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Review

New trends in fast liquid chromatography for food and environmental analysis

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ABSTRACT

There is an increasing need for applications in food and environmental areas able to cope with a large number of analytes in very complex matrices. The new analytical procedures demand sensitivity, robustness and high resolution within an acceptable analysis time. The purpose of this review is to describe new trends based on fast liquid chromatography applied to the food and environmental analysis. It includes different column technologies, such as monolithic, sub-2 μm, porous shell, as well as different stationary phases such as reversed phase (C8 and C18), hydrophilic interaction liquid chromatography (HILIC) and fluorinated columns. Additionally, recent sample extraction and clean-up methodologies applied to reduce sample manipulation and total analysis time in food and environmental analysis – QuEChERS (*Quick*, *Easy*, *Cheap*, *Effective*, *Rugged and Safe*), on line solid phase extraction coupled to ultrahigh pressure liquid chromatography (on line SPE–UHPLC), turbulent flow chromatography (TFC) and molecularly imprinted polymers (MIPs), were also addressed. The advantages and drawbacks of these methodologies applied to the fast and sensitive analyses of food and environmental samples are going to be discussed.

Contents

1. Introduction

Nowadays, there is a growing demand for high-throughput separations. Laboratories belonging to many different areas, such as toxicology, clinical chemistry, forensics, doping, and environmental and food analyses are interested in cost-effective methodologies, with reduced analysis time. High performance liquid chromatography (HPLC) is a common and well-established separation technique frequently used to solve multiple analytical problems, as it is able to separate quite complicated mixtures, of low and high molecular weight compounds, as well as different polarities and acid–base properties in various matrices. But conventional HPLC alone do not solve all the analytical problems related to the increasing number of analytes in very complex matrices. The compromise will either be related with the analysis time or chromatographic resolution when selecting this separation technique. Fast or ultra-fast

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chromatographic methods can overcome the limitations experienced by HPLC when analyzing such sample sets, by yielding high resolution within a reduced analysis time without a loss on separation efficiency.

There are several modern approaches in HPLC methods which enable the reduction of the analysis time without compromising resolution and separation efficiency: the use of monolith columns, liquid chromatography at high temperatures (although in some cases lower temperature can also improve resolution [1]), and ultrahigh pressure liquid chromatography (UHPLC methods) either using sub-2 μm particle packed columns [2] or porous shell columns (with sub-3 μm superficially porous particles) [3,4]. Another analytical approach which has become very popular is the use of other stationary phases such as hydrophilic interaction liquid chromatography (HILIC) or fluorinated stationary phase allowing better separation for highly polar compounds and in some cases even isomeric compounds than reversed-phase chromatography [5]. Some of these approaches were recently reviewed in the bioanalytical area [6].

However, due to the complexity of the matrix, the use of ultrafast separations is not enough to develop a fast analytical method in environmental and food analysis. Moreover, the possibility of analyzing multiple compounds for target or non-target screening, such as multi-residue methods in various matrices, minimizing the sample manipulation is demanded. So sample extraction and treatment must also be optimized when considering reducing the total analysis time. For multi-residue applications, QuEChERS (*Quick*, *Easy*, *Cheap*, *Effective*, *Rugged and Safe*) is a frequent and attractive alternative method for sample treatment. The QuEChERS method is particularly popular to determine moderately polar pesticide residues in various food matrices [7,8], although this methodology is also being used for the analysis of other family of compounds [9–11]. Other modern trends in sample preparation for environmental and food applications include the use of on-line solid phase extraction (SPE) methods, or the use of more SPE-based selective approaches such molecularly imprinted polymers (MIPs) [12,13]. Recently, the use of turbulent-flow chromatography (TFC) have also been reported for direct analysis of complex matrices such as milk with reduced or without any sample manipulation [14–16].

However, the reduction of the total analysis time originated from the development of ultra fast separations and the reduced sample treatment may introduce new analytical challenges during method development. By reducing the sample treatment more matrix related compounds may be introduced into the chromatographic system and although, high resolution and separation efficiency is achieved, the possibility of matrix effect, such as ion suppression or ion enhancement, may increase. The use of on-line SPE methods coupled to ultrahigh pressure liquid chromatography is not a problem-free approach. Many of the conventional on-line SPE systems are not compatible with UHPLC and a loss on the chromatographic efficiency may be observed when both methodologies are coupled. To solve many of these problems the use of liquid chromatography coupled to mass spectrometry (LC–MS) or tandem mass spectrometry (LC–MS/MS) is mandatory and for some applications, high resolution mass spectrometry (HRMS) is required [17].

The aim of this review is to discuss new trends in fast liquid chromatography and on-line sample preparation techniques applied into food and environmental analysis. It includes a selection of the most relevant papers recently published regarding instrumental and column technology and the use of new stationary phases focusing in environmental and food applications, particularly monolith columns, high and low temperature separations, UHPLC methods with sub-2 μm and novel porous shell particle packed columns. Sample treatment procedures such as QuEChERS, MIPs, on-line SPE methods, and turbulent flow chromatography will also be addressed.

2. Sample preparation

Although the technology related to chromatographic separations and mass spectrometry techniques advance, sample treatment is still one of the most important parts of the analytical process and effective sample preparation is essential for achieving good analytical results. An ideal sample preparation methodology should be fast, accurate, precise and demands sample integrity and high throughput. However, in most cases, matrix related compounds may also be co-extracted and interfere in the analysis. In order to minimize the effect of these interferences a selective clean-up step may be required in many cases. As an example, Mastosvska et al. [10] needed a more selective clean-up step using a dispersive-SPE with PSA sorbent in order to eliminate an isobaric interference in the analysis of acrylamide in various food matrices. Fig. 1 shows the effect of this selective clean-up, presumably reducing the effect of the amino acid valine in the quantification of acrylamide.

In this section, sample treatment methodologies for food and environmental analysis such as QuEChERS, on-line solid phase extraction, turbulent flow chromatography and molecularly imprinted polymers (MIPs) will be discussed.

2.1. QuEChERS

The need for a simple, rapid, cost-effective, multi residue method able to provide high quality of analytical results led Anastassiades et al. [7] to develop a new sample treatment method. QuEChERS, acronym of "Quick, Easy, Cheap, Effective, Rugged and Safe", is a sample preparation technique entailing solvent extraction with acetonitrile, ethyl acetate or other organic solvents, and partitioning with magnesium sulfate alone or in combination with other salts, generally NaCl, followed by a clean-up step using dispersive solid phase extraction (d-SPE) adding small amounts of bulk SPE packing sorbents to the extract. The most used d-SPE sorbent is the primary secondary amine (PSA), whereas other sorbents such as C18, OASIS HLB, graphite carbonor florisil can also be used. After the clean-up step the extract is centrifuged and the supernatant can be directly analyzed or, if it is necessary, can be concentrated [18]. This technique has attracted the attention of pesticides laboratories worldwide and it is the most commonly employed sample treatment methodology used for the multi-residue analysis of pesticides in fruit and vegetables [8]. In addition, this methodology is increasingly being used for the analysis of other compounds in food. The QuEChERS methodology has already been applied to the analysis of polycyclic aromatic hydrocarbons in fish and shrimp [9,19], and acrylamide in various food matrices such as chocolate, peanut butter, and coffee [10]. In this case the QuEChERS methodology allowed the accurate determination of acrylamide in foodstuffs since the use of salt and the PSA sorbent increased the selectivity of the method by reducing the content of more polar matrix co-extractives. The extraction of veterinary drugs in animal tissues [11] and milk [20,21], and UV ink photoinitiators such as benzophenone, ITX, DETX, EHDAB, in packaged foods [22] have also been reported using QuEChERS. The extraction of more than 80 compounds with suitable recoveries (>70%) has also been reported in the analysis of mycotoxins in cereals [23] and the simultaneously analysis of pesticides, mycotoxins, plant toxins and veterinary drugs from different type of matrices such as cereals or cereal-based processed foods, vegetables and wines. Furthermore, this methodology has been applied in environmental analysis. Pinto et al. [24] developed a simplified QuEChERS method for the extraction of chlorinated compounds in soil samples.

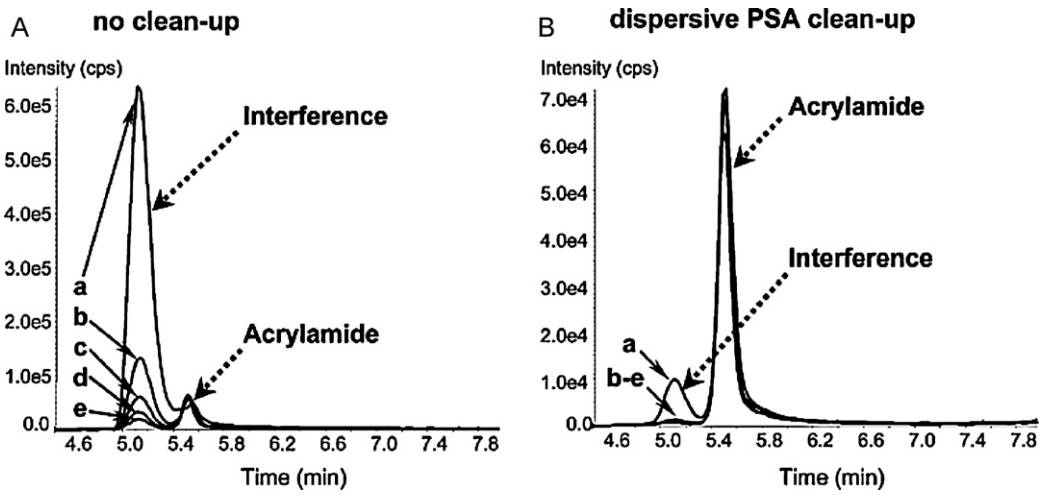

Fig. 1. LC–MS/MS analysis of acrylamide (m/z 72 → 55) in potatoes chips. (A) After and (B) before dispersive-SPE clean-up with PSA. Chromatographic conditions: Phenomenex Aqua C18 (150 mm × 3 mm, 5 μm) column. Mobile phase: water:methanol 99.5:0.5 (v/v) at 200 μL min^{-1}.
Reproduced from Ref. [10], with permission of American Chemical Society.

2.2. On-line solid phase extraction (SPE)

Since in environmental and food analysis the contaminants are found at very low concentrations levels (ng L^{-1} to μg L^{-1}) a preconcentration and clean-up step is mandatory. Off-line SPE is commonly used for these purposes, but in some cases large-sample volumes followed by solvent evaporation are required. Most of these procedures are time consuming and error-prone, as in the

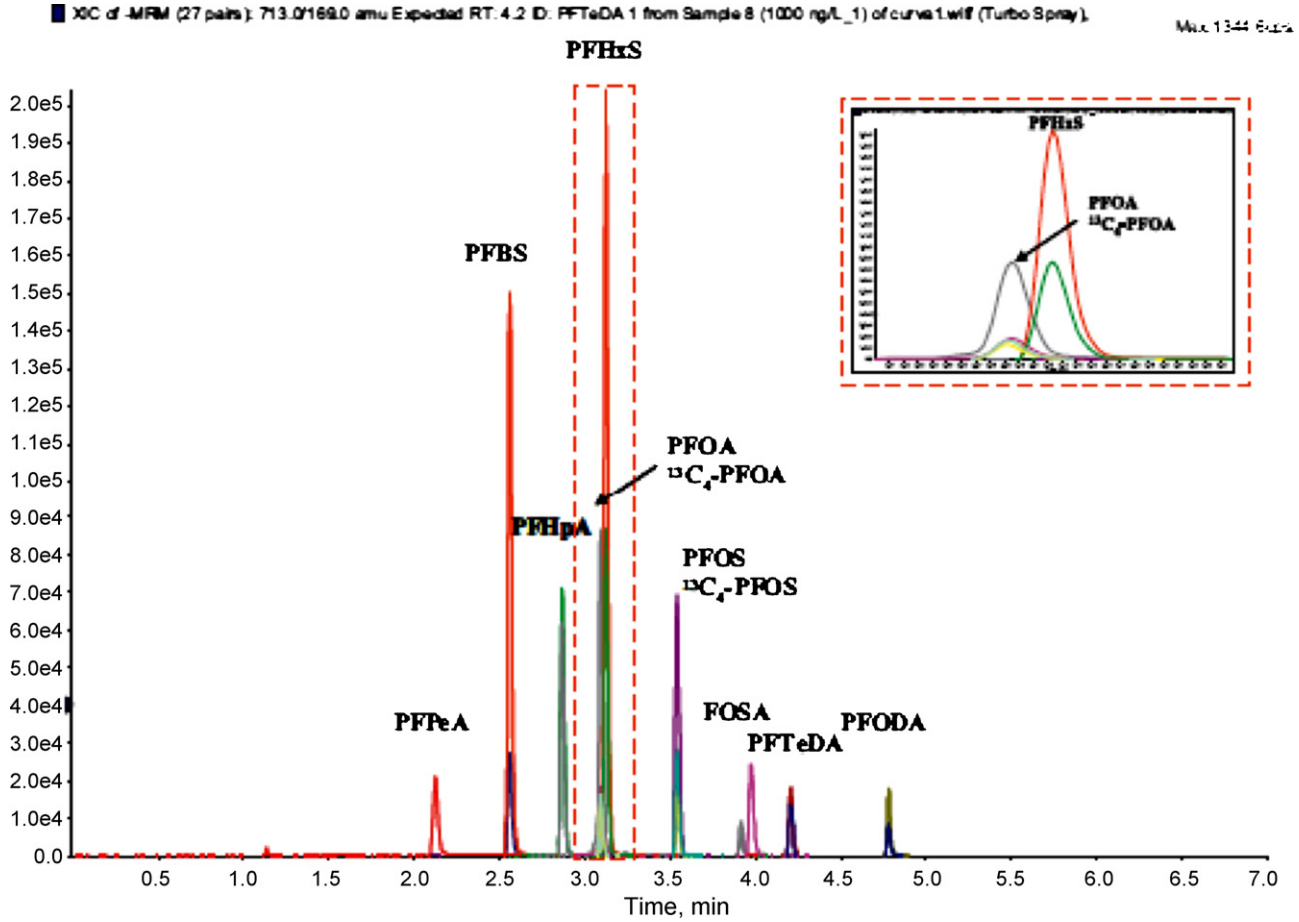

Fig. 2. On-line SPE UHPLC–MS/MS chromatogram of a standard solution of eleven perfluorinated compounds. Chromatographic conditions: Zorbax Eclipse XDB-C18 (4.6 mm × 50 mm, 1.8 μm). Mobile phase: gradient elution with 0.01% NH_4OH solution in 5 mM ammonium acetate (component A) and 0.01% NH_4OH solution in acetonitrile (component B), eluting at a flow rate 1 mL min^{-1}. On-line SPE conditions: Poros HQ column (2.1 mm × 30 mm, 10 μm), injection volume: 350 μL, elution with mobile phase initial composition.
Reproduced from Ref. [30], with permission of Elsevier.

analysis of bisphenol A (BPA). In this case, BPA may leach from the cartridges used in off-line SPE at concentration levels similar to those that can be found in water samples [25,26]. As off-line SPE, on-line SPE offers a series of advantages. The use of on-line SPE has made possible the development of faster methods by reducing the analysis time and thus increasing the sample throughput. Taking into account such benefits, several papers have been published using on-line SPE in environmental and food analysis [27–29] using liquid chromatography columns with 5 μm particle size. However, although UHPLC is commonly used in environmental and food analysis, until now only few methods have been published in the literature that couple on-line SPE systems to UHPLC using sub-2 μm particle size columns, providing fast and ultra-fast run times in combination with highly efficient chromatographic separations. Only Gosetti et al. [30], developed an on-line SPE UHPLC–MS/MS method using a sub-2 μm particle size column for the analysis of 9 perfluorochemicals in biological, environmental and food samples with an analysis time of 7 min (Fig. 2). The direct hyphenation of on-line SPE to UHPLC using sub-2 μm particle size columns is challenging. Firstly, the high flow rates generally used in UHPLC (>400 $\mu L\,min^{-1}$) in combination with the particle size generates high backpressure (>9000 psi), which is not directly compatible with the conventional on-line SPE systems that operates at low backpressures <6000 psi. To overcome this problem Gallart-Ayala et al. [31] developed an on-line SPE UHPLC–MS/MS method using a porous shell column as an analytical column. These columns provides fast and highly efficient chromatographic separations, similar to sub-2 μm particle size columns, at low backpressure (<9000 psi), enabling the direct hyphenation with a conventional on-line SPE system. This method allowed the direct analysis of BPA and its chlorinated derivatives in 1 mL of water samples at $ng\,L^{-1}$ level in less than 10 min. Later on, this methodology was applied for the analysis of BPA and other bisphenols, such as BPF, BPE, BPB and BPS, in soft-drinks by the direct injection of 1 mL of soft-drink sample [32]. However, in this case an important matrix effect (80–95%) was observed due to the presence of matrix components that caused ion suppression in the ESI source. In this work several strategies to reduce the matrix effect were evaluated, concluding that only when the analytes were higher retained in the analytical column and force to elute in a cleaner chromatographic area, the matrix effect was reduced. This fact shows that in some cases to obtain a good identification and quantitation of the target analytes it is necessary to sacrifice the analysis time. This methodology was also applied by Lu et al. [33] for the analysis of *cis*- and *trans*-resveratrol in wine samples. This approach affords high-throughput analysis (6 min per sample), improved accuracy since aqueous calibration standards are processed in the same way as samples, and also provides high sensitivity and selectivity.

On the other hand, the large amounts of organic solvents (MeOH and ACN) generally used in the SPE elution step produces band broadening and interferes in the retention. The direct introduction of the eluted extract into the UHPLC system is not allowed. To solve this problem, Bentayed et al. [34] proposed the addition of water after the SPE column for the analysis of bile acids in human serum.

2.3. Turbulent-flow chromatography (TFC)

The cost-effectiveness of the analytical procedure is becoming crucial in all laboratories. Turbulent Flow Chromatography (TFC) is a technique that combines high-throughput and high reproducibility by means of separating analytes from various matrices with reduced sample handling. The sample can be injected directly onto a narrow diameter column (0.5 or 1.0 mm) packed with large particles (30–60 μm) at a high flow rate (higher than $1\,mL\,min^{-1}$) helping creating a very high linear velocity inside the turbulent flow column. Under turbulent flow conditions the improved mass transfer across the bulk mobile phase allows for all molecules to improve their radial distribution, however, under these conditions a laminar zone around the stationary phase particles still exists, where diffusional forces still dominate the mass transfer process [35]. Molecules with low molecular weight diffuse faster than molecules with a high molecular weight, forcing large molecules to quickly flow to waste while retaining the small analytes. The retained compounds are then back-flushed and focused on the analytical column for chromatographic separation. It is extremely important to effectively avoid interferences from the matrix on the analysis of a contaminant. The optimization of the different on-line extraction steps is crucial, as parameters like mobile phase composition, flow rates and extraction time windows will affect recovery and extraction efficiency in general.

TFC seems to be more efficient at removing proteins based on their size than restricted access media (RAM) or solid phase extraction (SPE) (Fig. 3A) [36]. However, as expected, the flow rate used is an important parameter on the exclusion of proteins, based on their molecular weight. Using a cumulative Gaussian fit and extrapolating to zero the molecule weight completely excluded from the TFC column (99%) are approximately 8.7, 12.1, 13.0, 13.6 and 15.0 kDa for 2.0, 1.75, 1.5, 1.25 and $1.0\,mL\,min^{-1}$ respectively (Fig. 3B).

Table 1 shows some recent applications of TFC in food and environmental analysis. This technique has been used mainly in the handling of biological samples containing a large amount of proteins, such as blood plasma [35,37–42] (from 2010 to date). In a recently published review dedicated to sample preparation methodologies for the isolation of veterinary drugs and growth promoters from food, Kinsella et al. [14] described turbulent flow chromatography as a technique that eliminates time-consuming sample clean-up, increases productivity and reduces solvent consumption without sacrificing sensitivity. Food matrices have a high content of fat and proteins, which helps to understand the applicability of this technique for the determination of a specific class of contaminants in various matrices such as honey, tissues and milk [15]. Two examples are described in the literature concerning the determination of quinolones in honey and animal tissue [43,44]. Sample preparation of honey only required a simple dilution with water, followed by filtration. Recoveries of 85–127% were obtained, while matrix effects were still observed which led to the use of standard addition for calibration. The proposed methodology has also shown robustness, with over 400 injections of honey extracts without any TFC column deterioration, with the consumption of 44 mL of solvent per sample [43]. In the case of animal tissue, the sample was extracted with a mixture of an ACN/H_2O 1:1 acidified with 0.01% formic acid for the determination of enrofloxacin and its metabolite ciprofloxacin. Mean recovery rates for the tissues of the different species (cattle, pig, turkey and rabbit) were in the range of 72–105% in a run time of only 4 min [44].

Other example of the use of turbulent flow chromatography is reported in the screening of veterinary drugs in milk samples. Protein precipitation was induced before analysing samples of whole, skimmed and semi-skimmed milk samples. While matrix effects – ion suppression and enhancement – were obtained for all analytes, the method has proved to be useful for screening purposes because of its sensitivity, linearity and repeatability [16].

This technique has also been applied successfully to environmental samples. Anti-infectives analysis in wastewater has been reported with good recovery (86–141%) and LOQs (45–122 $ng\,L^{-1}$) [45]. Signal distortion, represented as matrix effect, was still observed probably due to the fact that small molecules (below 1000 Da) present in wastewater samples will have affinity for the stationary phase and will not be completely removed in the clean-up step. Takino et al. have minimized the matrix effect observed by using atmospheric pressure photoionization (APPI) instead of electrospray (ESI) as ionization mode [46]. Moreover, TFC

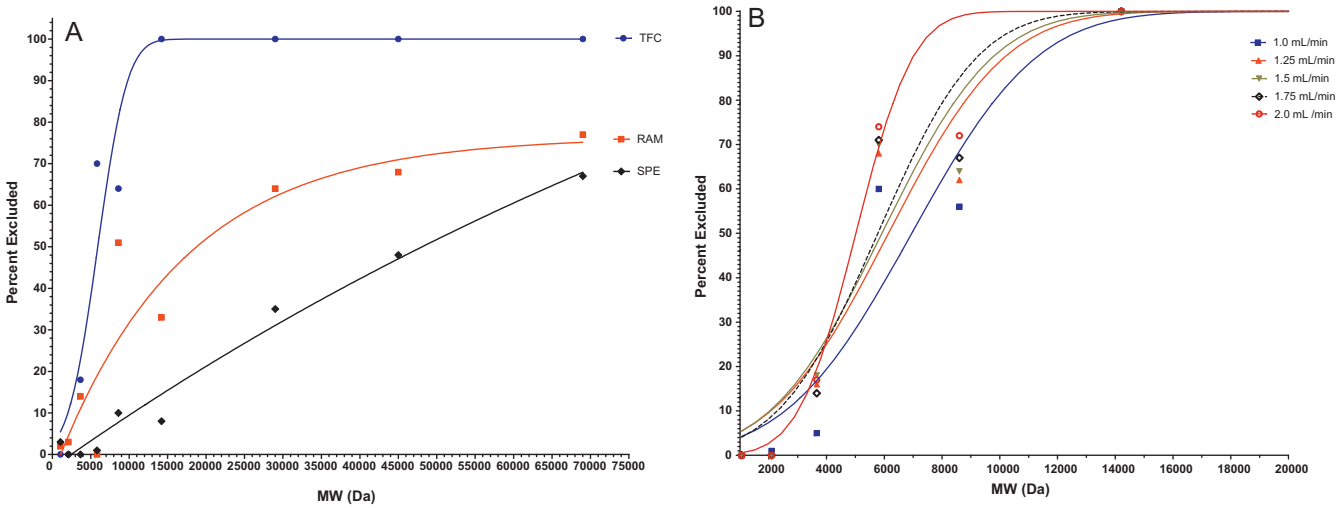

Fig. 3. (A) Comparison of the percentage of compounds excluded according to their molecular weight for turbulent flow chromatography (TFC), restricted access media (RAM) and solid phase extraction (SPE). (B) Percentage of Proteins excluded as function of flow rate at pH 8.
Adapted from Ref. [36], with permission of the authors.

significantly reduced the sample preparation time for the analysis of perflurooctane sulfonate (PFOS) in river water [46]. TFC columns packed with organic polymers or graphitized carbons were also found to be highly capable for enrichment of trace pesticides from drinking and surface water samples [47].

2.4. Molecularly imprinted polymers (MIPs)

Molecularly imprinted polymers (MIPs) are synthetic polymeric materials with an artificially generated three-dimensional network able to specifically rebind a target analyte, or a class of structurally related compounds [48]. These materials are obtained by polymerizing functional and cross-linking monomers around a template molecule, leading to a specific recognition sites complementary in shape, size and functional groups to the target molecule. These recognition sites mimic the binding sites of biological receptors such as antibody–antigen with the advantages of being very selective without suffering from stability problems associated to natural receptor such as storage limitations, pH, organic solvents and temperature. Therefore, MIPs have been successfully employed in several analytical fields such as stationary phase on liquid chromatography [49–51], capillary electrochromatography [52,53], immunoassay determinations [54,55], and sensors [56]. Regarding MIP synthesis, bulk polymerization is the most used procedure. The resulting bulk polymer should be ground and sieved to obtain particles with desirable diameter. Thereafter the particles must be washed extensively to minimize bleeding of the template. Despite the fact that this methodology is relatively simple and the reaction conditions can be easily controlled, this method presents a numbers of disadvantages such as of being tedious and time-consuming. Moreover, the particles obtained after the polymer block crushing are irregularly sized and shaped,

Table 1
Use of TFC columns in food and environmental analysis.

Target compounds	Application field Sample	TFC column	Flow-rate Injection volume	Detection	MLOD	Reference
PFOS	Environmental analysis	50 mm × 1.0 mm, 50 μm C18 (Cohesive Technologies)	1 mL min^{-1}	APPI-MS	5.35 ngL^{-1}	[14]
	River water		1 mL			
Anti-infectives	Environmental analysis	50 mm × 1.0 mm, 50 μm C18 XL (Cohesive Technologies)	3 mL min^{-1}	ESI-MS/MS	15–53 ngL^{-1}	[15]
	Wastewater		1 mL			
Enrofloxacin and ciprofloxacin	Food analysis	50 mm × 1.0 mm, 50 μm Cyclone (Thermo Fisher Scientific)	5 mL min^{-1}	ESI-MS/MS	LOQ	[43]
	Edible tissues		20 μL		25 μg kg^{-1}	
Pesticides	Environmental analysis surface, drinking water	50 mm × 1.0 mm, 35 μm	5 mL min^{-1}	APCI-MS/MS	0.4–283 ngL^{-1}	[44]
		Oasis HLB (Waters)	10 mL			
Quinolones	Food analysis	50 mm × 0.5 mm, 60 μm, Cyclone (Thermo Fisher Scientific)	1.5 mL min^{-1}	ESI-MS/MS	MLOQ	[16]
	Honey		160 μL		5 μg kg^{-1}	
Veterinary drugs	Food analysis	50 mm × 0.5 mm, 60 μm Cyclone–Cyclone P connected in tandem (Thermo Fisher Scientific)	1.5 mL min^{-1}	ESI-MS/MS	0.1–5.2 μg L^{-1}	[45]
	Milk		50 μL			

leading to unsatisfactory chromatographic performance of these particles, i.e., wide and tailing peaks. All these aspects, together with the heterogeneity of the binding sites distribution of varying affinity and poor site accessibility for the target analyte [57], have prevented the use of MIPs particles obtained by bulk polymerization as chromatographic media and in on-line MIP–SPE application. To overcome these drawbacks, alternative methodologies have been proposed for the direct preparation of uniform MIP particles of a desired size such as multi-step swelling polymerization [58,59], suspension polymerization [60], and precipitation polymerization [61], as well as surface imprinting on the spherical silica and polymer particles [62]. Chromatographic performance of five different bupivacaine-MIP formats has been presented by Oxelbark et al. [63]. Iniferter-silica composites and monolith capillaries were shown to be feasible for much faster analyses compared to the classical bulk format, where non-specific binding was considerably higher. Jiang et al. have established a method for direct analysis of bisphenol A (BPA) trace in water using BPA-imprinted polymer microsphere obtained by modified precipitation polymerization (MPP) as HPLC stationary phase [64]. The use of the BPA-imprinted microspheres as selective stationary phase of analytical column allowed to determine trace BPA in biological samples with satisfactory accuracy and repeatability. Silica–MIP composite material was also successfully tested as HPLC packing for the LC–UV screening of phenylurea herbicides from vegetable sample extracts. In this study, the chromatographic behaviors of the MIP column were compared with that of commercial C_{18} column, where the detection of pesticides was not possible due to the coelution of matrix-interfering compounds with target analytes [65]. Another approach consists of the in situ polymerization of MIP monolithic polymer. MIP monolith has been successfully employed as HPLC stationary phase for environmental or food analysis such as xanthine derivatives caffeine and theophylline in green tea [66] and sulfamethoxazole and its analogs in pharmaceutical tablets [67]. MIP monoliths can also be used as stationary phases for capillary electrochromatography (CEC) and this hybrid technique have been recently applied for the selective determination of the fungicide thiabendazole (TBZ) in citrus samples [68] and for the enantiomeric separation of ornidazole in tablet samples [69].

However, among the wide range of possible MIPs applications mentioned above, the use of MIP particles as selective sorbents for solid-phase extraction (MIP–SPE) is by far the most advanced technical application of MIPs. Solid-phase extraction (SPE) is a well-established method routinely used for clean-up and preconcentration step of analytes in the areas of environmental, food and pharmaceutical analysis. Nevertheless conventional SPE sorbents lack selectivity resulting in co-extraction of interfering matrix components. Therefore, specificity, selectivity and sensitivity can be obtained using sorbents based on molecularly imprinted polymers (MIPs). A good example of high selectivity obtained employing off-line MIP–SPE was reported recently by Hadj Ali et al. [12], who compared a commercial immunoaffinity cartridge (IAC) and a MIP for extracting ochratoxin A from wheat samples. Their study showed similar selectivity results with very reliable baselines in both cases. In addition, the MIP–SPE column capacity was determined to be at least eight times higher than that of IAC. These results were similar to those previously obtained by Lucci et al. [13]. In the off-line mode, MIP–SPE have also been used for the selective extraction-preconcentration of a wide range of analytes, such as phenols and phenoxyacids in honey [70], benzimidazole compounds in water samples [71], natural and synthetic estrogens from aqueous samples [72], 17β-estradiol in fish and prawn tissue [73], fluoroquinolones from milk [74], β-agonists in pork and pig liver samples [75], diclofenac in surface and wastewater samples [76] or domoic acid from seafood [77]. Moreover, in recent years, the number of applications of MIP–SPE in the on-line mode has significantly increased. Zhao et al. [78] developed an on-line MIP–SPE procedure coupled to HPLC for selective extraction of the four sudan dyes in samples from Yellow River water, tomato sauce and sausage. The proposed method showed that the new MIP obtained using attapulgite as matrix was feasible in the determination of these sudan dyes in real samples. The LODs were in the range of 0.01–0.05 ng mL^{-1} for Yellow River water, 1.0–3.0 ng g^{-1} for tomato sauce and 0.8–3.0 ng g^{-1} for sausage. On-line MIP–SPE was also successfully applied to the simultaneous multi-residue analysis of six tetracyclines in spiked milk and honey samples [79]. In this work, a tetracycline imprinted monolithic column was prepared by in situ molecular imprinting technique and used as SPE sorbent. High recoveries of 73.3–90.6% from milk samples and 62.6–82.3% from honey samples were obtained. An interesting on-line configuration coupled with capillary electrophoresis to determine trace BPA in complex samples was recently published [80]. The results obtained showed that MIP–SPE had higher selectivity and recovery for BPA than did C_{18} SPE. Furthermore, the authors suggest that the developed method has the potential to solve the two main problems of a CE–UV method, improving sensitivity and selectively cleaning up the target analytes from matrix-interfering compounds.

3. Trends in chromatographic approaches

3.1. Monolithic columns

Monolithic columns have proven to be a very good alternative to particle-packed columns for high efficiency separations in HPLC [49,81,82]. Because of their small-sized skeletons and wide through-pores, much higher separation efficiency can be achieved than in the case of particle-packed columns at a similar pressure drop [83]. One of the main advantages of monolithic columns is that they can work at high flow-rates (up to 10 mL min^{-1}) in conventional column lengths (4.6 mm I.D.) without generating high back-pressures. Monolithic columns can be prepared from organic polymers by in situ polymerization of suitable organic monomers. According to the nature of the monomer, uncharged and hydrophobic monoliths that allow reversed-phase (RP) interactions could be obtained [49]. Silica-gel based monolithic capillary or rod columns can be prepared by sol–gel technology in a way to create a continuous network throughout the column formed by the gelation of a sol solution within the column [84,81], which enables the formation of highly porous material, containing both macropores and mesopores in its structures. Such an LC column consists of a single rod of silica or polymer-based material with two kinds of pores, the large ones (typically 2 μm) enabling low flow resistance and therefore allowing the application of high mobile-phase flow-rates, while the small ones (about 12 nm) ensuring sufficient surface area in order to reach high separation efficiencies. These properties allow using much higher flow-rates while the resolution of the monolithic rod column is much less affected in regards to particulate materials, thus allowing the development of fast liquid chromatography methods. Another practical advantage of monolithic columns is the short-time needed for column equilibration when a mobile phase gradient is used. Moreover, monoliths allow the coupling of several columns together in order to increase separation efficiency [85].

Nevertheless, there are several drawbacks to the use of monolithic columns. The first one is that only few stationary phases are commercially available basically C8, C18 or plain silica based columns. Another point to take into account is the internal diameters of monolith columns (i.e., 4.6 and 3.0 mm, or 100 μm I.D. most commonly found; however, 2.0 or 3.0 mm have not been manufactured in all common column lengths). These two disadvantages reduce their application domains substantially, especially in food

Table 2
Use of monolithic columns in food and environmental analysis.

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Nut allergens	Food analysis Cereals and biscuits	C18 Chromolith Performance column (100 mm × 2 mm I.D.)	Gradient elution: (A) 0.1% HCOOH (B) 0.08% HCOOH in ACN 350 μL min^{-1}	Mass spectrometry (LTQ XL liner ion trap instrument) SRM acquisition mode	7.5 min	[87]
Fumonisins B1 and B2	Food analysis Corn, rice, juices, animal feeds	C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	Methanol:0.1 M dihydrogenphosphate (78:22, v/v) 1 mL min^{-1}	Fluorescence detection Excitation 335 nm Emission 440 nm	4.5 min	[88]
Flavonoids	Food analysis Tomato	C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	50 mM phosphate buffer (pH 2.2):ACN (75:25, v/v) 1 mL min^{-1}	UV detection 254 nm Mass spectrometry SRM acquisition mode	9 min	[89]
Sulfonamides	Food analysis Shrimp	C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	0.1 M phosphate buffer (pH 3):ACN:MeOH (80:15:5, v/v/v)	Boron-doped diamond amperometric detection	8 min	[90]
Tetracyclines	Food analysis Milk, honey	Molecularly imprinted poly(methacrylic acid) monolithic column (100 mm × 4.6 mm I.D.)	ACN:acetic acid (98:2, v/v) 0.5 mL min^{-1}	UV detection 270 nm	33 min	[79]
Corticoids	Food analysis	C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	ACN:H_2O (28:71, v/v) 3 mL min^{-1}	UV detection 245 nm	5 min	[91]
Isoflavones	Food analysis Soy	Two coupled C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	Gradient elution: (A) 0.1% acetic acid (B) 0.1% acetic acid in MeOH 5 mL min^{-1}	UV detection 254 nm	10 min	[92]
Phenolic acids	Food analysis Fruits	C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	Gradient elution: (A) 50 mM phosphate buffer (pH 2.2) (B) ACN 2 mL min^{-1}	UV detection 280 nm	29 min	[93]
Caffeine, theophylline	Food analysis Green tea	Molecularly imprinted poly(acrylamide) monolithic column (150 mm × 4.0 mm I.D.)	Methanol 4 mL min^{-1}	UV detection 271 nm	18 min	[94]
Fluoroquinolone antibiotics	Environmental analysis Surface waters	C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	25 mM phosphoric acid (pH 3.0) with tetrabutylammonium and methanol (960:40, v/v) 2.5 mL min^{-1}	Fluorescence detection Excitation 278 nm Emission 450 nm	14 min	[95]
Pharmaceutical residues	Environmental analysis	Two coupled C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	Gradient elution: (A) 1 mM ammonium formate/formic acid buffer (pH 4.5) (B) MeOH 3 mL min^{-1}	UV detection 225 nm	55 min	[96]
Zinc pyrithione	Environmental analysis Water	C18 Chromolith Performance column (100 mm × 4.6 mm I.D.)	Gradient elution (A) 10 mM ammonium acetate (B) MeOH 10 mL min^{-1}	Mass spectrometry Ion trap mass analyzer	10 min	[97]

Table 3
Applications of UHPLC in food and environmental analysis.

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Perfluorochemicals	Food analysis	Zorbax Eclipse XDB-C18 (50 mm × 4.6 mm, 1.8 μm)	Gradient elution:	Mass spectrometry	5 min	[30]
	Fish and cooked fish samples		(A) 0.01% NH_4OH solution in 5 mM ammonium acetate (B) 0.01% NH_4OH solution in acetonitrile 1 mL min^{-1}	QTrap mass analyzer SRM acquisition mode		
Aflatoxins and metabolites	Food analysis	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	4 min	[105]
	Baby food and milk		(A) 0.5 mM ammonium acetate, 0.1% HCOOH (B) 0.5 mM ammonium acetate in MeOH, 0.1% HCOOH 300 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Oleopentanedialdheydes	Food analysis	Hypersil GOLD C18 (50 mm × 2.1 mm, 1.9 μm)	Gradient elution:	Mass spectrometry	–	[106]
	Olive oil		(A) 0.1% TFA in water (B) Methanol 400 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Bisphenol A-diglycidyl ether (BADGE), bisphenol F-diglycidyl ether (BFDGE) and derivatives	Food analysis	Fused-core Ascentis Express C18 (150 mm × 2.1 mm, 2.7 μm)	Gradient elution:	Mass spectrometry	5 min	[163]
	Canned food and beverages		(A) 25 mM formic acid–ammonium formate buffer (pH 3.75) (B) Methanol 600 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Amoxicillin, penicillin G and metabolites	Food analysis	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution:	Mass spectrometry	6 min	[107]
	Bovine milk		(A) 0.15% formic acid with 5 mM ammonium acetate (pH 2.8) (B) Acetonitrile 250 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Pesticides, biopesticides and mycotoxins	Food analysis	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	12 min	[108]
	Cereals, vegetables and alcoholic beverages		(A) 5 mM ammonium formate (B) methanol 450 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Antibiotic residues	Food analysis	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	–	[109]
	Eggs		(A) 0.02% formic acid and 1 mM oxalic acid in water (B) 0.1% formic acid in acetonitrile 300 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		

Table 3 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Aflatoxins, ochratoxin A, zearalenone	Food analysis	Fused-core Ascentis Express C18 (150 mm × 2.1 mm, 2.7 μm)	Gradient elution:	Fluorescence detection	12 min	[164]
	Barley		(A) 0.5% formic acid in water	Mycotoxin confirmation by mass spectrometry		
			(B) 0.5% formic acid in acetonitrile:methanol (1:1, v/v) 900 μL min^{-1}	SRM acquisition mode		
Ractopamine	Food analysis	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	3.5 min	[110]
	Swine		(A) 0.1% formic acid in water	Triple quadrupole mass analyzer		
			(B) 0.1% formic acid in acetonitrile 300 μL min^{-1}	SRM acquisition mode		
Bisphenols	Food analysis	Fused-core Ascentis Express C18 (50 mm × 2.1 mm, 2.7 μm)	Gradient elution:	Mass spectrometry	5 min	[32]
	Soft drinks		(A) Water	Triple quadrupole mass analyzer		
			(B) Methanol 600 μL min^{-1}	SRM acquisition mode		
Sulfonamides	Food analysis	Fused-core Halo C18 (50 mm × 2.1 mm, 2.7 μm)	Gradient elution:	Mass spectrometry	7 min	[27]
	Grass carp tissues		(A) 0.1% formic acid in water	Triple quadrupole linear ion trap mass analyzer		
			(B) Acetonitrile 400 μL min^{-1}	SRM acquisition mode		
Cimaterol, salbutamol, terbutaline and ractopamine	Food analysis	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Fluorescence detection	20 min	[111]
	Feed		(A) 10 mM sodium dihydrogen phosphate buffer (pH 2.7)	Excitation 304 nm		
			(B) Methanol 200 μL min^{-1}	Emission 372 nm		
Phenolic compounds and caffeine	Food analysis	Fused-core Kinetex C18 (100 mm × 4.6 mm, 2.6 μm)	Gradient elution:	UV detection 200–400 nm	5 min	[165]
	Tea, mates, instant coffee, soft drink and energetic drinks		(A) 1% phosphoric acid in water	Fluorescence detection		
			(B) 1% phosphoric acid in acetonitrile 2.2 mL min^{-1}	Excitation 280 nm Emission 310 nm		
Corticosteroids	Food analysis	Fused-core Ascentis Express C18 (150 mm × 4.6 mm, 2.7 μm)	Methanol:acetate buffer (5 mM ammonium acetate buffer and 0.01% acetic acid in water, pH 5.4) 60:40 (v/v)	Mass spectrometry	7.5 min	[166]
	Pig fat		800 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		

Table 3 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Marker residue olaquindox	Food analysis Fish tissue	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.3% aqueous formic acid (B) Methanol 300 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	3 min	[112]
Triazolopyrimidine herbicides	Food and environmental analysis Soil, water, and wheat	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.1% formic acid in water (B) Acetonitrile 300 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	2 min	[113]
Pesticides	Food analysis Tea	Acquity UPLC BEH C18 (150 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.02% formic acid in water (B) 0.02% formic acid in acetonitrile 300 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	18 min	[114]
Chloramphenicol	Food analysis Egg, honey and milk	Fused-core Halo C18 (50 mm × 2.1 mm, 2.7 μm)	Gradient elution: (A) 0.1% formic acid in water (B) Acetonitrile 400 μL min^{-1}	Mass spectrometry Triple quadrupole linear ion trap mass analyzer SRM acquisition mode	17 min	[167]
Heterocyclic aromatic amines	Food analysis Meatballs	Shim-pack SR ODS (7.5 mm × 3 mm, 2.2 μm)	Gradient elution: (A) Methanol:acetonitrile:water:acetic acid (8:14:76:2, v/v/v/v) at pH 5.0 (B) Acetonitrile 900 μL min^{-1}	UV detection	5 min	[115]
Toltrazuril and metabolites	Food analysis Meat	Fused-core Ascentis Express C18 (150 mm × 2.1 mm, 2.7 μm)	Gradient elution: (A) Water (B) Methanol 500 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	2 min	[168]
Sterols	Food analysis Vegetable oils	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.01% acetic acid in water (B) 0.01% acetic acid in acetonitrile 800 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SIR acquisition mode	5 min	[116]
Pesticides	Food analysis Fruits and vegetables	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 10 mM ammonium acetate with 2% acetonitrile in water (B) Acetonitrile 400 μL min^{-1}	Mass spectrometry Quadrupole/time-of-flight (QTOF) mass analyzer	14 min	[117]

Table 3 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Mycotoxins	Food analysis	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution:	Mass spectrometry	14 min	[118]
	Grain		(A) 0.2% aqueous ammonia	Triple quadrupole mass analyzer		
			(B) Acetonitrile:methanol (99:19, v/v) 250 μL min^{-1}	SRM acquisition mode		
Aflatoxins B1, B2, G2, G2 and ochratoxin A	Food analysis	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	3.3 min	[119]
	Animal feed		(A) 5 mM ammonium formate in water (B) Methanol 350 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Sex hormones	Food analysis	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	7.5 min	[120]
	Egg products		(A) 0.1% formic acid in water	Triple quadrupole mass analyzer		
			(B) 0.1% formic acid in methanol 200 μL min^{-1}	SRM acquisition mode		
Polyphenols	Food analysis	Hypersil Gold C18 (50 mm × 2.1 mm, 1.9 μm)	Gradient elution:	UV detection 265 nm	0.55–20 min	[121]
	Tea samples	Acquity UPLC BEH C18 (50, 100 and 150 mm × 2.1 mm, 1.7 μm)	(A) 0.1% formic acid in water	Mass spectrometry		
			(B) 0.1% formic acid in acetonitrile 500 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Novolac glycidyl ethers (NOGE)-related and BADGE-related compounds	Food analysis	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	5.5 min	[122]
	Canned food		(A) 0.2% formic acid in water (B) Acetonitrile 400 μL min^{-1}	QTrap mass analyzer SRM acquisition mode		
Mycotoxins	Food analysis	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	19 min	[123]
	Tea, herbal infusions		(A) 0.3% formic acid in water	Triple quadrupole mass analyzer		
			(B) 0.3% formic acid in methanol 550 μL min^{-1}	SRM acquisition mode		
Pesticides	Food analysis	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	25 min	[124]
	Cereal grains		(A) 10 mM ammonium formate in water (pH 3.0) (B) 10 mM ammonium formate in methanol 450 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		

Table 3 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Fusarium mycotoxins	Food analysis	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution:	High resolution mass spectrometry	18 min	[125]
	Cereals		(A) 5 mM ammonium formate (pH 5.6) (B) Methanol 300 μL min^{-1}	Time-of-flight mass analyzer Orbitrap mass analyzer		
Neonicotinoid pesticides	Food analysis	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution:	Mass spectrometry	5.5 min	[126]
			(A) 0.1% formic acid in water (B) Acetonitrile 300 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Carotenoids, retinol and tocopherols	Food analysis	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution:	UV detection	40 min	[127]
	Forages, bovine plasma and milk		(A) 50 mM ammonium acetate in water (B) Acetonitrile-dichloromethane-methanol (75:10:15, v/v/v) 400 μL min^{-1}	285–458 nm		
Fluoroquinolones, tetracyclines and sulfonamides	Food analysis	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	9 min	[128]
	Chicken muscle		(A) 0.01% formic acid in water (B) Methanol 300 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		
Pesticides	Food analysis	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution:	Mass spectrometry	8 min	[129]
	Fruits and vegetables		(A) 0.5 mM ammonium acetate in water (B) 0.5 mM ammonium acetate in methanol 300 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode QTOF mass analyzer		
Biogenic amines	Food analysis	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution:	UV detection	9 min	[130]
	Cheese		(A) 50 mM sodium acetate, 1% tetrahydrofuran in water (pH 6.6) (B) Methanol 1 mL min^{-1}	254 nm		
Anthelmintic drug residues	Food analysis	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution:	Mass spectrometry	8.5 min	[21]
	Milk		(A) 0.01% acetic acid in water:acetonitrile (90:10, v/v) (B) 5 mM ammonium formate in methanol:acetonitrile (75:25, v/v) 600 μL min^{-1}	Triple quadrupole mass analyzer SRM acquisition mode		

Table 3 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Sulfonamides and tetracyclines	Food analysis Fish tissue	Zorbax Eclipse plus C18 (50 mm × 4.6 mm, 1.8 μm)	Gradient elution: (A) 0.1% formic acid in water (B) Acetonitrile 100 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM and data dependent scan acquisition modes	15 min	[131]
Phenolic compounds	Food analysis Chamomile flowers and tea extracts	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.1% formic acid in water (B) Methanol 450 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	18.5 min	[132]
Anabolic steroids and derivatives	Food analysis Herbal mixtures	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.1% formic acid in water (B) Acetonitrile:0.1% formic acid in water (9:1, v/v) 400 μL min^{-1}	Mass spectrometry Time-of-flight mass analyzer	14 min	[133]
Mycotoxins	Food analysis Maize kernels, pasta, multicereal baby food	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.5 mM ammonium acetate, 0.1% formic acid in water (B) 0.5 mM ammonium acetate, 0.1% formic acid in methanol 300 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	5 min	[134]
Biologically active amines	Food analysis Wine, fish, cheese and dry fermented sausage	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.1 M sodium acetate, 10 mM sodium octanesulphonate (pH 4.8) (B) 0.2 M sodium acetate, 10 mM sodium octanesulphonate (pH 4.5):acetonitrile (6.6:3.4, v/v) 800 μL min^{-1}	Fluorescence detection Excitation 340 nm Emission 445 nm	6 min	[135]
Pesticides	Food analysis Fruit- and vegetable-based infant foods	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 10 mM ammonium (B) Acetonitrile 400 μL min^{-1}	Mass spectrometry QTOF mass analyzer MS/MS acquisition	12 min	[136]
Coccidiostat residues	Food analysis Egg and chicken	Acquity UPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) 0.1% formic acid (B) Methanol 450 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	8 min	[137]

Table 3 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Pesticides	Food analysis Fruit and vegetables	Zorbax Eclipse XDB-C18 (50 mm × 4.6 mm, 1.8 μm)	Gradient elution: (A) 0.1% formic acid in water:acetonitrile (95:5, v/v) (B) 0.1% formic acid in acetonitrile:water (95:5, v/v) 600 μL min^{-1}	Mass spectrometry Time-of-flight mass analyzer	17 min	[138]
Pharmaceuticals, antibiotics	Environmental analysis Surface waters, effluent Wastewaters	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution: (A) 0.1 mM ammonium acetate, 0.01% formic acid in water (B) 0.1 mM ammonium acetate, 0.01% formic acid in methanol 300 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	10 min	[139]
UV filters and antimicrobial agents	Environmental analysis Water samples	Zorbax Eclipse XDB-C18 (50 mm × 4.6 mm, 1.8 μm)	Gradient elution: (A) Acetic acid (pH 2.8) in water (B) Methanol 600 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	8 min	[140]
Triclosan, triclocargban and methyl-triclosan	Environmental analysis Water samples	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) Boric acid buffer (pH 9) (B) Acetonitrile 300 μL min^{-1}	UV detection 283 nm	3.2 min	[141,142]
EPA 16 priority pollutants polynuclear aromatic hydrocarbons	Environmental analysis Water samples	Agilent Zorbax Eclipse PAH 600Bar (50 mm × 4.6 mm, 1.8 μm)	Gradient elution: (A) Water:acetonitrile (90:10m v/v) (B) Acetonitrile 650 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	3 min	[143]
Steroidal oral contraceptives	Environmental analysis Water samples	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) Water (B) Methanol or acetonitrile 100 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	8.5 min	[144]
Androgenic and estrogenic hormones	Environmental analysis Water samples	Acquity UPLC BEH C18 (100 and 150 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) Water (B) Acetonitrile 400 μL min^{-1}	Mass spectrometry QTrap mass analyzed SRM acquisition mode	6 min	[145]
Pesticides	Environmental analysis Water samples	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution: (A) 0.1 mM ammonium acetate in water (B) 0.1 mM ammonium acetate in acetonitrile 300 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	8.5 min	[146]

Table 3 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Pharmaceuticals	Environmental analysis	Acquity UPLC high strength silica (HSS) (100 mm × 2.1 mm, 1.8 μm)	Gradient elution: (A) 2 mM ammonium acetate and 2 mM acetic acid in water:acetonitrile (95:5, v/v) (B) 2 mM ammonium acetate and 2 mM acetic acid in water:acetonitrile (5:95, v/v) 500 μL min^{-1}	Mass spectrometry Triple quadrupole mass analyzer SRM acquisition mode	10 min	[147]
	Surface waters					
Estrogens	Environmental analysis	Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm)	Gradient elution: (A) Water (B) Acetonitrile 400 μL min^{-1}	Mass spectrometry QTOF mass analyzer	13 min	[148]
	Water samples					

and environmental analysis. Silica-based monoliths possess also a limited chemical stability (pH range 2–8) [86], which again limits their applicability.

Some applications of monolithic columns in food [79,87–94] and environmental analysis [95–97] are summarized in Table 2. As in other application fields, Chromolith commercial monolith columns have been used in food and environmental analysis, typically using 100 mm × 4.6 mm I.D. columns. The coupling of two monolithic columns was also proposed to increase separation capacity and resolution [92,96], although in some cases this produced a considerable loss in analysis time [96]. Molecularly imprinted polymer (MIP) monolithic columns have also been reported for the analysis of some tetracyclines in milk and honey [79] and xanthine derivatives caffeine and theophylline in green tea [94], methods that also presented quite long analysis times. Monoliths are often used with UV detection [79,89,91–94,96], and in some cases fluorescence [88] or amperometric [90] detection. Although it seems that the extremely high flow-rates generally applied in monoliths makes the compatibility with mass spectrometry detection difficult, a few LC–MS methods using monolith columns begin to be proposed in several application fields including environmental and food analysis [87,89,97], using, in some cases, considerably high flow-rates [89,97]. Developing new LC–MS methods using monoliths will be a field to explore in deep in the future for fast, sensitive and selective applications in food safety and environmental analysis.

3.2. Ultrahigh pressure liquid chromatography

The demands of high sample throughput in short time frames have given rise to high efficiency and fast liquid chromatography using reversed-phase columns packed with sub-2 μm particles (see Table 3). Fast chromatography has become a necessity in laboratories that analyze hundreds of samples per day or those needing short turnaround times. Using rapid resolution liquid chromatography (RRLC), results of a sample batch can be reported in a few hours rather than a few days which is very important for environmental and food safety issues. Regarding the definition of RRLC, liquid chromatographic separations that are less than 10 min are considered fast, and separations less than 1 min are widely known as ultrafast [98].

Columns packed with sub-2 μm particles in UHPLC have also emerged in a powerful approach particularly because of the ability to transfer existing HPLC conditions directly. In addition, the reduction of particle size down to sub-2 μm (compared to conventional columns packed with 5 μm particles) allows either speeding up of the analytical process by a factor of 9 while maintaining similar efficiencies or a theoretical three-fold increase in efficiency for a similar column length [99].

Fast chromatographic separations can be achieved either by increasing the mobile phase flow-rate, by decreasing the column length or by reducing the column particle diameter. In conventional 3 μm or 5 μm particle size columns the efficiency decreases with the increase in mobile phase flow-rate as can be expected by the van Deemter plot shown in Fig. 4. On the other hand, a reduction on column length also improves the analysis time because the retention of the analytes decreases, but a reduction in number of theoretical plates will also be observed. Based on the van Deemter theory [100], then on Giddings [101], and later on Knox [102] and further interpretations, efficiency expressed as the HETP (H) can be described as:

$$H = A + \frac{B}{u} + Cu = 2\lambda d_p + \frac{2\gamma DM}{u} + \frac{f(k)d_p^2 u}{D_M}$$

where u is the linear velocity of mobile phase, and A, B, and C are constants related to eddy diffusion, longitudinal diffusion and mass transfer in mobile and stationary phase, respectively, as previously

Table 4
Application of HILIC and PFPP columns in food and environmental analysis.

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Biogenic amines	Food analysis	Atlantis HILIC column (150 mm × 2.1 mm I.D., 3 μm)	(A) Ammonium formate/formic acid buffer (50 mM, pH 4.0)	Mass spectrometry	10 min	[170]
	Cheese		(B) ACN 300 μL min^{-1}	Q-Trap		
Chlormequat and mepiquat	Food analysis	Atlantis HILIC column (150 mm × 2.1 mm I.D., 3 μm)	(A) Ammonium formate/formic acid buffer (50 mM, pH 3.75)	Mass spectrometry	4 min	[169]
	Beer, bread, fruit juice, baby food, tomatoes, coffee, fruits, vegetables and mushrooms		(B) ACN 400 μL min^{-1}	Triple quadrupole		
Melamine	Food analysis	SeQuant ZIC–HILIC column (250 mm × 2.1 mm I.D., 5 μm)	(A) Ammonium acetate/acetic acid buffer (25 mM, pH 6.8)	Mass spectrometry	8 min	[171]
	Milk powder		(B) ACN 1000 μL min^{-1}	Triple quadrupole		
Amprolium	Food analysis	Ascentis Express HILIC column (100 mm × 2.1 mm I.D., 2.7 μm)	(A) Ammonium formate/formic acid buffer (50 mM, pH 4.0)	Mass spectrometry	2 min	[172]
	Chicken muscle and eggs		(B) ACN 600 μL min^{-1}	Triple quadrupole		
Melamine an related compounds	Food analysis	Venusil HILIC column (250 mm × 4.6 mm I.D., 5 μm)	(A) Ammonium formate/formic acid buffer (10 mM, pH 3.5)	Mass spectrometry	7 min	[176]
	Eggs, milk, ice-cream		(B) ACN	Single quad		
Veterinary drugs (sulfamides, quinolones, tetracyclines, penicillins, aminoglycosides, lincosamides, coccidiostats, macrolides)	Food analysis	ZIC–HILIC column (100 mm × 2.1 mm I.D., 3.5 μm)	(A) Ammonium formate/formic acid buffer (50 mM, pH 2.0)	Mass spectrometry	8 min	[177]
	Chicken muscle		(B) ACN 200 μL min^{-1}	Triple quadrupole		
Melamine	Food analysis	Acquity BEH HILIC column (100 mm × 2.1 mm I.D., 1.7 μm)	(A) Ammonium acetate/acetic acid buffer (10 mM)	Mass spectrometry	1 min	[178]
	Milk, milk products, bakery goods and flour		(B) ACN 700 μL min^{-1}	Triple quadrupole		
Aromatic amines (aniline, 1-naphthylamine, N,N-diethylaniline, N,N-dimethylaniline, benzidine)	Environmental analysis	Kromasil 100-5SIL column (250 mm × 4.6 mm I.D., 5 μm)	A) Phosphate buffer 10 mM	UV detection (254 nm)	10 min	[179]
	River water and WWTP influent		(B) ACN 1000 μL min^{-1}			
Estrogens	Environmental analysis	SeQuant ZIC–HILIC column (100 mm × 2.1. mm I.D., 5 μm)	(A) Ammonium acetate 5 mM	Mass spectrometry	20 min	[180]
	River water		(B) ACN 150 μL min^{-1}	Q-Trap		
Cytostatics	Environmental analysis	SeQuant ZIC–HILIC column (150 mm × 2.1. mm I.D., 3.5 μm)	(A) Ammonium acetate 30 mM	High resolutions mass spectrometry	25 min	[181]
	Wastewater		(B) ACN 200 μL min^{-1}	LTQ-Orbitrap		

Table 4 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
Albuterol, cimetidine, ranitidine, metformin	Environmental analysis	Agilent Zorbax HILIC Plus column (100 mm × 2.1. mm I.D., 3.5 μm)	(A) Ammonium acetate 10 mM	Mass spectrometry	22 min	[182]
	Water and sludge		(B) ACN 200–300 μL min^{-1}	Triple quadrupole		
13 pharmaceuticals	Environmental analysis	Luna HILIC column (150 mm × 3 mm I.D., 5 μm)	(A) Ammonium acetate 5 mM	ICP-MS	20 min	[183]
	Wastewater		(B) ACN:MeOH 300 μL min^{-1}			
Cocaine and metabolites	Environmental analysis	Zorbax RX-Sil column (150 mm × 2.1. mm I.D., 5 μm)	(A) Ammonium acetate 2 mM, pH 4.5	Mass spectrometry	14 min	[184]
	Wastewater		(B) ACN 250 μL min^{-1}	Ion trap		
9 drugs of abuse	Environmental analysis	Luna HILIC column (150 mm × 3 mm I.D., 5 μm)	(A) Ammonium acetate 5 mM	Mass spectrometry	7 min	[185]
	Wastewater		(B) ACN 400 μL min^{-1}	Triple quadrupole		
Organophosphorus pesticides	Environmental analysis	Atlantis HILIC column (150 mm × 2.1 mm I.D., 3 μm)	(A) Ammonium formate 200 mM, pH 3.0	Mass spectrometry	5 min	[173]
	Water		(B) ACN:IPA 200 μL min^{-1}	Triple quadrupole		
Diquat and paraquat	Environmental analysis	Atlantis HILIC column (150 mm × 2.1 mm I.D., 3 μm)	(A) Ammonium formate 10 mM, pH 3.7	Mass spectrometry	12 min	[186]
	Drinking water		(B) ACN	Triple quadrupole		
2-ITX, 4-ITX	Food analysis	Discovery HS F5 column (150 mm × 2.1 mm I.D., 3 μm)	(A) Ammonium formate 25 mM, pH 3.75	Mass spectrometry	6 min	[5]
	Packaged food		(B) ACN 300 μL min^{-1}	Triple quadrupole		
11 UV ink photoinitiators	Food analysis	Discovery HS F5 column (150 mm × 2.1 mm I.D., 3 μm)	(A) Ammonium formate 25 mM, pH 3.75	Mass spectrometry	5.5 min	[22]
	Packaged food		(B) ACN 450 μL min^{-1}	Triple quadrupole		
Medicinal ingredients (FF, NFF, SIB, SDF, VDF, TDF, XAZ)	Food analysis	Discovery HS F5 column (50 mm × 2.1 mm I.D., 3 μm)	(A) Ammonium formate	Mass spectrometry	20 min	[187]
	Health promoting food		(B) ACN 200 μL min^{-1}	Triple quadrupole		
Phenethylamine alkaloids	Food analysis	Discovery HS F5 column (150 mm × 4.6 mm I.D., 3 μm)	(A) Ammonium acetate 10 mM	UV detection (225 nm)	8 min	[175]
	Citrus natural products		(B) ACN 1000 μL min^{-1}			
54 polyphenols	Food analysis	Luna PFP column (250 mm × 4.6 mm I.D., 3 μm)	(A) Sodium acetate 2 mM	UV detection (640 nm)	180 min	[188]
	Sainfoin extracts		(B) MeOH 500 μL min^{-1}			

Table 4 (*Continued*)

Target compounds	Application field/sample	Column/stationary phase	Mobile phase/flow-rate	Detection	Analysis time	Reference
5-Hydroxymethylfurfural	Food analysis	Discovery HS F5 column (150 mm × 2.1 mm I.D., 3 μm)	(A) Water	Mass spectrometry	8 min	[174]
	Fruit juice, honey, breakfast cereals, plum jam, biscuits and fruit		(B) MeOH	Ion trap		
			200 μL min^{-1}			
9 basic pharmaceuticals	Environmental analysis	PFP column (100 mm × 4.6 mm I.D., 5 μm)	(A) Ammonium acetate 2 mM	Mass spectrometry	12 min	[189]
	Wastewater and surface water		(B) ACN (ammonium acetate 2 mM)	Triple quadrupole		
			1000 μL min^{-1}			

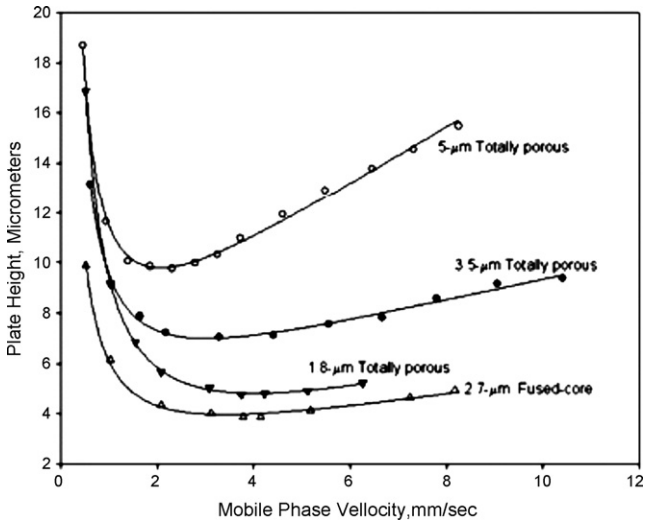

Fig. 4. Theoretical van Deemter curves plotted for 5, 3.5 and 1.8 μm totally porous particles and 2.7 μm porous shell particles.

described. d_p is the particle diameter of column packing material, D_M is the analyte diffusion coefficient, λ is the structure factor of the packing material, γ is a constant termed tortuosity or obstruction factor and k is the retention factor for an analyte [100]. The smaller the particle diameter of the column packing material, the higher the column efficiency.

However, the use of small particles induces a high pressure drop, and according to Darcy's law, the pressure drop is inversely proportional to the square of particle size diameter at the optimum linear velocity:

$$\Delta P = \frac{\Phi \eta L u}{d_p^2}$$

where Φ is the flow resistance, η is the mobile phase viscosity, L is the column length, u is the mobile phase linear velocity and d_p is the particle size. This means that under optimal flow velocity a 1.7–1.8 μm particle packed column will generate 8–9 times higher pressure than a 5 μm particle packed column at similar flow rate. Therefore, new ultra-high pressure resistant systems are necessary in order to profit fully from the advantages of the use of sub-2 μm particles. Moreover, one of the most challenging parts of an UHPLC system is sample introduction at very high pressures in a miniaturized volume. This has been studied by MacNair et al. [103] and by Wu et al. [104] who developed the first static split injection and later the pressure balance valve. In 2004 the Waters Corporation introduced the first commercially available UHPLC system, which was extensively followed by other important manufactures. Individual UHPLC systems differ in their amounts of maximum reachable back-pressure, flow-rate range possibilities and dead volume, between other parameters. An UHPLC system must withstand the high backpressures, but this is not the only requirement. It must also be adapted to operate in fast and ultra-fast mode with reduced column diameters such as 2.1 mm I.D., limiting frictional heating and substantially reducing solvent consumption [86]. However, it should be pointed out that in many cases UHPLC systems are used for conventional liquid chromatography separations with conventional 3–5 μm particle packed columns so not all UHPLC methods published in the literature are dealing in fact with fast or ultra-fast separations.

Several recent applications of UHPLC methods in food [21,30,105–138] and environmental [139–148] analysis using sub-2 μm particle size packed columns are summarized in Table 3. As can be seen, during the last three years UHPLC using columns

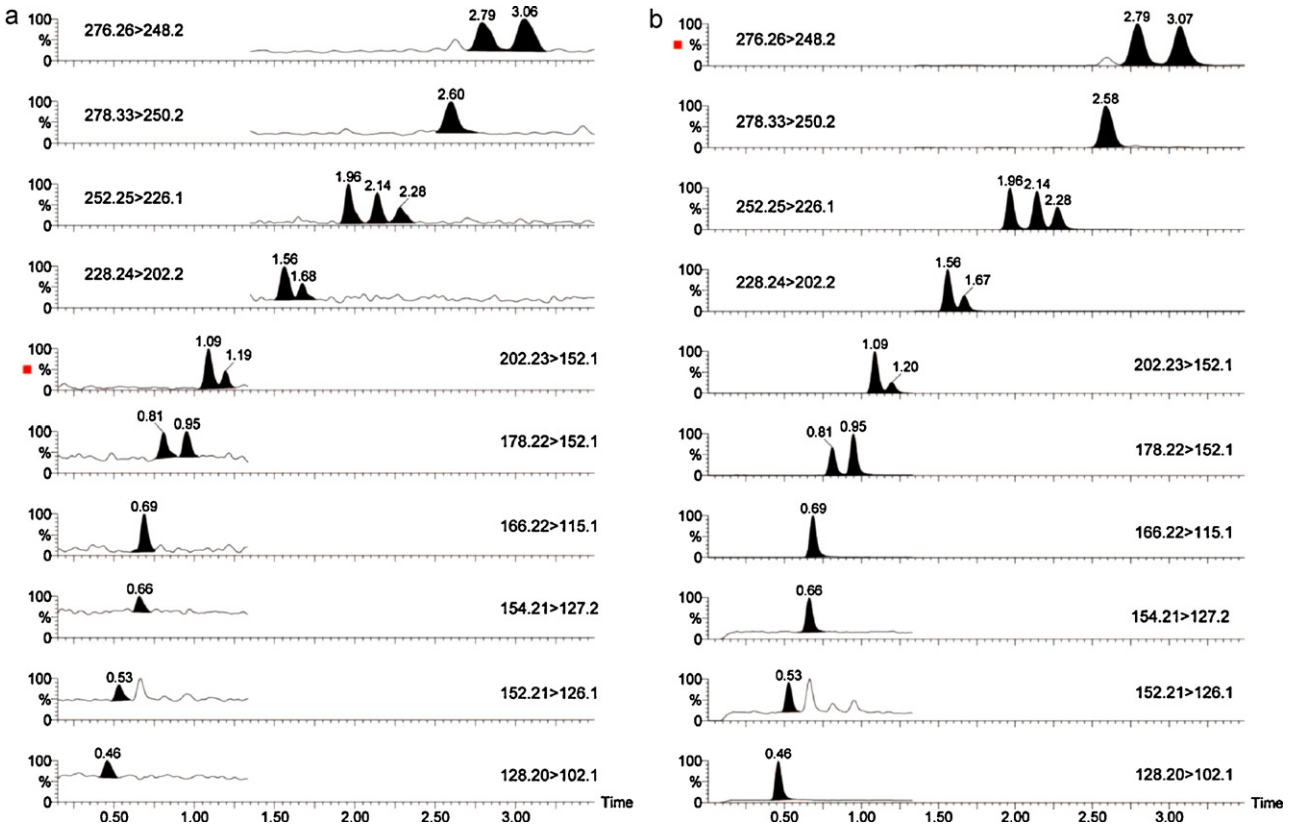

Fig. 5. (a) PAH MRM chromatograms for RT 0.46, naphthalene (48.8 pg); 0.53, acenaphthylene (390 pg); 0.66, acenaphthene (195.4 pg); 0.69, fluorene (24.4 pg); 0.81, phenanthrene (12.2 pg); 0.95, anthracene (12.2 pg); 1.09, fluoranthene (24.4 pg); 1.19, pyrene (24.4 pg); 1.56, benzo[a]anthracene (12.2 pg); 1.68, chrysene (12.2 pg); 1.96, benzo[b]fluoranthene (12.2 pg); 2.14, benzo[k]fluoranthene (12.2 pg); 2.28, benzo[a]pyrene (12.2 pg); 2.60, dibenzo[a,h]anthracene (12.2 pg); 2.79, benzo[ghi]perylene (12.2 pg); 3.06, indeno[1,2,3-cd]pyrene (12.2 pg). Injection: 2 μL. Peak top labels denote retention time on column. (b) PAH MRM chromatograms. Injection amount: 1.56 ng for each analyte. Parameters and conditions same as panel a. Chromatographic conditions: Agilent Zorbax Eclipse PAH 600Bar (2.1 mm × 50 mm, 1.8 μm) column. Mobile phase: gradient elution with 90:10 (v/v) water:acetonitrile (component A) and acetonitrile (component B). Mobile phase flow rate: 600 μL min^{-1}. Dopant chlorobenzene flow rate: 65 μL min^{-1}. Column temperature: 15 °C, injection volume: 2 μL.
Reproduced from Ref. [143], with permission of American Chemical Society.

packed with sub-2 μm particles has been widely used in food analysis compared to environmental applications. Most of the applications are based on reversed-phase separations using the Acquity UPLC BEH C18 columns of 1.7 μm particle size with different columns lengths, but other C18 reversed-phase columns such as Zorbax Eclipse XDB-C18 (1.8 μm particle size) [30,131,138,140] or Hypersil GOLD C18 (1.9 μm particle size) [106,121] have also been used. As an example, Gosetti et al. reported an automated on-line SPE UHPLC–MS/MS method for the analysis of nine perfluorochemicals in biological, environmental and food samples using a Zorbax Eclipse XDB-C18 column (50 mm × 4.6 mm I.D., 1.8 μm particle size) [30]. By working at a mobile phase flow-rate of 1 mL min^{-1} under gradient elution a fast chromatographic separation in less than 5 min was achieved. Quantitation and confirmation was performed by using a QTrap mass analyser in SRM acquisition mode, obtaining limits of quantitation (LOQs) in the range 10–50 ng L^{-1} with recoveries higher than 82.9%. Some specific stationary phases for columns packed with sub-2 μm particles has also been reported, such as the use of an Agilent Zorbax Eclipse PAH 600Bar column (1.8 μm particle size) for the analysis of EPA 16 priority pollutants polynuclear aromatic hydrocarbons in water samples (Fig. 5) [143]. The UHPLC–atmospheric pressure photoionization (APPI)-MS/MS (triple quadrupole instrument) method developed allowed the analysis of the 16 EPA priority PAH pollutants in less than 3 min and improving instrumental sample throughput by at least 10-fold compared with existing U.S. EPA methods. Today, several other stationary phases such as high strength silica (HSS) columns [107], HILIC, ion-exchange and normal phases may be used under UHPLC conditions, therefore its use will be discussed in the next section.

From the point of view of detection, the narrow peaks produced by fast UHPLC require a small detection volume and fast acquisition rate to ensure high efficiency. Most commercial UHPLC instruments are equipped with a modified UV detector to ensure the optimal peak capture. The flow cell volume is usually much lower than that for conventional HPLC to minimize the extra-column volume, typically 0.5–2.0 μL. On the last years, few applications were reported either using UV detection [121,127,130,141,142] or fluorescence detection [111,135], but with complex matrices such as food and environmental samples, mass spectrometry has become the technique of choice in order to guarantee confirmation of target compounds. Those MS instruments are required to work at low dwell times and low inter-channel and inter-scan delays in order to obtain a sufficient amount of data points per peak for UHPLC applications. The MS instrument of choice in food and environmental applications by UHPLC is the triple quadrupole mass analyzer as it can be seen in Table 3, working in selected reaction monitoring (SRM) acquisition mode because of its high sensitivity and selectivity. Other MS analyzers such as Qtrap mass analyzers [30,122,145] have also been used for UHPLC applications. High resolution MS has also been proposed for UHPLC applications in food or environmental samples, such as the use of time-of-flight (TOF) analyzers [125,133,138], hybrid quadrupole-TOF analyzers [117,129,136,148] or even Orbitrap mass analyzers [125]. For instance, Zachariasova et al. developed a rapid and

simple UHPLC method coupled to high resolution mass spectrometry for the effective control of occurrence of 11 major *Fusarium* toxins in cereals and cereal-based products to which they might be transferred during processing [125]. The use of Orbitrap technology at a mass resolving power of 100,000 at full width height maximum (FWHM) clearly allowed the possibility to eliminate sample handling steps and to directly analyze crude extracts, with mass accuracies in the range of −0.7 to +0.3 ppm.

3.3. Fused-core particle packed columns

Fast chromatographic and high efficiency separations can also be achieved using columns packed with superficially porous particles, also known as fused-core columns. The use of this kind of particles was first reported in 1960s with the objective of reducing analyte diffusion distance to minimize mass transfer [149]. Today, these columns are commercially available under the brand name *HALO*, consisting of silica particles of a 1.7 μm fused core and 0.5 μm layer of porous silica coating, creating a total particle diameter of 2.7 μm or *Ascentis* fused-core silica columns (Sigma–Aldrich), *Kinetex* (Phenomenex) with a 1.9 μm fused core and 0.35 μm layer of porous silica coating, obtaining a 2.6 μm particle and *Accucore* (Thermo Fisher Scientific) with also total particle diameter of 2.6 μm. The use of fused-core silica particles has improved chromatographic column efficiency over fully porous particles in reversed-phase separations [150]. These particles exhibit efficiencies that are comparable to sub-2 μm porous particles, but with modest backpressures. This may be due to the narrow particle size distribution and higher density of fused-core particles [151,152]. Further, the small diffusion path for the analyte may reduce the resistance to mass transfer (*C*-term in van Deemter equation) thus allowing operation at higher flow rates with minimal losses in efficiency [153]. As an example, Fig. 6 shows the separation obtained for a mixture of BPA and chlorinated-BPA compounds in a sub-2 μm particle sized Acquity BEH C18 column and a fused-core Ascentis Express C18 column. As can be seen, both columns provided similar column efficiency with the advantage that the fused-core column presented lower column backpressure (300 bar against 725 bar) being possible to achieve a fast chromatographic separation using conventional HPLC systems. The performance of fused-core particle columns have extensively been studied by Guiochon and co-workers [154–158], and today many publications on experimental work comparing sub-2 μm particles with fused-core columns are reported in the literature [3,159–162].

However, as the use of fused-core particles is a relatively recent trend in chromatographic separation, only a small amount of food applications are described in the literature, and some of the most recent ones have been included in Table 3 [27,32,163–168]. As in the case of columns packed with sub-2 μm particles, most of the applications are dealing with C18 reversed-phase separations. In general, mass spectrometry is the technique of choice to guarantee confirmation of target analytes, but UV detection [165] or fluorescence detection [164,165] are also employed. Triple quadrupole instruments are also the MS analyzers of choice for these kinds of applications. As an example, Gallart-Ayala et al. proposed UHPLC–MS/MS methods using fused-core *Ascentis Express* columns for the analysis of bisphenols [32] and BADGE, BFDGE and their derivatives [163] in canned food and canned soft drinks with analysis times lower than 5 min. In this case the use of a hyperbolic triple quadrupole instrument working in enhanced resolution (H-SRM) mode allowed to minimize interferences and background noise when dealing with the analysis of bisphenols in complex matrices, providing LODs 5–10 times lower than those obtained using conventional SRM acquisition mode [32]. However, other MS analyzers such as triple quadrupole linear ion traps have also been reported for the analysis of phenolic compounds in beverages [27] or chloramphenicol in egg, honey and milk samples [167].

3.4. Use of other stationary phases (HILIC, PFPPs)

Due to its wide applicability and ease of use, reversed-phase liquid chromatography with alkylsiloxane-bonded silica stationary phase is commonly used in environmental and food analysis (Table 3). In such cases, the chromatographic separation is usually optimized by varying the mobile phase composition and temperature. When these approaches are not enough to afford a good chromatographic separation, variation of the stationary phase is a useful option. Nowadays, stationary phases such as HILIC, fluorinated reversed phase, amide, porous graphitic carbon, phenyl, mix-mode, among others are commercially available and can be easily tested in order to improve chromatographic separation. In this section only the results obtained with HILIC and fluorinated reversed-phase columns will be discussed since these are the most common stationary phases used as an alternative to alkyl reversed-phase in food and environmental analysis, and the most relevant applications are summarized in Table 4 [5,22,169–189].

Hydrophilic interaction liquid chromatography (HILIC) is becoming a popular alternative to both normal and reversed-phase chromatography for the analysis of polar and ionic compounds. Highly polar compounds may get poorly retained in reversed phase mode making its analysis difficult. On the other hand, the same compounds may be strongly retained in normal phase columns resulting in better separations. In 1990, Alpert [190] proposed a new term, hydrophilic interaction liquid chromatography, to describe a method using polar stationary phases (bared silica, aminopropyl, diol and switterionic phases bonded to silica or polymeric supports), in combination with aqueous-organic mobile phases. When more than 1% of water is used in the mobile phase the layer of water adsorbed on the polar stationary phase is usually thick enough to induce the liquid-liquid partition between the bulk mobile phase and the adsorbed aqueous layer. HILIC retention is controlled by a combination of partition and other interactions such as ion-exchange, H-bonding and dipole–dipole affecting the selectivity of the separation [191,192]. An advantage of this technique is that in HILIC mode the elution order is often the opposite of that obtained with a reversed-phase chromatography and ion-pair additives are not necessary, thus coupling to mass spectrometry is easier. In addition, the use of high percentage of organic solvents (acetonitrile) enhanced the ionization and increase sensitivity. Another important parameter that affects the retention of polar compounds in HILIC is the ionic strength. Polar compounds have generally slightly higher retention when increasing ionic strength if there is no ionic interaction between the stationary phase and the analyte. As it is reported by Ihunegbo et al. [193] the reason may be that the increased salt concentration promotes the enrichment water layer improving the retention. However, if there is electrostatic interaction between a charged stationary phase and the analyte the retention decreases with increasing the ionic strength because of the competition between the analyte and the buffer ions.

Nowadays as it is reviewed by van Nuijs et al. [194] HILIC has been established as a valuable complementary approach to reversed-phase liquid chromatography in food and environmental analysis of polar compounds, both ionic and non-ionic such as pharmaceutical, drugs of abuse, pesticides and others (Table 4). As an example, Gianotti et al. [170] developed a fast and sensitive method based on HILIC–MS/MS for the analysis of seven biogenic amines (BAs) in cheese avoiding the matrix effects generally observed when these compounds are analyzed by reversed phase LC. Whereas, Esparza et al. [169] developed a sensitive HILIC–MS/MS method as an alternative for the analysis of

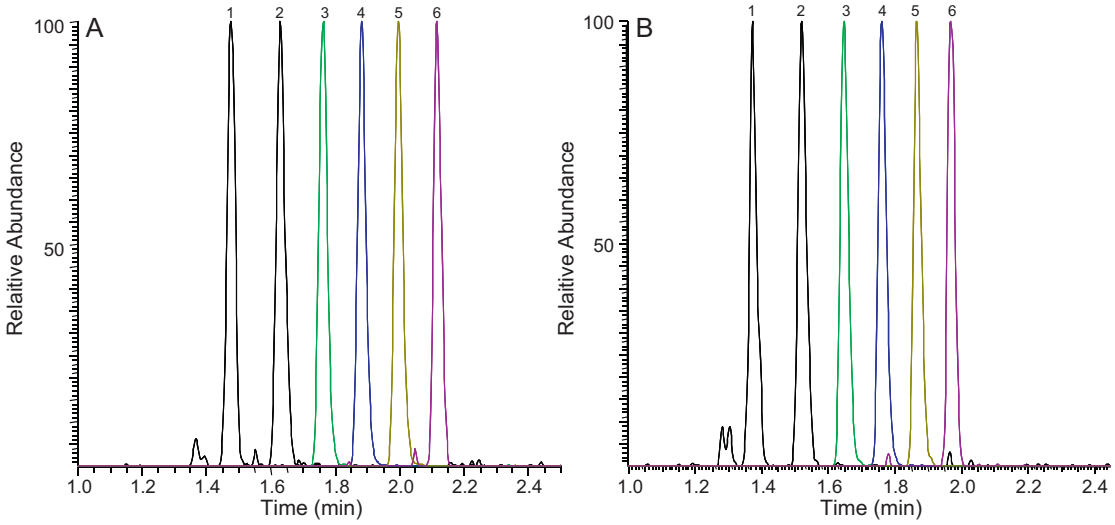

Fig. 6. Separation efficiency obtained with (A) sub-2 μm column (Acquity BEH C18 50 mm × 2.1 mm I.D., 1.7 μm particle size) and (B) porous shell column *fused-core* (Ascentis Express C18 50 mm × 2.1 mm I.D., 2.7 μm particle size). Chromatographic conditions: gradient elution with 80:20 water (component A) and MeOH (component B) at 600 μL min^{-1}. 1, BPA; 2, MCBPA; 3, DCBPA; 4, TCBPA; 5, TeCBPA; 6, TBBPA.

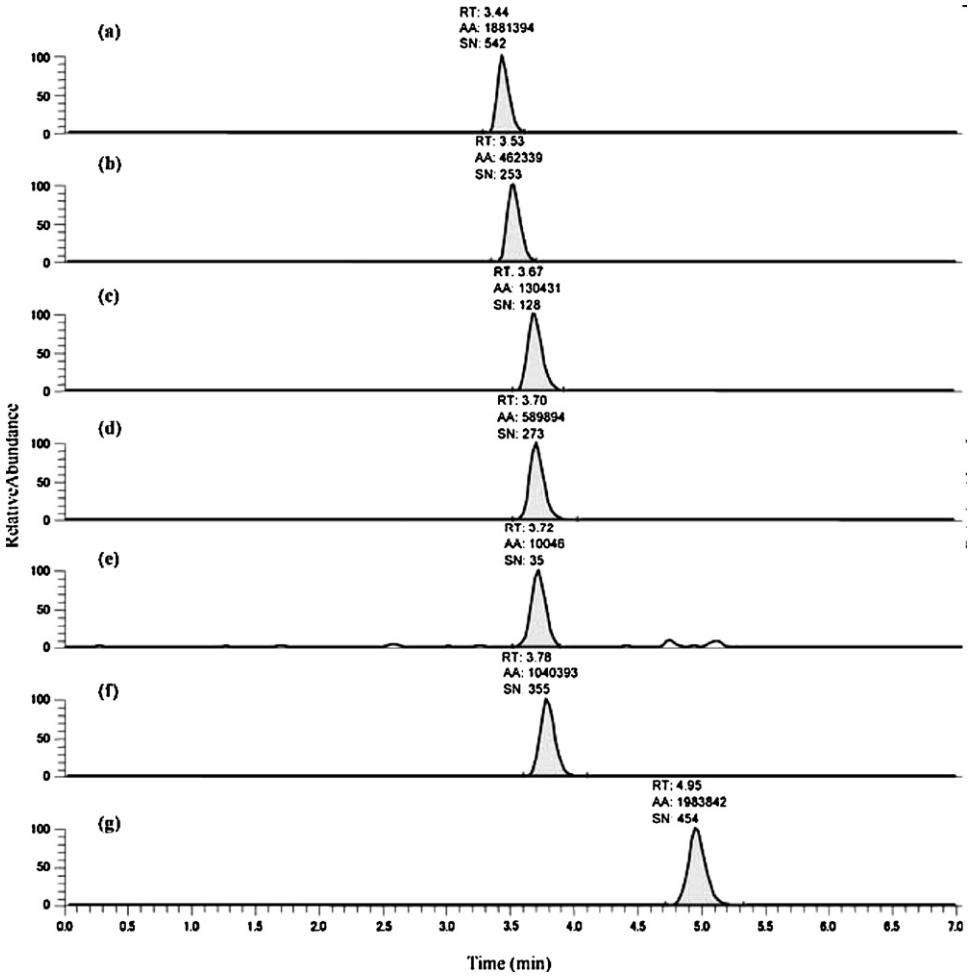

Fig. 7. Chromatographic separation of polar organophosphorus pesticides using and HILIC column. Peak identification, (a) vamidothion, (b) monocrotophod, (c and d) $^{2}H_{6}$-acephate, (e) methamidophos, (f) omethoate and (g) oxydemeton-methyl. Chromatography conditions: Atlantis HILIC silica (150 mm × 2.0 mm, 5 μm) column. Mobile phase: isocratic elution with acetonitrile:isopropanol:200 mM ammonium formate buffer (pH 3.0) (92:5:3, v/v/v). Mobile phase flow rate: 200 μL min^{-1}. Column temperature: 40 °C. Reproduced from Ref. [173], with permission of Wiley and Sons.

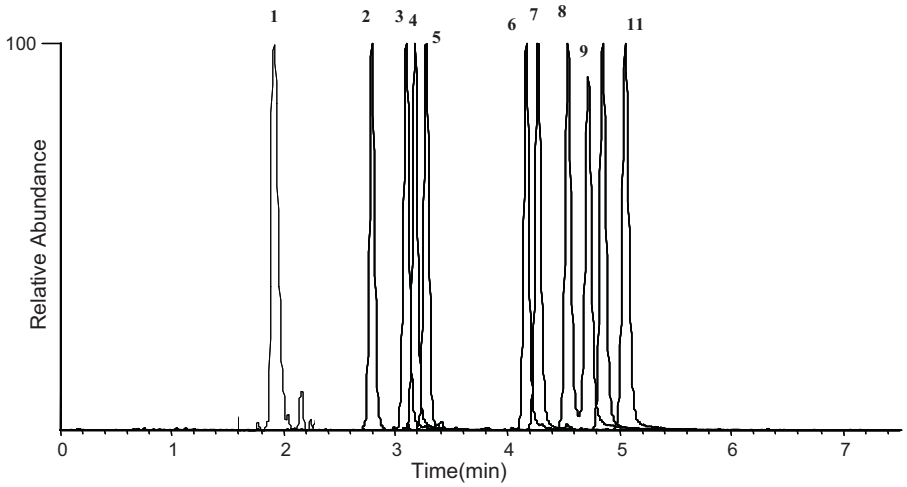

Fig. 8. Chromatographic separation of 11 UV ink photoinitiators using a PFPP column at 5 °C and 450 μL min^{-1}. Chromatographic conditions: Discovery HS F5 (150 mm × 2.1 mm, 3 μm) column. Mobile phase: gradient elution with acetonitrile (component A) and 25 mM formic acid–ammonium formate buffer (pH 2.7) (component B). Mobile phase flow rate: 450 μL min^{-1}. Column temperature: 5 °C. Peak identification: 1, HMPP; 2, HCPK; 3, EDMAB; 4, DMPA; 5, BP; 6, PBZ; 7, DEAB; 8, 2-ITX; 9, 4-ITX; 10, EHDAB; 11, DETX.

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chlormequat (CQ) and mepiquat (MQ) in food matrices avoiding the use of ion-pair reagents. Hayama et al. [173] proposed HILIC–MS/MS method for the analysis of organophosphorus pesticides (OPPs) in water samples obtaining a good chromatographic separation in less than 5 min (Fig. 7). Since this family of compounds is generally analyzed by GC–MS but some OPPs are thermally labile or very polar and therefore not suitable for GC methods, alternative LC–MS methods have been introduced to their determination. However, alkyl reversed-phase columns barely retain these compounds, and important matrix effects were observed.

Other stationary phases complementary to the alkyl-type (C8 and C18) are fluorinated reversed ones. Two types of highly fluorinated siloxane-bonded stationary phases can be distinguished, perfluoroalkyl and pentafluorophenyl, showing different separation characteristics [195]. Perfluoroalkyl ones exhibit enhanced retention and selectivity for the separation of halogenated compounds and shape selectivity for the separation of positional isomers and non-planar molecules but this type of stationary phases are rarely used in food and environmental analysis. However, the pentafluorophenyl stationary phases are more hydrophobic and display higher shape selectivity. In particular, pentafluorophenyl propyl (PFPP) phases have shown novel selectivity and enhanced the retention of several classes of compounds. Compared to traditional alkyl-type stationary phases which achieved selectivity based on hydrophobic interactions, the pentafluorophenyl stationary phases uses multiple retention mechanisms such as dipole–dipole, π–π and dispersion interactions in addition to hydrophobic interactions. Due to its unique selectivity and the higher retention observed for polar compounds the use of these columns is becoming popular in food and environmental analysis. One of the principal advantages of these columns is that the higher retention obtained for some polar compounds make possible to increase the organic percentage of the mobile phase improving the ESI ionization efficiency in mass spectrometry. For instance, Teixido et al. [174] developed a LC–MS/MS method for the analysis of 5-hydroxymethylfurfural in food using a PFPP column. In this case the PFPP stationary phase provided higher retention than an alkyl-reversed phase one and as consequence the percentage of organic solvent was increased improving the ionization efficiency. Furthermore, these stationary phases have proved to be useful resolving some isomeric compounds such as, tocopherols [196] and taxanes. This selectivity has been used by Pellati and Benvenuti [175] and Gallart-Ayala et al. [5] to separate a phenethylamine alkaloids mixture in citrus natural products without the use of ion-pair reagents, and to separate 2- and 4-ITX in packaged food, respectively. In this last case, 2- and 4-ITX are generally analyzed using alkyl-reversed phase columns without achieving the chromatographic separation of the two isomers. This chromatographic separation was used at a later stage for the simultaneous analysis of eleven photoinitiators in packaged food [22] obtaining a good chromatographic separation including the separation of the two ITX isomers (Fig. 8).

3.5. Use of temperature in liquid chromatography

The influence of temperature in liquid chromatography has been widely studied in many fields in order to improve separation efficiency. In general, working at high temperature (>60 °C) in liquid chromatography can be used to perform rapid analysis using standard columns since mobile phase viscosity and column back-pressures will decrease [197,198]. Efficiency, mass transfer, and optimal velocity increases simultaneously with temperature, allowing the application of high mobile phase velocity. As it has been previously described, the dependence of the height equivalent to a theoretical plate (HETP) on the linear velocity of the mobile phase can be written as:

$$H_u = A + \frac{B}{u} + Cu$$

The HETP depends on three terms, which are the band broadening due to Eddy diffusion (A-term), longitudinal diffusion (B-term) and the resistance to mass transfer in the mobile phase and in the stationary phase (C-term). It is often assumed that A-term does not depend on temperature, while B- and C-terms are both temperature dependent, the B-term being directly proportional to the diffusion coefficient while the C-term is inversely proportional to the diffusion coefficient. The diffusion coefficient of a given analyte is directly proportional to temperature and also inversely proportional to viscosity, meaning that by increasing the temperature, the diffusion of the analytes in both the mobile phase and the stationary phase will be increased. This effect is also enhanced by the fact that viscosity is also a strong function of temperature. Consequently, it can be considered that increasing temperature will lead to an increase of the absolute plate number for a given column.

Nevertheless, some reports are coming to a different conclusion. Yang et al. [199] noted that column efficiency was either improved or almost unchanged with increasing temperature (between 60 and 120 °C) but decreased at higher temperatures (between 120 and 160 °C). This means that there are other factors which are responsible for band broadening and thus a loss in efficiency in high temperature liquid chromatography.

Despite some of the advantages of working at high temperature it is not yet routinely used in food and environmental analysis since it has some drawbacks, and only relatively high temperature (up to 60 °C) are frequently employed. In general there is a limitation in the stability of packing materials at high temperatures and potential degradation of unstable compounds can occur. In these cases the temperature is generally used in order to decrease column backpressure in sub-2 μm particle size columns. However, some environmental applications at high temperature are described in the literature. As an example, the analysis of triazine herbicides by UHPLC at 160 °C was proposed using an Hypercarb column (100 mm × 1 mm, 3 μm particle size), allowing the separation of 12 herbicides in less than 2.5 min [200].

High-speed and high-resolution UHPLC separation at zero degrees Celsius has also been reported in the literature [1], so it should be mentioned that working at lower column temperature (below room temperature) must also be evaluated because in some cases separation could be improved (the decrease in temperature will produce an increase in resolution). As an example, Fig. 8 shows the effect of column temperature (between 5 and 25 °C) in the separation of eleven UV ink photoinitiators [22]. By decreasing temperature down to 5 °C, chromatographic separation in a 3 μm particle size pentafluorophenyl propyl (PFPP) column of eleven photoinitiators without an important lost in analysis time was reported. The column packed with 3 μm particles allowed to work at higher mobile phase flow-rates without worsening resolution, affording a fast LC–MS/MS method (total analysis time of about 5 min) for the analysis of this family of compounds in packaged foods. Evaluating separations at relatively low and high column temperature must then be explored to propose fast chromatographic methods for food and environmental analysis.

4. Conclusions and future perspectives

There is a growing demand for high-throughput chromatographic separations in food and environmental analysis where very different and complex matrices may be analyzed. Fast or ultra-fast separation methods are required to satisfy the necessity of reducing the total analysis time in fields where the number and variety of samples is increasing. Moreover, the number of target and non-target compounds is also increasing, especially when addressing food and environmental safety issues.

The most recent approaches in fast liquid chromatography methodology for food and environmental analysis have been discussed in this review. The advantages and drawbacks of these methodologies, i.e. the use of monolithic columns, the use of temperature in liquid chromatography, as well as UHPLC either using sub-2 μm particle size column or fused-core column technologies, have been pointed out. Monolithic columns seems to be a good alternative for high-efficiency separations due to their high permeabilities and low backpressures but the main drawback of these columns is the lack of commercially available stationary phases (in general only C8, C18 or plain silica based columns are available). Although some applications using home-made monolithic stationary phases are available (such as the use of MIP monoliths in food analysis), developing new LC and LC–MS methods using monoliths will be a field to explore in the future to achieve fast, sensitive and selective applications for food and environmental analysis.

High temperature liquid chromatography is a good alternative to improve separation efficiency and reduce analysis time, but despite the advantages of working at high temperature such as the reduction of organic solvents (becoming a green approach in LC methodology) or the possibility of changing the selectivity of the separation, this approach is not yet routinely used in food and environmental analysis. The use of temperature in these field has been limited only to relatively increase temperature up to 60–80 °C with the objective of reducing mobile-phase viscosity and, consequently, column backpressure, but not focusing on the main advantages of high temperature. Some drawbacks are still present such as the limitation of stable high-temperature-resistant packing materials or the limitation of temperature stability of many target or even non-target compounds frequently analyzed in food and environmental applications. So the development of more stable and high-temperature-resistant packing materials is necessary in the near future to enable exploring high temperature liquid chromatography applications in food and environmental fields.

Today, the most convenient approach to achieve modern, high-throughput, efficient, economic and fast LC separations in food and environmental applications is UHPLC technology using both sub-2 μm and porous shell particles. This technology provides the most substantial reduction in analysis time and very high efficiency. Moreover, different stationary phases – reversed phase, HILIC, PFPP, etc. – are available in both sub-2 μm and 2.7 μm porous shell particles providing complementary selectivities. The use of columns packed with sub-2 μm particles requires special instrumentation because of the high pressure; this drawback can be compensated by the use of porous shell columns, which can be used in any HPLC or UHPLC instrument, because the backpressure is considerably reduced but keeping similar efficiency as sub-2 μm particle size columns. From this point of view, columns packed with porous shell particles seems to be a more advantageous approach to easily achieve fast LC separations even with conventional LC instrumentation, becoming a field to explore in the next years, especially in food and environmental applications where the use of sub-2 μm particle size columns is unequivocally leading fast liquid chromatographic applications (Table 3).

Despite the important advances in fast liquid chromatography, food and environmental matrices are very complex, and although multi-residue methods with minimal sample manipulation are demanded, sample extraction and clean-up treatments must be carefully developed to reduce total analysis time. The most recently introduced sample treatment methodologies in food and environmental applications have also been addressed in this review, such as QuEChERS, on-line SPE methods, turbulent-flow chromatography and the use of MIPs for both, separation and sample treatment. Many current sample preparation techniques are focusing on the reduction of sample manipulation and the number of treatment steps prior to analysis. However, it should be pointed out that sample preparation techniques must be chosen and optimized regarding the method purpose and in consideration of the chromatographic separation. In some cases, a simple and fast sample treatment procedure will not be compatible with a fast liquid chromatographic separation as problems concerning matrix related interferences or matrix effect may arise. Some examples approaching this fact have also been discussed in this review. Sometimes chromatographic analysis time must be sacrificed to prevent matrix effects or even additional clean-up steps must be considered to improve chromatographic sensitivity.

QuEChERS appeared as a simple, rapid and inexpensive sample extraction and clean-up (using dispersive-SPE) procedure generally employed for multi-residue methods, especially in the analysis of pesticides. The good results provided in this field promoted this sample extraction procedure to the analysis of other family of compounds in food and environmental matrices such as

acrylamide, veterinary drugs, mycotoxins, PAHs, chlorinated compounds, among others, although there are many other families of compounds and matrices to evaluate, regarding sensitivity and recovery for some specific compounds. SPE is one of the most frequently used technique in food and environmental analysis. On-line SPE is reported as a good alternative since it provides faster methods by reducing sample preparation time and increasing sample throughput. However, although UHPLC is the most convenient approach for fast liquid chromatography, not many methods are yet published in the literature coupling on-line SPE with UHPLC technology. Some drawbacks need to be improved in the future: the high backpressures obtained in UHPLC technology (>9000 psi) which are not compatible enough with conventional on-line SPE systems that generally operate at low backpressures (<6000 psi), and the band broadening produced by the large amounts of organic solvents used for the SPE elution step. Although instrumentation allowing a successful coupling is now commercially available, more comprehensive tests will be necessary to assess their applicability in food and environmental analysis.

Turbulent-flow chromatography appears as a very useful approach for sample treatment by removing proteins based on their size better than restricted access media or SPE procedures. Although not many applications in food and environmental samples are yet available, it will become a very useful method basically in food and especially in matrices with a high content of fat and proteins.

Finally, the use of MIP materials is a very useful approach for some food and environmental applications because it allows not only a preconcentration, but also a selective separation of target analytes from real samples, which is crucial for the quantitative, sensitive and selective determination of compounds in very complex matrices. One of the main advantages of MIPs is the possibility to prepare selective sorbents pre-determined for a particular substance or a group of structural analogs, which will become very useful for some specific applications. However, some features still need to be improved, such as the increase of binding sites to achieve higher capacity and selectivity.

There are many methodologies to choose from in the literature. Comprehensive testing is needed in order to evaluate some of these methodologies applied into food and environmental applications. Both sample treatment and chromatographic separations must be developed and optimized in alignment, focusing in the reduction of the total analysis time and guaranteeing an accurate analysis.

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