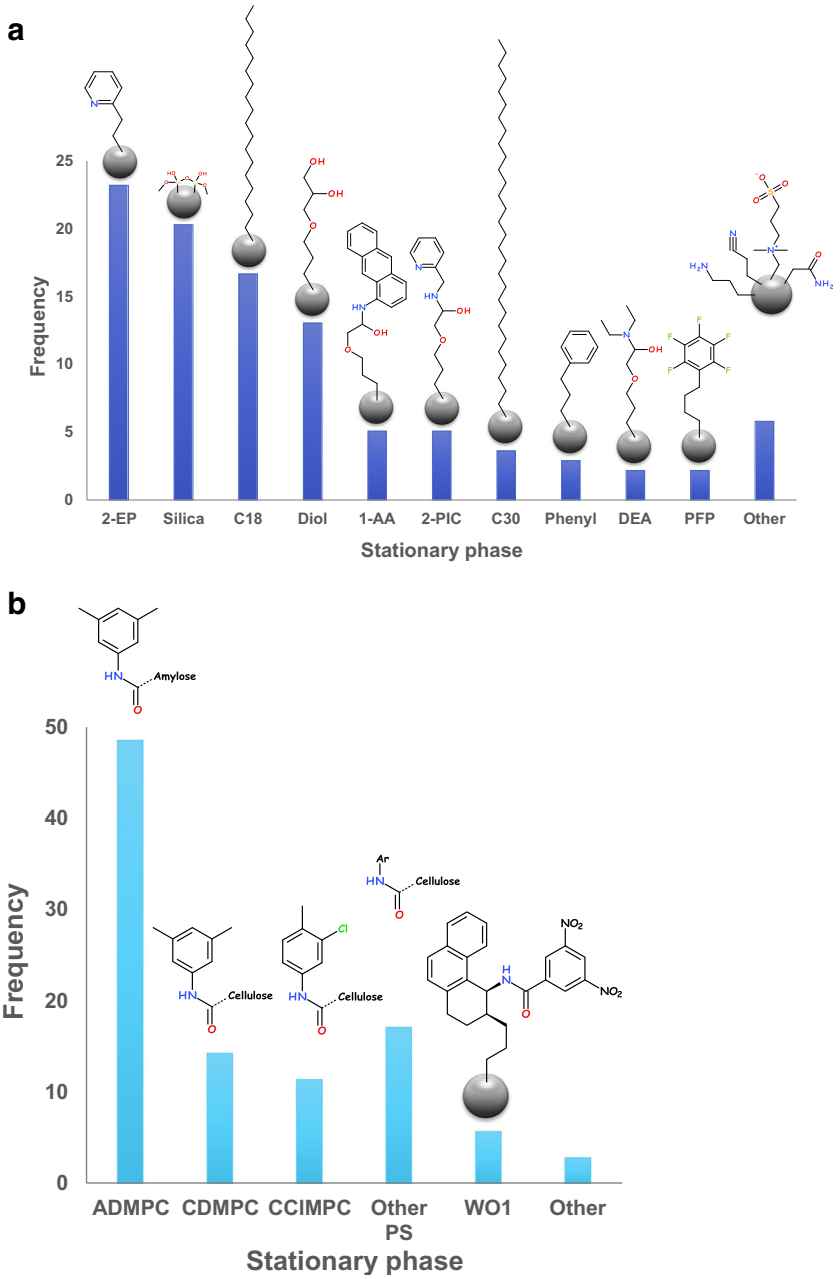

Fig. 1 Frequency of use of stationary phases with chemistries, for analytical applications of SFC observed in the years 2016–2018. **(a)** achiral applications and **(b)** chiral applications (see text for further details). Based on Scopus search conducted in April 2018

achiral applications, followed by octadecyl-bonded silica (C18). The latter is often employed in the analysis of lipids [26–29], when intra-class separation is desired (according to carbon chain length and double bonds) but has been found to be useful in many other applications like phthalate esters [30], polyaromatic hydrocarbons [31], pesticides [32], or drug candidates [33]. The fourth most frequently cited stationary phase is a diol-bonded silica, which was, for instance, often selected in the analysis of natural products [34–37], but also for lipidomics when a separation based on the polar head is desired [38, 39], or in bioanalysis [13, 40]. Other frequently cited phases are 1-aminoanthracene (1-AA) that may be used for fat-soluble vitamins [41]; 2-picolylamine (2-PIC) that is a recent variation of the 2-EP; triacontane-bonded silica (C30), which was often employed for the separation of carotenoid pigments [8]; phenyl-bonded silica; diethylamine-bonded silica (DEA) [42], and pentafluorophenyl-bonded silica (PFP) [43]. Many other stationary phases have been employed, with a short selection of them appearing in Fig. 1 (for instance, aminopropyl-bonded silica [44], cyanopropyl-bonded silica, amide [45] or sulfobetaine [46, 47]). As the screening of stationary phases is usually the first step in developing a method in achiral SFC, diversity of stationary phase chemistry is highly desirable and should still progress in the years to come.

For chiral applications at the analytical scale (Fig. 1b), modified polysaccharide stationary phases are the most often

used with amylose *tris*-(dimethylphenylcarbamate) (ADMPC) being cited in about half the analytical applications. Cellulose *tris*-(dimethylphenylcarbamate) (CDMPC) and cellulose *tris*-(3-chloro-4-methylphenylcarbamate) (CClMPC), and several other sorts of modified polysaccharides were employed in recent papers. The Pirkle-type phase WhelkO-1 was also present in recent studies [48], especially as it is now available with sub-2-μm particles.

Similarly to the evolutions seen in high-performance liquid chromatography, smaller particle size (inferior to 2 μm) [49] and superficially porous particles [50–52] were both introduced to SFC practice. For chiral stationary phases, the switch to smaller particles is more recent and has thus not been seen in many papers yet. The different trends in particle size stationary phases can be observed in Fig. 2, where it appears that achiral analytical-scale applications are now majorly conducted on sub-2-μm stationary phases (77% in the most recent publications, years 2016–2018) while chiral separations are still essentially conducted on larger particle sizes (2.5, 3, and 5 μm).

The joint use of efficiency-optimized instruments and modern stationary phase technologies is producing ultra-high efficiency separations [53] in what is often termed now "ultra-high-performance supercritical fluid chromatography" (UHPSFC). As mentioned in the "Introduction", the low viscosity of the fluids employed in SFC causes less pressure issues than the liquids employed in UHPLC. Thus, current SFC systems have pumping pressure limits of 40 to 66 MPa, depending on the manufacturer. For instance, a 40-MPa upper pressure limit allows the use of a 100 × 3.0 mm column packed with 1.7-μm particles at 1–2 mL/min (depending on operating parameters). Obviously, a higher pressure may still be desirable when large proportions of co-solvent are desired,

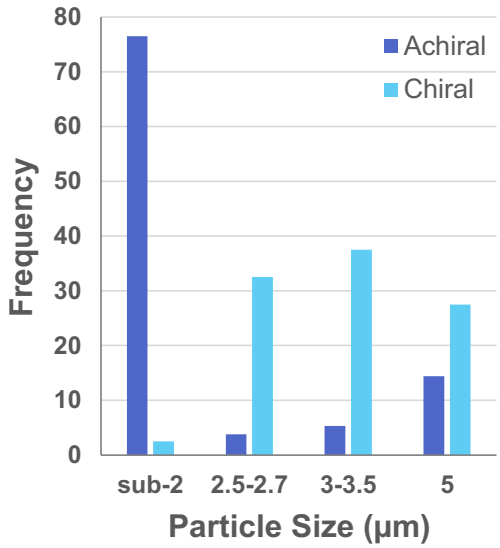

Fig. 2 Frequency of use of stationary phases with different particle sizes, for analytical applications of SFC observed in the years 2016–2018. Based on Scopus search conducted in April 2018

or if higher flow rates or longer column lengths would be necessary for faster analysis or for higher efficiency. Typical column lengths employed are mostly in the 100–150-mm range (about 90% of the analytical applications), with rare examples of shorter columns for faster analysis [54–56] (for instance when the SFC separation must be the second dimension of a two-dimensional chromatographic system [17, 18]), or longer columns for higher efficiency [57]. In this respect, superficially porous particles offer the extra advantage over fully porous particles to allow for much longer column lengths without creating so much pressure drop [50, 58].

Who is publishing SFC science?

Reviewing the recent literature, from 2014 to early 2018, about 500 papers, majorly referenced in Scopus database, were examined in preparing this article, taking all sorts of papers into account (fundamental research, applications, or reviews). This is not an exhaustive search, as, for instance, only papers published in English were reviewed. Spanning on a large number of publishers, the observations presented here should however be representative of the overall SFC production. Several features of this production were examined to gain a clear view of current SFC chromatographers.

First, the geographical origin of the corresponding author was noted. A heat map representing the proportion of papers published per country is presented in Fig. 3. It appears that the USA and China are the two major sources of SFC science, with about 23 and 18% papers reviewed respectively. China would probably have a higher share if papers published in Chinese had also been counted. This observation is especially interesting when related to the fields of applications, as will be further discussed below. From Asian countries, another significant part of the production is issuing from Japan (5% of the total) and, to a lesser extent, from India (2%). Europe is actually the first major region for SFC-related articles, with 45% papers originating from this area. In Europe, most active countries are France (10%), Belgium (6%), Sweden, and Switzerland (5% each). Not far behind is Czech Republic (4%), followed by Germany, Austria, and Italy (about 2% each).

Secondly, another feature of the authors was observed; this time taking all authors into account, the academics, industry users, or manufacturers were observed (Fig. 4). Not surprisingly, academics make up the largest part of the production, with 71% papers being produced solely by academic institutions. Industry users are thus still present, with 17% papers produced solely by industry chromatographers. Eight percent of the papers were produced by academics and industry chromatographers working together. Finally, manufacturers were little present with 1% papers produced by manufacturers only, and 3% by collaborations between academics and manufacturers. Possibly, taking account of application notes would

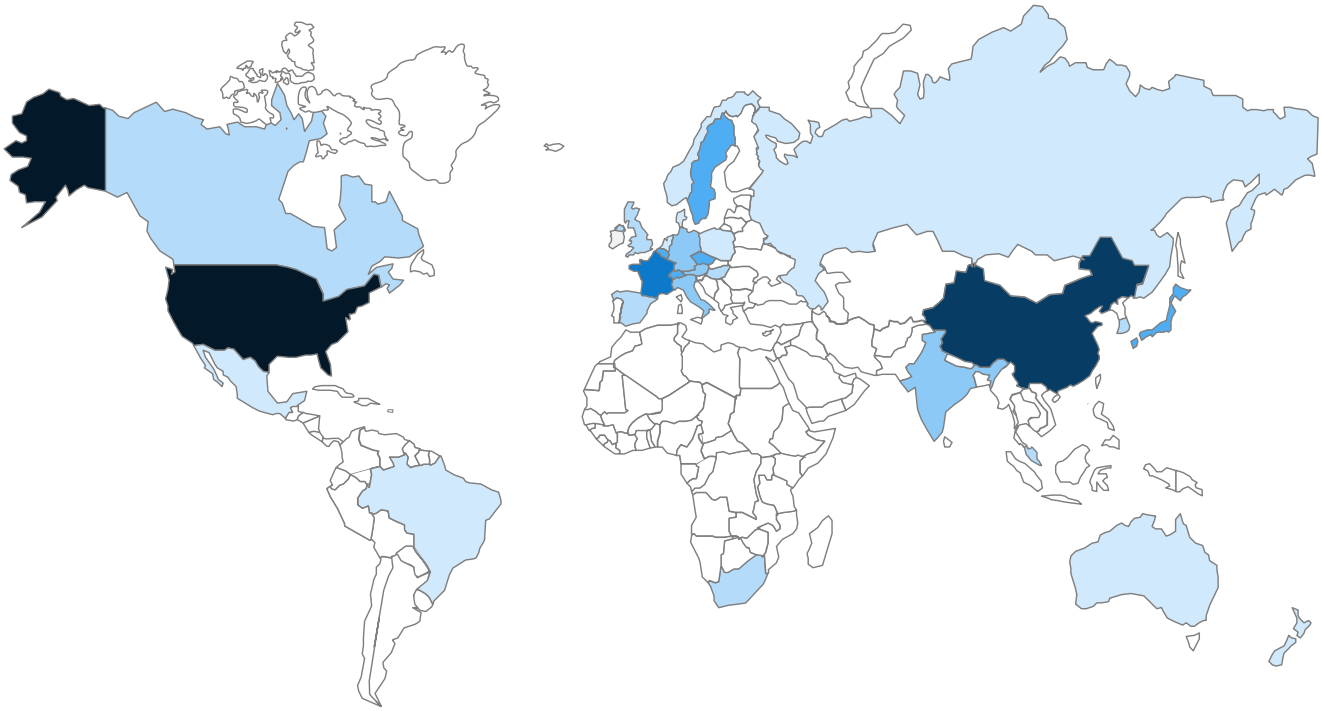

Fig. 3 Geographical origin of the authors of articles related to supercritical fluid chromatography published in the years 2014–2018. Based on Scopus search conducted in April 2018

increase the share of manufacturers, but as these are mostly published on the manufacturer's websites and not in peer-reviewed journals, they are not referenced by major bibliographic search engines and were not counted to prepare this review. These proportions have changed over time. Understandably, in the early years of SFC developments, in the 1980s and 1990s, academics were the major producers of SFC research. But in the years 2000s, when university researchers had deserted the field, the portion of industry papers was more significant, reaching as high as 35% contribution. It may be taken as a good sign that university chromatographers are again investing the field, as the fundamental understanding of the technique still requires some work.

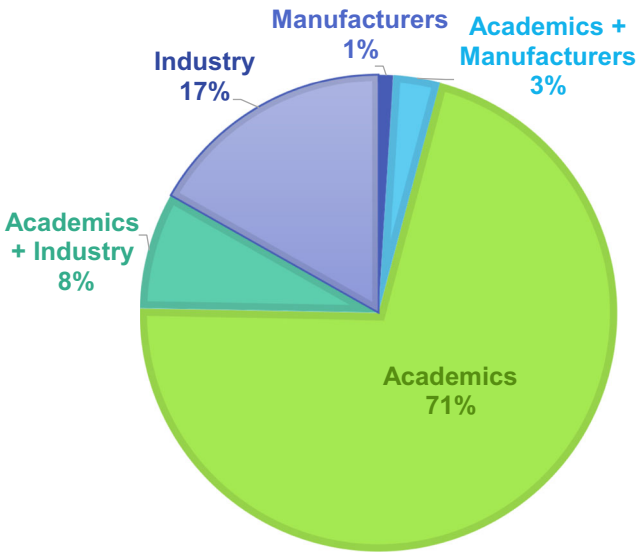

Fig. 4 Job origin of the authors of articles related to supercritical fluid chromatography published in the years 2014–2018. Based on Scopus search conducted in April 2018

Fundamental studies

From the beginnings of SFC to the years 2000s, the part taken by fundamental papers was essentially decreasing, which seems rather logical as early developments of a technique require fundamental investigations prior to clever applications. The renewal of the technology has brought a surge of new fundamental studies. They now make up about 20–25% of the articles published in the years 2014–2018. Note that the frontier between fundamentals and applications is not always easy to trace, hence the imprecision in the statistics.

Apart from instrument developments described above, fundamental studies are mainly related to the following topics.

(i) Efficiency issues [59–63] and the best means to evaluate efficiency were mostly investigated in the years 2012–2014, when new instrument technologies were released, but are now less explored. Extra-column band broadening is however still a concern, and should be addressed by further improvements in systems [53, 62, 64, 65].

(ii) Injection and dilution solvent effects at the analytical scale [62, 66, 67] or preparative scale [68] are a concern to avoid peak deformation that may be due to limited

miscibility of the diluent solvent and the mobile phase (especially at the beginning of a gradient elution program where carbon dioxide proportion may be high) and to avoid viscosity mismatch causing viscous fingering. While this was long a concern at the preparative scale, it has most recently been explored also at the analytical scale.

(iii) Several mobile phase-related issues have been explored, namely, the adsorption of mobile phase components on stationary phase [69] and its effect on peak shapes [70–73]; the effects of additives (acids, bases, salts) on chromatographic quality in achiral or chiral modes [74–77]; and the acidity caused by carbon dioxide coming into contact with water or alcohols [78, 79].

(iv) Stationary phases have been explored for their durability [23, 80] and selectivity (achiral or chiral separations) [24, 25, 81], and have been compared to liquid-phase behavior [82, 83]. The interest of combining two stationary phase in tandem column systems was also investigated [84, 85].

(v) Retention behaviors in SFC, both in achiral [86] and chiral [77, 87, 88] modes, are still a matter of interest. In addition, retention modeling [89–91] is desirable to facilitate method development with computer-assisted processes and compound identification in complex samples. As tendency curves relating retention to mobile phase composition or operating parameters (temperature, pressure, flow rate) are usually not linear over a large range of conditions (and sometimes not even monotonous), modeling retention is not as straightforward as it may be with GC or reversed-phase HPLC.

(vi) Preparative scale has been the major topic of a series of papers from the group of Fornstedt [92, 93], inspired by a seminal paper from Guiochon and Tarafder [94]. In particular, transferring methods between analytical and preparative scale [95–97] is also setting some additional problems as compared to liquid-phase scaling up, due to compressibility of the fluid.

Finally, the hyphenation to mass spectrometry (MS) has been the topic of many recent studies. First, the ways of hyphenating the chromatographic system to the mass spectrometer have experienced many changes over the years [98, 99], partly due to the fact that the preferred ionization source has changed (from atmospheric pressure chemical ionization APCI to electrospray ionization ESI) [100]. Most recently, a new design of atmospheric pressure ionization source was introduced called UniSpray and was evaluated for the analysis of 120 natural compounds [101]. This source was found to provide improved sensitivity to certain classes of analytes, and decreased sensitivity for others, when compared to ESI. Secondly, it was shown on several occasions that the MS response may vary depending on the SFC mobile phase composition, even though a make-up fluid is most often introduced prior to the MS [74, 102, 103]. Akbal and Hopfgartner thoroughly investigated the effect of post-column addition on 20 analytes belonging to different classes (beta-blockers, HIV protease inhibitors, steroids, and polar metabolites), with variations of make-up flow rate, solvent composition, pH level, and buffer concentration. They concluded that the introduction of ammonia in the make-up fluid was useful, especially when it was not previously introduced in the chromatographic mobile phase. Ammonia would perhaps counteract the acidification of the mobile phase by carbon dioxide. In addition, dimethylsulfoxide (DMSO) was found to be particularly useful in enhancing SFC-ESI-MS response. The post-column addition may also be advantageously employed to favor ionization of certain species, as was demonstrated by Touboul and co-workers with the use of lithium iodide to favor the detection of acetogenins [104]. Finally, matrix effects are a very significant topic, especially when analysis of complex biofluids (urine, serum etc.) is concerned. In particular, Haglind et al. [105] indicated that the abundant presence of alkali ions (sodium and potassium) in biological fluids (plasma and urine) was causing major ion suppression for the analytes co-eluting with them. Sample preparation to get rid of these ions, or adjustment of chromatographic conditions could both be successful strategies to avoid these complications. Comparing matrix effects between SFC-MS and GC-MS [55] is generally to the advantage of the former, while comparing SFC-MS and LC-MS shows that both of them may be positively or negatively impacted by matrix effects [106–108].

Application domains

While the number of fundamental studies has increased only moderately in the recent years, application papers have faced a tremendous increase. Meanwhile, the trends in application domains have greatly changed. Figure 5 presents the most significant application domains. In addition to the expansion of SFC technology, the increased accessibility to mass spectrometers has favored SFC-MS application to new domains, where simpler, less informative detections modes like UV are not considered sufficient. Therefore, while SFC-MS studies in 2014 represented about 35% of analytical applications, they have reached 75% in 2017.

Only 10 years ago, about 75% of the papers related to SFC concerned the pharmaceutical industry, either for analysis or purification of synthetic drugs [109, 110], mostly in chiral separations. In 2014, still 40% of the analytical applications were related to this topic. Considering the 2014–2018 years, the analysis of chemical pharmaceuticals (as opposed to natural products) is now only the third application domain in terms of number of papers published (Fig. 5). Possibly,

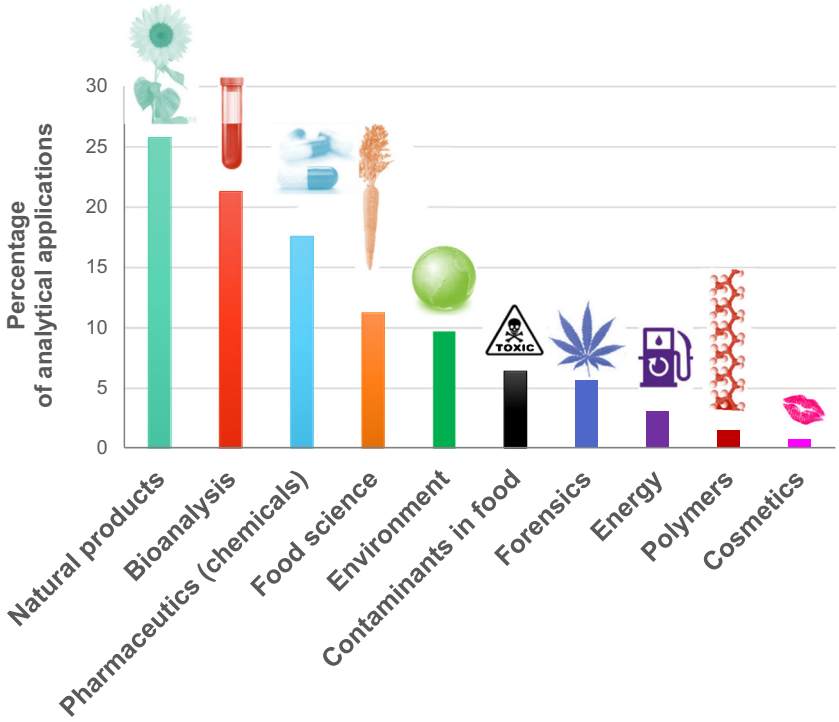

Fig. 5 Application domains for analytical applications of supercritical fluid chromatography published in the years 2014–2018. Based on Scopus search conducted in April 2018

because pharmaceutical analysis with SFC has been explored for a long time, there are perhaps less expectations in this area than in other, less investigated domains. However, there are still interesting features to explore with modern SFC of pharmaceutical products. Most importantly, the capability of analytical SFC or UHPSFC to comply with the requirements of good manufacturing practice (GMP) [111] and to obtain methods that can be validated [42, 112] according to the recommendations of the International Conference of Harmonization (ICH) are the topic of several recent studies. This is especially important in order for the technique to spread in quality control laboratories. Other concerns in this field are related to the determination of generic conditions to achieve analytical separations of chemical or chiral impurities with minimal effort [33, 74, 113] or to the acceleration of analysis, either through ultra-fast separations [114–117] or through multiple injections within a single run [118], in cases when large numbers of samples must be analyzed within a short time. Apart from active pharmaceutical ingredients and impurities, other components of drug formulations or contaminants have been analyzed like polymers [119] and plasticizers issuing from plastic medical devices [120]. In the future, it may be expected that the analysis of full drug formulations will be seen, because SFC is equally capable to handle polar, non-polar, ionic [121], small and large chemical species.

While chemical and enantiomeric analyses of drug compounds are not as significant as they used to be, chemical pharmaceuticals still explore in pharmacokinetic studies, in urine, or in plasma samples. Thanks to SFC-MS expansion [122], the years 2014–2018 have seen a strong increase in bioanalysis applications [123], which are now the second most important application domain for SFC. Pharmacokinetic studies constitute about a half of these bioanalysis studies. The other half comprises forensic applications (doping agents [40, 108] or drugs of abuse [124–126]), and a significant portion of lipidomics [127–131].

Another portion of pharmaceutical applications may be found in the "natural products" section. As pointed out above, China is now one of the most productive countries regarding SFC publications. However, traditional Chinese medicine (TCM) is based on natural products. China has started the huge project of investigating these natural products in more details to improve knowledge on the bioactive species. This task requires several high-performance separation methods with orthogonal selectivities in order to achieve the broadest picture of these TCM. In this respect, SFC has a natural place next to reversed-phase liquid chromatography, of which it is generally found to be complementary [56, 132]. Also for quality control of TCM, modern SFC has found its place [133]. Similarly, natural products are being (re-)examined in occidental medicine and their SFC analysis has produced several publications [134]. The variety of structural families having been explored in this field is an excellent example of the versatility of the technique. Indeed, while it had been known for a long time that lipids [29, 50, 135] or carotenoid pigments [136–141] were well soluble in pressurized carbon dioxide mobile phases, other molecular families have been observed in recent papers such as alkaloids [37, 132, 142, 143], anthraquinones [144, 145], coumarins [146, 147], furostanol saponins [36], triterpenoid saponins [148], flavonoids [43, 149],

carbohydrates [45, 150, 151], or nucleobases and nucleosides [152]. Some papers related to medicinal cannabis have also shown that SFC can be an interesting complement to UHPLC for this fast rising application field [48]. The variety of possibilities is now making natural products the first application domain for analytical SFC (Fig. 5). Natural products have also been a significantly growing field at the preparative scale [35, 37, 153–162], not only at the analytical scale. In addition to the above examples of structural families, purification of lignans [14] and polyphenols [163] with preparative SFC has been demonstrated.

Natural products are also a part of the food science application domain, which appears as the fourth most significant at the analytical scale. Most papers in this field relate the analysis of lipids (not only in vegetable oils but also in milk products [164, 165]), carotenoids and lipophilic vitamins [41, 166].

The food industry is increasingly concerned with contaminants, which may issue from packaging [167], drug residues from contaminated irrigation or, most frequently, pesticides. Here again, China has been the most productive in the investigation of the latter.

Pesticides (along with other contaminants) may also be looked for in soils [168–174], water [46], or wastewater [175, 176], thereby belonging to the field of environment applications. Other environmental applications were observed with the analysis of emerging contaminants in aqueous ecosystems [177], allergenic textile dyes [178, 179], flame retardants [180], and halogenated pollutants [181, 182].

Petroleum products have been a classical application domain for SFC for a long time [183]. As petroleum components have limited polarity, it is feasible to analyze them with neat carbon dioxide and thus maintaining compatibility to GC-like detectors (typically flame ionization detector). However, the field of energy is changing with the growing introduction of biomass-related products. Biodiesel is a new type of energy source requiring deep investigation. In conjunction with other chromatographic methods, SFC may furnish interesting information in the composition of such samples [184–186].

A small portion of papers related to cosmetic applications is emerging [187, 188]. The cosmetic industry is currently highly demanding of natural ingredients produced with environmentally friendly solvents and processes, which should naturally place SFC as a favorite method in this field.

Finally, a word should be said regarding the relative proportions of achiral and chiral separations. While chiral separations used to be the major application field for SFC, it is no longer the case, with only 20% of the analytical applications related to chiral separations in the years 2014–2018. However, analytical chiral SFC is still in use especially to measure the enantiomeric excess of synthetic compounds [189, 190], in pharmacokinetic studies [191, 192], to assess the fate of chiral pesticides [168, 170, 173, 193, 194] and chiral drugs in the environment [195] and as a first step of method development prior to purification with preparative-scale chiral SFC [196–199]. At the preparative scale, chiral separations still make up about 60% of the publications.

Trends in method development

The use of design of experiments (DoE) to develop analytical SFC methods is increasing. Most often, an initial screening of stationary phase with either isocratic or gradient conditions is done, and then an experimental design is proposed to optimize the conditions of mobile phase composition, temperature, pressure, or even flow rate [42, 73, 91, 200, 201]. The importance of measuring the exact conditions inside the system rather than relying on instrument settings was pointed out in several occasions [93, 202–204]. Considering most recent papers (years 2016–2018), methanol is still the most frequently employed co-solvent in achiral analytical applications as can be seen in Fig. 6a. Acetonitrile, which was rarely employed in the past, is progressing, especially in mixtures with an alcohol. For chiral applications, methanol is also dominant but isopropanol is also very frequently used. The use of water in ternary mobile phase compositions, along with carbon dioxide and a major co-solvent (alcohol or acetonitrile), has been noted in many recent achiral applications (about 17% of the recent papers). A large portion of the applications (50 and 60% of the achiral and chiral applications respectively) is based on the sole use of such simple mobile phase compositions, namely carbon dioxide, major co-solvent, and sometimes water. Other applications mention the additional use of acids, bases, or salts to favor the elution with satisfactory peak shapes or to improve resolution. For achiral applications, the recent years have seen increasing use of ammonium formate, ammonium acetate, and ammonium hydroxide, along with formic acid. All of them are usually observed to favor chromatographic quality in addition to mass spectrometric response with electrospray ionization.

The advantages of the so-called enhanced-fluidity liquid chromatography (EFLC) region (when carbon dioxide is the minor component of the mobile phase, as opposed to SFC where it is the major component) have long been known and explored, principally by Olesik and co-workers [45, 205, 206]. The interest in introducing a small portion of carbon dioxide in an aqueous reversed-phase HPLC system was to improve efficiency and reduce analysis time through reduced mobile phase viscosity. This is also allowing to elute analytes with higher polarities than normally encountered in “more classical” SFC conditions with a larger portion of carbon dioxide. A most innovative paper from the team of Bamba [207] has demonstrated the SFC-MS analysis of a mixture of lipophilic and hydrophilic vitamins in a single run, with a wide elution gradient starting in classical SFC conditions (large proportion of CO_2, low proportion of co-solvent), moving to

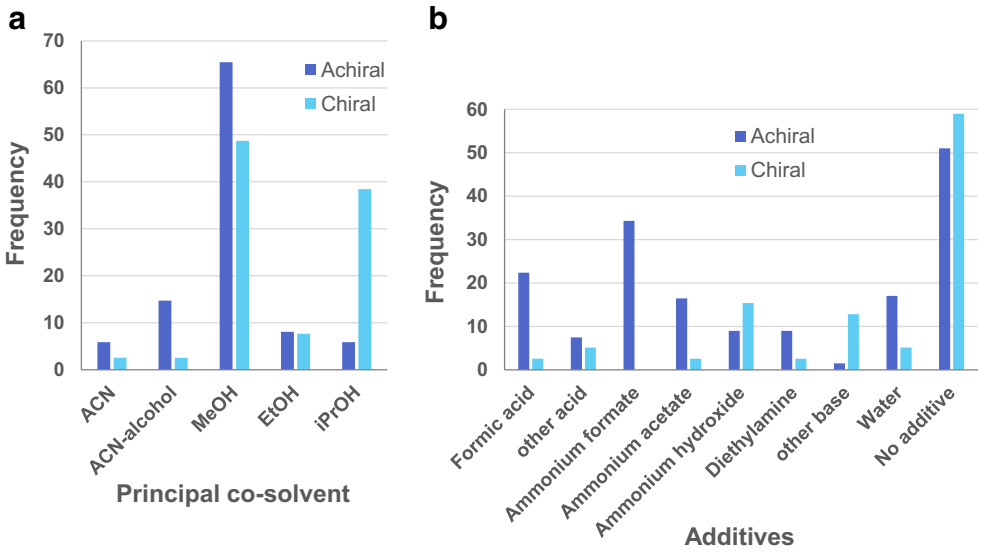

Fig. 6 Choice of (**a**) solvents and (**b**) additives observed in the recent analytical applications (2016–2018). Based on Scopus search conducted in April 2018

EFLC and finishing with a pure liquid (methanol-water 95:5 *v*/*v*) mobile phase. This was definitely breaking the imaginary barrier between SFC and HPLC. Since this fundamental paper, other research have been produced to investigate in details the "transition" from HPLC to SFC [208]. More research is expected in the near future, which will show that the former views on operating conditions are no longer valid and that using the full gradient range from 0 to 100%, co-solvent should open new application possibilities, especially for samples containing a wide diversity of analyte polarities.

Outlook

Supercritical fluid chromatography is clearly facing changing trends in many respects: less chiral but more achiral applications; less preparative-scale but more analytical-scale applications; less pharmaceutics applications but more natural products, food science, bioanalysis, and environmental applications. Many of these application domains have benefited of the increasing availability of mass spectrometry. Also, the way of developing methods is changing, with less trial-and-error and more design of experiment processes. Still, some improvement in retention modeling is desirable to help predict the outcome of a separation and favor analyte identification in complex mixtures. The improvements in instruments and developments of innovative stationary phases have both been great contributors to these changes but further improvement, especially in reducing extra-column volumes and expanding stationary phase diversity, should be observed in the near future. The frontiers between SFC and HPLC are fading and more versatile methods, moving from one to the other within the course of a single analysis, should be seen in future papers to expand the range of analyte polarities eluted within one experiment. SFC research is very active in many geographical regions of the world and it is hoped that it will further develop in the years to come.

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Compliance with ethical standards

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