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Determination of bisphenols in beverages by mixed-mode solid-phase extraction and liquid chromatography coupled to tandem mass spectrometry☆

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ABSTRACT

Facing growing restrictions on the use of bisphenol A in food contact materials, several bisphenol analogs are arising as major alternatives to replace this chemical in most of its applications. This work reports a simple and robust method based on mixed-mode solid-phase extraction and stable-isotope dilution liquid chromatography–tandem mass spectrometry for the analysis of bisphenol A and its main analogs – bisphenol S, 4,4′-sulfonylbis(2-methylphenol), bisphenol F, bisphenol E, bisphenol B, bisphenol Z, bisphenol AF, bisphenol AP, tetrabromobisphenol A and bisphenol P – in alcoholic and non-alcoholic beverages. Mixed-mode solid-phase extraction, combining cationic exchange and reversed-phase mechanisms, was optimized to provide a selective extraction and purification of the target analytes. Derivatization of bisphenols with pyridine-3-sulfonyl chloride allowed increasing their ionization efficiency by electrospray ionization. Validation of the proposed method was performed in terms of selectivity, matrix effects, linearity, precision, measurement uncertainty, trueness and limits of detection. Satisfactory repeatability and intermediate precision were obtained; the related relative standard deviations were ≤9% and ≤12%, respectively. The relative expanded uncertainty ($k = 2$) was below 20% for all bisphenol analogs and the trueness of the method was demonstrated by recovery experiments. Limits of detection (LOD) ranged from 1.6 ng L^{-1} to 27.9 ng L^{-1} for all compounds. Finally, several canned and non-canned beverages were analyzed to demonstrate the applicability of the method. Only bisphenol A and three bisphenol F isomers were detected in any of the samples. Bisphenol A concentration ranged from <LOD to 1.26 ± 0.09 μg L^{-1}, whereas 4,4′-bisphenol F varied from <LOD to 1.00 ± 0.08 μg L^{-1}. To the best of our knowledge, 2,2′-bisphenol F and 2,4′-bisphenol F were reported for the first time in beverages, at concentration levels up to 0.12 and 0.51 μg L^{-1}, respectively.

1. Introduction

Bisphenol A (BPA), a chemical widely used in the manufacture of polycarbonate plastics and epoxy resins, is gathering increasing attention due to its endocrine disrupting potential. BPA-containing materials are employed in a large variety of applications including food and liquid containers, kitchenware, inner linings of metal cans and bottle tops, surface coatings, toys, medical devices, dental fillings and cash register receipts, among others [1–4].

Facing growing restrictions on the use of BPA in food contact materials [5–8], the plastic and canning industries are moving fast to seek alternative chemicals which allow replacing BPA in many of its applications. Thus, over the past few years products labeled as "BPA-free", potentially containing BPA substitutes, are becoming frequent in store shelves [3,9]. These new compounds have been designed to resemble the physicochemical properties of BPA, and most of them belong to the same chemical family of *p,p′*-bisphenols (Fig. S1, supporting information). Among these structural analogs, bisphenol S (BPS), bisphenol F (BPF), bisphenol B (BPB) and bisphenol AF (BPAF) are apparently the major BPA replacements [10,11].

The determination of these emerging contaminants in foodstuffs requires the development and validation of appropriate and robust analytical methods. To date, nevertheless, few methods have been developed for the analysis of BPA analogs in this kind of samples in general, and in beverages, other than canned soft drinks,

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in particular. Liquid–liquid extraction and solid-phase extraction (SPE) are the most common techniques for the extraction of BPA from liquid samples, and they have been also applied for the extraction of some BPA analogs from beverages [11–13]. Gallart-Ayala et al. [12] developed an on-line C18 SPE method coupled to liquid chromatography–tandem mass spectrometry (LC–MS/MS) for the determination of BPA, BPF, bisphenol E (BPE), BPB and BPS in canned soft drinks. Recently, molecular imprinted polymers (MIPs) have been used as sorbent for SPE of BPA, BPF, BPS, BPB, BPAF, tetrachlorobisphenol A and tetrabromobisphenol A (TBBPA) from beverages and canned foods [14]. MIPs sorbents normally allow obtaining a high degree of selectivity based on specific recognition of the template molecules. Nevertheless, the presence in some beverages (wine, beer, juices, tea, coffee, etc.) of high amounts of phenolic compounds, such as flavonoids and phenolic acids, presenting similar structures to the template molecules, may reduce the extraction efficiency and selectivity of MIPs. Other techniques, such as dispersive liquid-liquid microextraction [15] and stir bar sorptive extraction [16] have also been applied to the extraction of some bisphenol analogs.

As regards the determination of bisphenols in food and beverages, most of methods are based on gas chromatography coupled to mass spectrometry (GC–MS) following a derivatization step with acetic anhydride [13,15,16], *N*,*O*-bis(trimethylsilyl)trifluoroacetamide [16] or *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide [17], although some authors have also used LC–MS/MS [11,12,18–20].

In a very recent study conducted by our group [21], a sensitive LC–MS/MS method based on ultrasound assisted extraction preceded by sample disruption with sand and selective clean-up by primary secondary amine (PSA) SPE was proposed for the analysis of thirteen bisphenols in complex solid food samples. Due to the presence of strongly electronegative fluorine atoms on the phenyl ring, pentafluorophenylpropyl HPLC stationary phase was shown to provide an efficient separation of all the studied bisphenols. Indeed, baseline resolution was achieved for the three BPF isomers, which made possible their individual quantification.

The objective of the present work was to develop and validate a robust method based on stable-isotope dilution (SID) LC–MS/MS for the sensitive determination of BPA and its main analogs – BPS, 4,4′-sulfonylbis(2-methylphenol) (DMBPS), BPF, BPE, BPB, bisphenol Z (BPZ), BPAF, bisphenol AP (BPAP), TBBPA and bisphenol P (BPP) – in both alcoholic and non-alcoholic beverages. Mixed-mode SPE, combining cationic exchange and reversed-phase mechanisms, was optimized to provide a selective extraction of the target analytes. Derivatization of bisphenols with pyridine-3-sulfonyl chloride allowed increasing their ionization efficiency by electrospray ionization (ESI), thus improving the limits of detection (LODs). Validation of the proposed method was performed in terms of selectivity, linearity, precision, measurement uncertainty, trueness, LODs and matrix effects. Several canned and non-canned beverages purchased from different supermarkets in Belgium were finally analyzed to demonstrate the applicability of the method to commercial samples.

2. Materials and methods

2.1. Standards, reagents and materials

Bisphenol A (≥99%), bisphenol AF (97%), bisphenol AP (99%), 2,2′-bisphenol F (>98%), 4,4′-bisphenol F (98%), bisphenol P (99%), bisphenol S (98%), bisphenol Z (98%), 4,4′-sulfonylbis(2-methylphenol) (97%), tetrabromobisphenol A (≥97%) and pyridine-3-sulfonyl chloride (95%) were purchased from Sigma–Aldrich (Diegem, Belgium). Bisphenol B (>98%), bisphenol E (>98%) and 2,4′-bisphenol F (>98%) were obtained from TCI (Zwijndrecht, Belgium). Bisphenol A-$^{13}C_{12}$ (99.2% ^{13}C, 98% chemical purity), 4,4′-bisphenol F-D_{10} (96.8% D, 98% chemical purity) and bisphenol S-$^{13}C_{12}$ (99.6% ^{13}C, 97% chemical purity) were purchased from Toronto Research Chemicals (North York, Canada). Bisphenol AF-3,3′,5,5′-D_4 (99.4% D, 99% chemical purity) was obtained from C/D/N Isotopes (Pointe-Claire, Canada) and $^{13}C_{12}$-tetrabromobisphenol A (99% ^{13}C, 50 μg/mL in methanol) was from Cambridge Isotope Laboratories (Andover, MA,USA). Chemical structures of the analyzed compounds are shown in Fig. S1 (supporting information). Individual stock solutions of each analyte (ca. 1000 mg L^{-1}) and a mixture of them were prepared in methanol. Working standard solutions were made by appropriate dilution in methanol and then stored in amber glass vials at −20 °C.

All organic solvents (acetonitrile, ethyl acetate and methanol) were HPLC or LC/MS grade and all other chemicals were analytical reagent grade. Ultrapure water was produced using a Milli-Q Gradient water purification system from Merck Millipore (Bedford, MA, USA). Formic acid (98–100%), hydrochloric acid (37%), ammonium hydroxide (28–30%), sodium hydroxide and anhydrous sodium carbonate were purchased from Merck (Darmstadt, Germany).

SPE cartridges Oasis HLB (150 mg, 6 mL), Oasis MAX (150 mg, 6 mL) and Oasis MCX (150 mg, 6 mL) were purchased from Waters (Milford, MA). Regenerated cellulose membrane syringe filters (13 mm, 0.20 μm) were purchased from Grace (Lokeren, Belgium).

2.2. Samples

All beverages were purchased from local supermarkets in Belgium between April and December 2014. For method validation, two different pooled samples (alcoholic and non-alcoholic drinks) were prepared from glass bottled drinks, previously analyzed in order to guarantee the absence of bisphenols. The alcoholic pool consisted of malt whisky (40% alcohol by volume), blonde beer (5.2% alcohol) and red wine (13% alcohol) (1:1:1, v/v/v), whereas the non-alcoholic pool was composed by a cola soft drink, mineral water and English breakfast tea (1:1:1, v/v/v). The tea was infused as recommended on the label by manufacturer, i.e. 2 g/100 mL boiling water for 5 min.

2.3. Sample preparation

Carbonated beverages (beer, sparkling wine, sparkling water and soft drinks) were degassed in an ultrasound bath for 1 h prior to the extraction. Under optimized conditions, 10 mL sample were spiked with 2.5 ng of isotope-labeled standards in methanol (100 μL, 25 μg L^{-1}) and then extracted using Oasis MCX SPE cartridges (150 mg, 6 mL). The SPE cartridges were previously conditioned with 5 mL of ethyl acetate followed by 5 mL of methanol and by 5 mL of ultrapure water/formic acid (99:1, v/v).

For non-alcoholic drinks, 10 mL sample were directly loaded onto the SPE cartridges, whereas alcoholic drinks were first diluted 1:1 (v/v) with water/formic acid (99:1, v/v), and the resulting 20 mL of diluted sample were passed through the cartridge. After loading the sample, the cartridge was rinsed with 6 mL of water/formic acid (99:1, v/v) followed by 10 mL of a mixture of methanol/water/formic acid (30:69:1, v/v/v). The sorbent was then dried under moderate vacuum for 2 min and the analytes were finally eluted with 10 mL of a mixture of methanol/ethyl acetate/formic acid (8:91:1, v/v/v).

For juices containing pulp, 10 mL sample were transferred to a 50 mL polypropylene centrifuge tube and 5 mL of acetonitrile/methanol (80:20, v/v) were added. After vortex shaking for 10 s, the tube was immersed in an ultrasonic water bath Branson 2510 (Emerson, Dietzenbach, Germany) and sample was extracted at 40 kHz of ultrasound frequency at 30 ± 3 °C for 20 min. The resulting slurry was centrifuged at 3000 RCF for 5 min at 10 °C (Eppendorf

Table 1
MRM conditions used for the determination of bisphenols after derivatization with pyridine-3-sulfonyl chloride.

Compound	t_R (min)	Parent ion	Cone (V)	MRM1 (m/z)	CE1 (eV)	MRM2 (m/z)	CE2 (eV)	T1/T2 ± tol.[b]
BPS-diPS	5.43	$[M+H]^+$	60	532.9 > 327.1	23	532.9 > 391.1	23	1.7 ± 0.3
BPS-$^{13}C_{12}$-diPS[a]	5.43	$[M+H]^+$	60	544.9 > 339.1	23	544.9 > 403.1	23	1.7 ± 0.3
2,2′-BPF-diPS	5.55	$[M+H]^+$	70	483.2 > 199.0	25	483.2 > 277.2	25	1.5 ± 0.3
2,4′-BPF-diPS	6.21	$[M+H]^+$	70	483.2 > 199.0	25	483.2 > 277.2	25	1.9 ± 0.4
4,4′-BPF-D_{10}-diPS[a]	6.51	$[M+H]^+$	70	493.2 > 209.0	25	493.2 > 287.2	25	1.1 ± 0.2
4,4′-BPF-diPS	6.55	$[M+H]^+$	70	483.2 > 199.0	25	483.2 > 277.2	25	1.1 ± 0.2
DMBPS-diPS	6.74	$[M+H]^+$	60	561.3 > 355.1	23	561.3 > 419.1	23	1.6 ± 0.3
BPE-diPS	7.06	$[M+H]^+$	70	497.3 > 340.2	28	497.3 > 276.1	35	1.8 ± 0.4
BPA-diPS	7.62	$[M+H]^+$	70	511.3 > 354.2	28	511.3 > 290.1	35	2.2 ± 0.6
BPA-$^{13}C_{12}$-diPS[a]	7.62	$[M+H]^+$	70	523.2 > 366.2	28	523.2 > 302.1	35	2.2 ± 0.6
BPB-diPS	8.19	$[M+H]^+$	70	525.3 > 354.2	28	525.3 > 290.1	28	1.8 ± 0.4
BPZ-diPS	8.65	$[M+H]^+$	70	551.3 > 267.2	30	551.3 > 248.0	32	4.4 ± 1.1
BPAP-diPS	8.86	$[M+H]^+$	70	573.3 > 416.2	30	573.3 > 196.0	32	3.3 ± 0.8
BPAF-diPS	9.36	$[M+H]^+$	70	619.1 > 344.1	35	619.1 > 408.1	32	1.5 ± 0.3
BPAF-D_4-diPS[a]	9.36	$[M+H]^+$	70	623.1 > 348.1	35	623.1 > 412.1	32	1.5 ± 0.3
TBBPA-diPS	9.41	$[M+H]^+$	70	826.7 > 605.6	45	826.7 > 620.6	32	1.2 ± 0.2
TBBPA-$^{13}C_{12}$-diPS[a]	9.41	$[M+H]^+$	70	838.7 > 617.6	45	838.7 > 632.6	32	1.2 ± 0.2
BPP-diPS	10.31	$[M+H]^+$	70	629.4 > 276.1	28	629.4 > 134.0	35	2.0 ± 0.4

MRM1: quantifier transition; MRM2: qualifier transition; CE: collision energy; PS: pyridine-3-sulfonyl.
[a] Isotope-labeled standard.
[b] Quantifier-to-qualifier transition ratios and tolerances for positive identification.

5810R, Hamburg, Germany) and the supernatant was collected; the extraction procedure was repeated once more and both supernatants were combined. The combined extract was diluted with 10 mL of water/formic acid (99:1, v/v) and passed through the MCX cartridge as previously described.

The bisphenols were then derivatized with pyridine-3-sulfonyl chloride following the conditions recently reported [22]. Briefly, the SPE eluate was evaporated to dryness at 35 °C under a gentle nitrogen flow, reconstituted in 200 μL of sodium carbonate buffer (50 mmol L^{-1}, pH 9.8) and 200 μL of derivatization solution (4 mg mL^{-1} of pyridine-3-sulfonyl chloride in acetonitrile) were added. After vortex shaking for 10 s, the reaction mixture was placed in a dry block heater Techne DB100/2 (Bibby Scientific) at 70 °C for 15 min. Reaction was stopped by cooling down on ice and 100 μL of formic acid solution 1 mol L^{-1} were added. The extract was passed through 0.20 μm regenerated cellulose syringe filter and stored in amber glass vials at −20 °C until analysis.

2.4. LC–MS/MS analysis

Sample analyses were performed in an Agilent 1100 Series HPLC system (Agilent Technologies, Palo Alto, CA, USA) consisting of a binary pump, a vacuum degasser, an autosampler, and a column oven, coupled to a triple quadrupole mass spectrometer Waters Micromass Quattro Ultima PT (Waters, Milford, MA, USA) equipped with an ESI source.

Chromatographic separation was carried out on a pentafluorophenylpropyl Ascentis Express F5 column (100 mm × 2.1 mm, 2.7 μm) from Sigma–Aldrich, equipped with a F5 guard column (5 mm × 2.1 mm, 2.7 μm) and maintained at 25 °C. Mobile phases A and B were water/formic acid (99.8:0.2, v/v) and acetonitrile/water/formic acid (97.8:2:0.2, v/v/v), respectively. The following linear gradient was used: 0 min, 45% B; 0.5 min, 45% B; 9.5 min, 75% B; 10.5 min, 98% B; 12.0 min, 98% B; 12.5 min, 45% B and 18 min, 45% B. The flow rate was set to 240 μL min^{-1}, and the injection volume was 10 μL. To prevent salts from entering the ion source, the LC eluate was diverted to waste during the first 4.5 min of the chromatographic run.

The mass spectrometer was operated in the positive ESI mode under the following specific conditions: capillary voltage 3.60 kV, desolvation temperature 350 °C, source temperature 130 °C, cone gas flow 80 L h^{-1} and desolvation gas flow 750 L h^{-1}. Nitrogen (boil-off) was employed as nebulizer, desolvation and cone gas. The RF lens voltages 1 and 2 were set at 10 V and 0.4 V, respectively. The multiplier voltage was 650 V and the ion energies 1 and 2 were both 0.5 V. The entrance and exit voltages were −2 V and 1 V, respectively. Analyte detection was performed in multiple reaction monitoring (MRM) mode using Argon as collision gas at a pressure of 4.5×10^{-3} mbar. Two MS/MS ion transitions were monitored for each compound; the most intense transition was used for quantification, while the other one was employed for identification (Table 1). Confirmation was accomplished by comparing the quantifier-to-qualifier transition ratios in samples to those of the calibration standards; maximum permitted tolerances were taken from Commission Decision 2002/657/EC [23], which was used as a guide. Instrument control and data acquisition were performed with MassLynx v4.0 software from Waters.

2.5. Validation procedure

A full validation procedure was performed on the proposed method based on the recommendations of the Eurachem guide on analytical method validation [24] and the Commission Decision 2002/657/EC establishing criteria and procedures for the validation of analytical methods to ensure the quality and comparability of analytical results generated by official laboratories [23]. The ubiquity of BPA made not possible to obtain procedural blanks completely free of this compound, as previously reported by other authors [25,26]. Therefore, the background level was calculated for every batch of samples and then deducted from the BPA concentration in the analyzed samples. These experiments were accomplished using two different pooled blank samples corresponding to alcoholic and non-alcoholic beverages (see Section 2.2 for details), respectively.

2.6. Statistical analysis

Statistical calculations were made using the software package Statgraphics Centurion XV (Statpoint Technologies, Herndon, VA, USA). Unless otherwise specified, data are presented as the mean ± standard deviation (SD) and a 0.05 significance level was used.

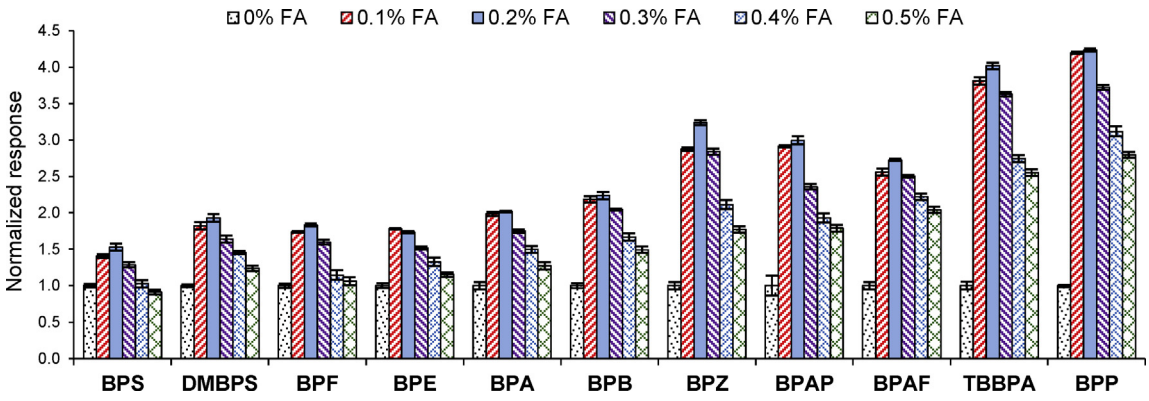

Fig. 1. Influence of formic acid (FA) percentage on the ionization efficiency of bisphenol derivatives. Responses were normalized to the intensities obtained without formic acid.

3. Results and discussion

3.1. Optimization of LC–ESI-MS/MS conditions

Over the last years, LC–ESI-MS/MS has consolidated as one of the most valuable analytical techniques in food analysis due to its sensitivity and selectivity for a wide array of compounds [27]. Optimization of the ESI-MS/MS parameters was carried out by post-column infusion and flow injection analysis (FIA) of individual standard solutions of the derivatized bisphenols in acetonitrile/water (1:1, v/v).

After derivatization with pyridine-3-sulfonyl chloride, ESI provided prominent $[M+H]^+$ ions corresponding to the protonated di-derivatized bisphenols. This derivatization reaction resulted in the introduction of a basic nitrogen into the target compounds, which enhanced the efficiency of positive ionization of the bisphenols derivatives [22]. Considering a pK_a value of around 2.5 (pK_a of the conjugate acid form of the amine), it was decided to evaluate the influence of the mobile phase pH on the ESI+ response. To this end, a standard solution of derivatized bisphenols (50 $\mu g\,L^{-1}$) was analyzed at increasing concentrations of formic acid in the mobile phases up to 0.5% (v/v). Fig. 1 shows the signal variation with the increase of formic acid content in the mobile phases. As can be noticed, ESI response increased significantly for all bisphenols until the percentage of formic acid reached 0.2%. Thus, the use of formic acid as mobile phase modifier shifts their acid-base equilibrium toward the charged forms, favoring the formation of the $[M+H]^+$ precursor ions, and consequently, increasing the intensity of the MS/MS transitions. Highest improvements were observed for the most lipophilic bisphenols (BPZ, BPAP, BPAF, TBBPA and BPP) which increased their response between 3- and 4.5-fold after the addition of the acid. Higher percentages of formic acid led to a progressive decrease in the monitored responses, possibly due to ionic suppression phenomena. Consequently, formic acid 0.2% (v/v) was selected as mobile phase modifier.

3.2. Selective solid-phase extraction procedure

The development of a method suitable for the determination of bisphenols in the wide variety of beverages available in the market represents a challenge. While relatively simple beverages, such as soft drinks, can be easily addressed by general SPE methods, the high complexity of other drinks (wine, beer, coffee, fruit juices, etc.) requires selective extraction and clean-up procedures in order to eliminate interferences potentially affecting their detection by ESI-MS/MS. Ethanol content of alcoholic beverages, usually varying from 4% to 40% by volume, entails an additional difficulty for the analysis of this kind of drinks.

Optimization of SPE conditions was carried out with a pooled sample of red wine (*Vitis vinifera* L. cv. Cabernet Sauvignon and Tempranillo, 13% alcohol), which is normally considered as one of the most complex beverages [28]. Three polymeric materials were evaluated as sorbents for the extraction of bisphenols, namely the reversed-phase hydrophilic-lipophilic balance sorbent Oasis HLB, the mixed-mode anion exchange/reversed-phase sorbent Oasis MAX and the mixed-mode cation exchange/reversed-phase sorbent Oasis MCX. These experiments were performed with 10 mL aliquots of wine spiked with bisphenols at 25 $\mu g\,L^{-1}$ level.

In a first series of extractions, samples were diluted with ultrapure water (1:1, v/v) to reduce the negative impact of ethanol on the retention of the analytes, and passed through the SPE cartridges at an approximate flow rate of 1 mL min^{-1}. Cartridges were then rinsed with 6 mL of ultrapure water to remove sugars and other polar interferents, dried with a gentle stream of nitrogen and eluted with 5 mL of methanol. Under these conditions, the main difference between the reversed-phase (HLB) and the mixed-mode (MAX and MCX) sorbents was the visual appearance of the extracts. Intense red extracts were obtained with the HLB sorbent, whereas clearer, pink extracts were achieved when the extraction was carried out with MAX or MCX sorbents. Probably, wine pigments with acidic/basic properties were retained by the mixed-mode sorbents due to electrostatic interactions with the charged groups existing in the surface of these polymers, resulting in cleaner extracts. Therefore, it was decided to further evaluate the possibilities of this kind of sorbents for the selective extraction of bisphenols.

In order to increase the ion exchange capabilities of MAX and MCX sorbents, 1% ammonia (v/v) and 1% formic acid (v/v) were used, respectively, during the washing and elution steps. Under the basic conditions provided by ammonia, acidic matrix inferences should remain ionized, being strongly retained by the quaternary amine groups of the MAX polymer. Conversely, the use of formic acid allows keeping basic interferences, such as wine anthocyanidins, positively charged during these steps, thus avoiding their elution due to strong electrostatic interactions with the sulfonic groups of the MCX polymer. Clearer, almost transparent extracts were obtained by using MAX cartridges; however, the most acidic bisphenols BPS ($pK_a = 7.4$) and TBBPA ($pK_a = 6.6$) could not be eluted, likely due to their stronger interactions with the anion exchangers under basic conditions. When elution was carried out with 1% formic acid (v/v) in methanol, these compounds were quantitatively recovered as most of pigments loaded onto the sorbent, rendering intense red extracts. Consequently, the use of MAX sorbent was discarded for further experiments.

For the MCX sorbent, an additional washing step with increasing percentages of methanol (0–40%, v/v) was evaluated (Fig. 2A). Since bisphenols are only retained by a reversed-phase

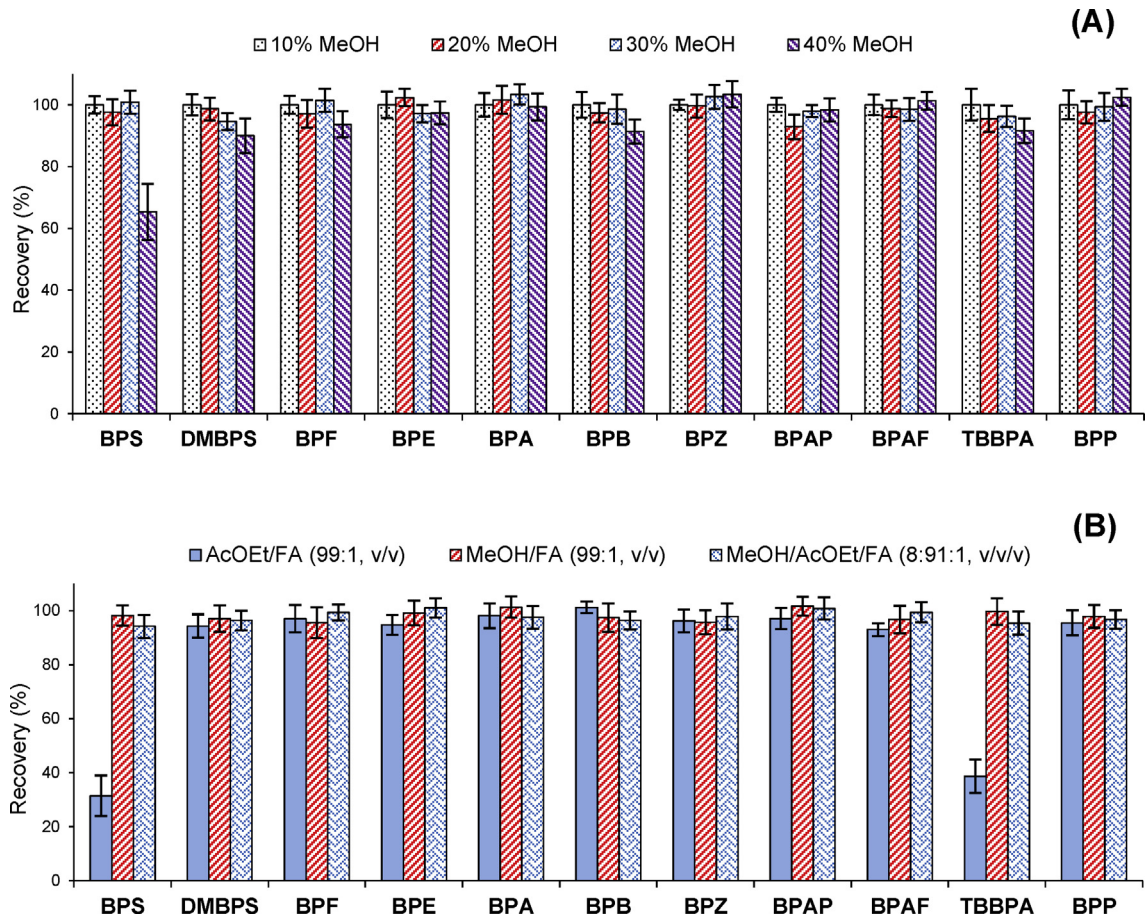

Fig. 2. Comparison of the SPE recoveries (A) by rinsing the cartridges with different percentages of methanol during the washing step and (B) by eluting the analytes with different solvents. MeOH: methanol; AcOEt: ethyl acetate; FA: formic acid.

mechanism, this study may be critical in order to avoid losses. As can be noticed, no decrease in the amount of any bisphenol was observed when the cartridge was rinsed with 10 mL of up to 30% methanol. However, the use of 40% methanol resulted in losses of around 35% for BPS, the most polar compound (log Kow = 2.3), whereas quantitative recoveries were still obtained for the rest of the bisphenols (log Kow 3.4–7.1). Therefore, a washing step with 10 mL of methanol/water/formic acid (30:69:1, v/v/v) was included in the final procedure.

Elution of bisphenols from the MCX cartridge was assessed with different solvents with the goal of obtaining a high level of selectivity paired with good recoveries. Thus, elution was accomplished with 10 mL of each of the following eluents: ethyl acetate/formic acid (99:1, v/v), methanol/formic acid (99:1, v/v) and methanol/ethyl acetate/formic acid (8:91:1, v/v/v). As shown in Fig. 2B, ethyl acetate provided quantitative recoveries (≥93%) for all bisphenols except for BPS and TBBPA, which were only recovered to 31% and 39%, respectively. This eluent rendered clear, colorless extracts, but it was unable to completely disrupt the interactions of these bisphenols with the MCX sorbent. When elution was performed with pure methanol, all bisphenols were quantitatively eluted from the cartridge (≥96%); however, the higher elution strength of this protic solvent led to apparently less clean extracts. The use of a small percentage of methanol (8%, v/v) in ethyl acetate allowed the bisphenols to be selectively eluted from the sorbent, yielding clear, pale yellowish extracts with high recoveries (≥94%) for all them. The extent of sample matrix reduction achieved by the proposed selective elution was demonstrated by the analysis of the red wine extracts eluted with methanol/formic acid (99:1, v/v) and methanol/ethyl acetate/formic acid (8:91:1, v/v/v) by HPLC coupled to a diode array detector (DAD) in the wavelength range from 200 to 600 nm. As can be observed in Fig. 3, a significantly lower baseline was obtained with methanol/ethyl acetate/formic acid (8:91:1, v/v/v), so this eluent was finally selected for the optimized SPE procedure.

Eventually, breakthrough experiments were performed by passing the spiked wine sample through two MCX cartridges (150 mg) connected in series. Using 10 mL of wine no breakthrough was observed for any of the bisphenols.

3.3. Method performance

3.3.1. Linearity

The linearity of the method was tested using standard solutions at eight concentration levels evenly distributed in the range of 0.5–160 $\mu g\,L^{-1}$ (Table S1, supporting information), resulting in a linear working range of 25–8000 $ng\,L^{-1}$ when considering the applied SPE concentration factor. Each concentration level was analyzed at least in triplicate. Calibration curves were constructed using the ratios of the peak area of the compounds to the peak area of the isotope-labeled internal standards. Determination coefficients (R^2) ≥0.998 were obtained for all compounds using weighted ($1/x^2$) linear calibration curves. The lack-of-fit (LOF) test was applied to statistically decide whether the selected linear model was adequate to describe the experimental data. The test compares the variability of the proposed model residuals to the variability between observations at replicate values of the independent variable. Results of the LOF test for the calibration range

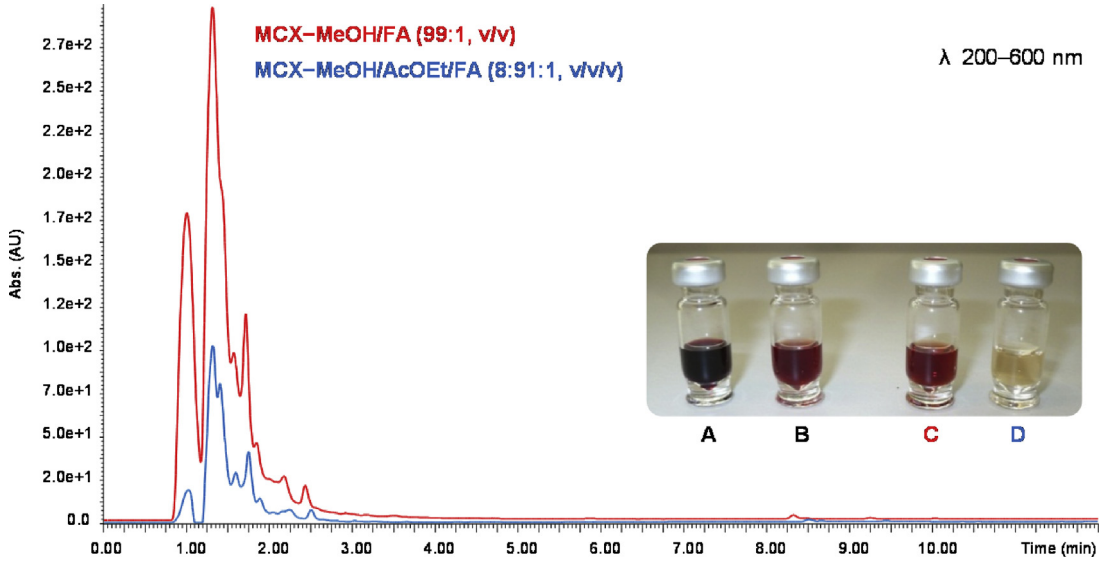

Fig. 3. HPLC-DAD chromatograms (λ 200–600 nm) corresponding to red wine extracts obtained after SPE with OASIS MCX cartridges eluted with MeOH/FA (99:1, v/v) and MeOH/AcOEt/FA (8:91:1, v/v/v). Inserted picture shows different extracts appearance: (A) HLB cartridge eluted with MeOH, (B) MAX cartridge eluted with MeOH, (C) MCX cartridge eluted with MeOH/FA (99:1, v/v) and (D) MCX cartridge eluted with MeOH/AcOEt/FA (8:91:1, v/v/v). MeOH: methanol; AcOEt: ethyl acetate; FA: formic acid.

considered, at a confidence level of 95% are also shown in Table S1 (supporting information). Since *p*-values were greater than 0.05 for all compounds, the linear regression models adequately fit the data.

3.3.2. Selectivity

The selectivity of the method was assessed via the analysis of procedural blank samples, blank beverage samples and different beverage samples spiked at 0.1 μg L^{-1}. MRM chromatograms obtained for quantifier and qualifier MS/MS transitions were checked for co-eluting interferents at the retention times of the corresponding bisphenols. No interferents were observed at the retention times of analytes ±0.1 min in any of the transitions.

3.3.3. Matrix effects

The post-extraction addition method was used for the assessment of potential matrix effects during the ESI process. The responses obtained for a spiked extract (R_{se}) were compared with those obtained for a standard solution (R_{std}) at the same concentration, and the percent matrix effect (%ME) was then calculated as $(R_{se}/R_{std} - 1) \times 100$ [29,30]. In this context, a negative result indicates ionization suppression, whereas a positive result indicates signal enhancement.

These experiments were performed using pooled beverage extracts spiked at three concentration levels equivalent to 0.1, 3.0 and 6.0 μg L^{-1}. For the alcoholic pool, matrix effects ranged from −23% for BPA at the lowest concentration level to −11% for TBBPA at 6.0 μg L^{-1} (Table 2). Although the observed %MEs were significant for most bisphenols, they were still considered satisfactory, especially when considering the complex nature of the pooled sample. Non-alcoholic beverages exhibited lower signal suppression, with %ME varying from −16% for BPB at 0.1 μg L^{-1} to around −3% for TBBPA at the highest concentration level.

3.3.4. Repeatability and intermediate precision

The precision of the method was evaluated under repeatability and intermediate precision conditions, using the pooled beverages samples spiked at 0.1, 3.0 and 6.0 μg L^{-1}. Three subsamples of each concentration level were analyzed under repeatability conditions (same operator, same laboratory and same equipment) over five days. Homogeneity of variances was checked by Cochran test and then analysis of variance (ANOVA) was applied to estimate within-days variance (σ^2_{within}) and between-days variance

Table 2
Matrix effects, limits of detection and limits of quantification for alcoholic and non-alcoholic beverages.

Compound	%ME ± SD (*n* = 3)						LOD (ng L^{-1})		LOQ (ng L^{-1})	
	Non-alcoholic			Alcoholic			Non-alcoholic	Alcoholic	Non-alcoholic	Alcoholic
	0.1 μg L^{-1}	3 μg L^{-1}	6 μg L^{-1}	0.1 μg L^{-1}	3 μg L^{-1}	6 μg L^{-1}				
BPS	−14 ± 8	−14 ± 5	−12 ± 4	−18 ± 5	−17 ± 5	−20 ± 6	17.6	19.4	58.6	64.6
DMBPS	−7 ± 7	−13 ± 7	−9 ± 5	−18 ± 5	−17 ± 6	−17 ± 6	22.5	27.9	75.1	93.1
2,2′-BPF	−9 ± 4	−12 ± 5	−11 ± 4	−22 ± 8	−21 ± 5	−18 ± 4	2.4	3.7	8.0	12.2
2,4′-BPF	−6 ± 7	−13 ± 2	−10 ± 3	−23 ± 5	−21 ± 4	−20 ± 6	8.0	8.2	26.6	27.2
4,4′-BPF	−8 ± 5	−11 ± 6	−5 ± 3	−17 ± 5	−20 ± 6	−18 ± 4	2.9	3.9	9.5	13.1
BPE	−12 ± 5	−6 ± 8	−9 ± 5	−22 ± 7	−22 ± 7	−18 ± 5	1.6	1.7	5.2	5.7
BPA	−11 ± 6	−14 ± 5	−12 ± 3	−23 ± 4	−23 ± 4	−19 ± 5	1.8	7.1	6.1	23.5
BPB	−16 ± 4	−14 ± 4	−10 ± 3	−23 ± 5	−20 ± 4	−17 ± 6	3.0	3.5	9.9	11.6
BPAP	−11 ± 7	−14 ± 6	−8 ± 5	−21 ± 8	−20 ± 9	−18 ± 8	2.3	2.4	7.8	7.9
BPZ	−7 ± 8	−13 ± 2	−7 ± 3	−21 ± 5	−20 ± 4	−17 ± 6	2.7	2.7	9.0	8.8
BPAF	−10 ± 5	−9 ± 8	−9 ± 3	−19 ± 4	−23 ± 5	−16 ± 6	1.6	2.0	5.3	6.8
TBBPA	−11 ± 8	−7 ± 6	−3 ± 5	−19 ± 6	−19 ± 7	−11 ± 4	7.5	8.1	24.9	27.0
BPP	−8 ± 2	−12 ± 2	−7 ± 4	−18 ± 5	−17 ± 3	−19 ± 3	1.9	2.0	6.3	6.7

Table 3
Repeatability and intermediate precision of the proposed method.

Compound	RSD_r (%)						RSD_{IP} (%)					
	Non-alcoholic beverages			Alcoholic beverages			Non-alcoholic beverages			Alcoholic beverages		
	0.1 μg L^{-1}	3 μg L^{-1}	6 μg L^{-1}	0.1 μg L^{-1}	3 μg L^{-1}	6 μg L^{-1}	0.1 μg L^{-1}	3 μg L^{-1}	6 μg L^{-1}	0.1 μg L^{-1}	3 μg L^{-1}	6 μg L^{-1}
BPS	3.2	1.1	1.2	2.8	3.0	1.4	3.2	1.1	1.2	2.8	3.0	1.4
DMBPS	5.3	4.1	6.9	6.7	8.6	4.6	10.5	5.6	8.2	7.2	9.4	8.7
2,2′-BPF	2.4	2.5	4.8	3.6	4.8	5.0	3.5	6.4	5.7	5.3	6.2	6.3
2,4′-BPF	2.7	3.4	4.4	3.1	4.6	3.6	3.4	6.5	4.9	4.5	5.4	6.6
4,4′-BPF	3.6	2.3	1.6	1.6	3.7	2.4	4.4	2.4	1.6	1.8	3.7	2.4
BPE	3.3	2.6	4.2	5.3	5.7	4.0	3.7	3.9	4.2	5.8	5.7	5.6
BPA	1.4	1.7	1.5	2.7	5.1	2.4	2.5	1.9	1.5	2.7	5.1	2.4
BPB	3.1	3.1	4.4	3.2	7.3	4.9	4.3	5.9	7.2	3.9	7.3	4.9
BPAP	3.4	3.6	4.5	5.9	8.1	5.0	8.8	10.0	12.0	6.0	8.1	5.0
BPZ	3.4	3.9	3.6	5.5	6.0	4.2	3.6	5.7	7.3	5.9	6.0	5.1
BPAF	3.9	2.7	2.4	2.7	3.7	2.2	3.9	2.8	2.4	3.0	3.7	3.3
TBBPA	5.3	2.9	2.2	2.9	3.4	3.3	5.3	4.2	4.3	3.1	4.2	4.1
BPP	2.8	3.4	4.8	6.1	6.4	4.5	2.9	4.4	5.2	6.1	8.6	8.2

($\sigma^2_{between}$). Repeatability was expressed as percent relative standard deviation (%RSD_r) calculated by dividing the root square of σ^2_{within} by the overall mean of the determinations. Intermediate precision (%RSD_{IP}) calculated by dividing the root square of the total variance ($\sigma^2_{within} + \sigma^2_{between}$) by the overall mean of the determinations (Table 3). Both, repeatability and intermediate precision were satisfactory, showing RSDs values ≤8.6% and ≤12%, respectively.

3.3.5. Measurement uncertainty

A combination of the bottom-up approach and the in-house validation data was used to estimate the measurement uncertainty as suggested by the EURACHEM/CITAC guide [31]. Main sources of uncertainty, including standards and sample preparation, intermediate precision, calibration and bias, were quantified and combined standard uncertainties (u_c) were calculated according to the law of error propagation. The expanded uncertainties (U) were finally estimated using a coverage factor (k) of 2, corresponding to a confidence level of 95% (Table 4). As can be observed, the relative expanded uncertainties ranged from 7% for BPS and BPA to 20% for DMBPS.

3.3.6. Trueness

As no certified reference materials (CRM) are available for bisphenols in food, the trueness of the method was assessed by recovery experiments using the pooled beverages samples spiked at 0.1, 3.0 and 6.0 μg L^{-1}. Samples were analyzed in triplicate over five days and bias was estimated for each analyte as the difference between the measured and the added concentration (Table 4). The magnitude of bias was expressed in terms of zeta-scores, which evaluate the agreement of the measured value with the nominal value, considering measurement uncertainty [32]. As shown, bias was statistically not significant for any of the analyte/concentration level combinations, as all zeta-scores were well below the absolute level of two (95% confidence interval).

3.3.7. Limits of detection

As previously discussed, a blank correction procedure was applied for the quantification of BPA, and therefore, also for the estimation of the LODs as suggested by the Eurachem guide on analytical methods validation [24]. The pooled samples were spiked at 0.1 μg L^{-1}, analyzed (n = 3) under repeatability conditions and the SD was calculated after procedural blank correction (n = 10). The SD was then corrected according to Eq. (1) as follows:

$$SD_c = SD\sqrt{\frac{1}{n} + \frac{1}{n_b}} \quad (1)$$

where n denotes the number of sample replicates and n_b is the number of procedural blank replicates used to calculate the blank correction. The LOD and the limit of quantification (LOQ) were then estimated as three and ten times the SD_c, respectively (Table 2). LODs of 1.8 ng L^{-1} and 7.1 ng L^{-1} were obtained for non-alcoholic and alcoholic beverages, respectively.

For the rest of bisphenols, LODs were estimated from the pooled samples spiked at low decreasing concentration levels. LODs were calculated as the average concentration of compound producing

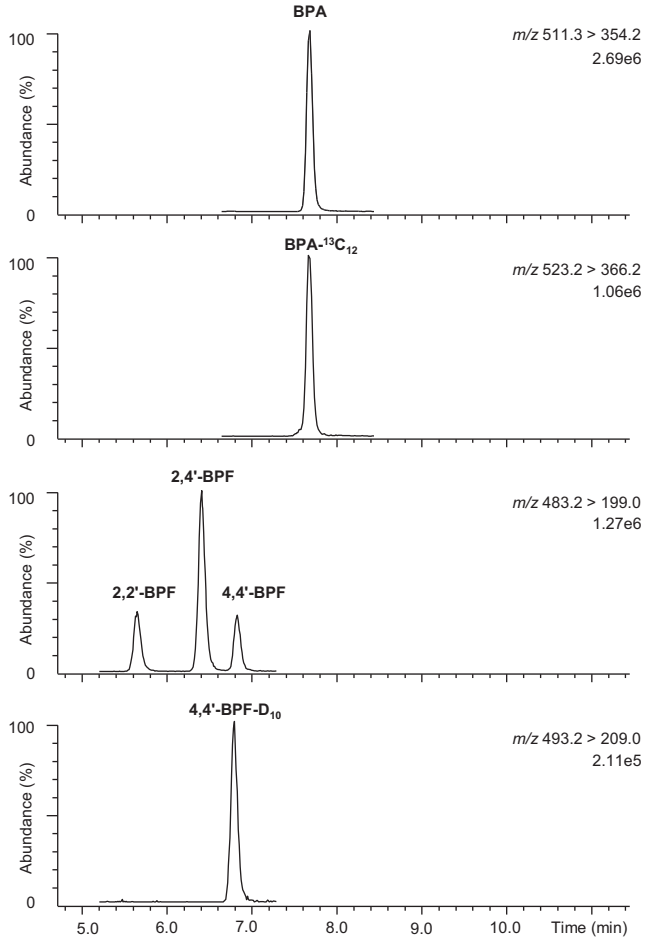

Fig. 4. MRM chromatograms obtained for an energy drink sample (BPA, 0.55 ± 0.04 μg L^{-1}, 2,2′-BPF, 0.12 ± 0.02 μg L^{-1}, 2,4′-BPF, 0.51 ± 0.06 μg L^{-1}, 4,4′-BPF, 0.25 ± 0.02 μg L^{-1}).

Table 4
Trueness assessment and expanded uncertainty of the proposed method.

Compound	Non-alcoholic beverages						Alcoholic beverages						%U (k = 2)
	Bias ± SD (μg L^{-1}) 0.1 μg L^{-1}	Z-score	Bias ± SD (μg L^{-1}) 3 μg L^{-1}	Z-score	Bias ± SD (μg L^{-1}) 6 μg L^{-1}	Z-score	Bias ± SD (μg L^{-1}) 0.1 μg L^{-1}	Z-score	Bias ± SD (μg L^{-1}) 3 μg L^{-1}	Z-score	Bias ± SD (μg L^{-1}) 6 μg L^{-1} %	Z-score	
BPS	0.003 ± 0.001	0.50	0.045 ± 0.008	0.21	0.038 ± 0.027	0.09	0.003 ± 0.001	0.51	0.032 ± 0.019	0.15	0.034 ± 0.022	0.08	7
DMBPS	0.008 ± 0.003	0.42	0.138 ± 0.084	0.23	0.405 ± 0.170	0.33	0.006 ± 0.004	0.30	0.159 ± 0.086	0.26	0.451 ± 0.416	0.36	20
2,2′-BPF	0.003 ± 0.003	0.26	0.151 ± 0.070	0.39	0.242 ± 0.157	0.31	0.004 ± 0.002	0.32	0.106 ± 0.088	0.27	0.245 ± 0.149	0.32	13
2,4′-BPF	0.002 ± 0.002	0.15	0.147 ± 0.081	0.39	0.140 ± 0.084	0.19	0.002 ± 0.002	0.19	0.098 ± 0.061	0.26	0.248 ± 0.216	0.35	13
4,4′-BPF	0.002 ± 0.003	0.30	0.029 ± 0.024	0.12	0.154 ± 0.012	0.32	0.001 ± 0.001	0.12	0.026 ± 0.033	0.10	0.124 ± 0.060	0.26	8
BPE	0.002 ± 0.001	0.16	0.083 ± 0.048	0.23	0.089 ± 0.076	0.13	0.004 ± 0.003	0.36	0.070 ± 0.039	0.20	0.282 ± 0.141	0.40	12
BPA	0.002 ± 0.001	0.27	0.137 ± 0.043	0.53	0.285 ± 0.038	0.57	0.002 ± 0.002	0.16	0.069 ± 0.046	0.27	0.125 ± 0.077	0.25	7
BPB	0.003 ± 0.002	0.27	0.140 ± 0.077	0.38	0.278 ± 0.231	0.38	0.004 ± 0.002	0.39	0.048 ± 0.025	0.13	0.215 ± 0.121	0.29	12
BPAP	0.007 ± 0.003	0.42	0.266 ± 0.117	0.49	0.526 ± 0.393	0.48	0.005 ± 0.004	0.30	0.055 ± 0.048	0.10	0.321 ± 0.125	0.29	17
BPZ	0.006 ± 0.002	0.48	0.124 ± 0.093	0.31	0.359 ± 0.309	0.45	0.004 ± 0.004	0.35	0.065 ± 0.027	0.16	0.248 ± 0.175	0.32	12
BPAF	0.002 ± 0.001	0.22	0.142 ± 0.059	0.43	0.058 ± 0.036	0.09	0.004 ± 0.002	0.38	0.146 ± 0.034	0.45	0.125 ± 0.126	0.19	10
TBBPA	0.003 ± 0.003	0.26	0.089 ± 0.030	0.27	0.209 ± 0.134	0.31	0.003 ± 0.002	0.30	0.085 ± 0.055	0.26	0.181 ± 0.128	0.28	11
BPP	0.001 ± 0.001	0.08	0.101 ± 0.028	0.17	0.129 ± 0.129	0.11	0.006 ± 0.003	0.35	0.170 ± 0.107	0.29	0.396 ± 0.476	0.33	18

a signal-to-noise ratio (S/N) of 3 using the less sensitive MS/MS transition, i.e. the one permitting the unambiguous identification of the analytes. LOQs were estimated in the same way considering a S/N of 10. For non-alcoholic beverages, LODs ranged from 1.6 ng L^{-1} for BPE to 22.5 ng L^{-1} for DMBPS; slightly higher LODs were obtained for the alcoholic drinks, varying from 1.7 ng L^{-1} for BPE to 27.9 ng L^{-1} for DMBPS. The achieved LODs for BPA and its main analogs are in the same range [14–16] or lower [12,13] than those previously reported.

3.3.8. Application to beverages

To demonstrate the applicability of the method, a total of twenty two beverage samples purchased in local supermarkets were analyzed. The selected samples comprised alcoholic and non-alcoholic beverages packaged in different materials including cans, polyethylene terephthalate (PET) bottles, glass bottles and carton packages.

Among all the considered bisphenols, only BPA and the three BPF isomers were detected in any of the analyzed samples. BPA ranged from <LOD to 1.26 ± 0.09 μg L^{-1}, whereas 4,4′-BPF varied from <LOD to 1.00 ± 0.08 μg L^{-1} in one canned cola soft drink. 2,4′-BPF and 2,2′-BPF were found at concentration levels up to 0.51 ± 0.06 μg L^{-1} and 0.12 ± 0.02 μg L^{-1}, respectively. To the best of our knowledge, these results constitute the first data on the presence of these BPF isomers in beverages.

Fig. 4 shows the MRM chromatograms obtained for a canned energy drink, where BPA and the three BPF isomers were determined (BPA, 0.55 ± 0.04 μg L^{-1}, 2,2′-BPF, 0.12 ± 0.02 μg L^{-1}, 2,4′-BPF, 0.51 ± 0.06 μg L^{-1}, 4,4′-BPF, 0.25 ± 0.02 μg L^{-1}).

4. Conclusions

Mixed-mode SPE, combining cationic exchange and reversed-phase mechanisms, provided a selective extraction and clean-up of the target analytes. ESI ionization efficiency of bisphenols was highly improved by applying a simple derivatization step with pyridine-3-sulfonyl chloride, which allowed decreasing the LODs of the method to levels ranging from 1.6 ng L^{-1} for BPE to 27.9 ng L^{-1} for DMBPS. Performance of the method was assessed in terms of selectivity, matrix effects, linearity, precision, measurement uncertainty, trueness, LODs and LOQs. Repeatability and intermediate precision were satisfactory, showing RSDs values ≤9% and ≤12%, respectively. The estimated relative expanded uncertainty (k = 2) was below 20% in all cases and bias was not significant for any of the studied bisphenols.

Finally, several beverages were analyzed to demonstrate the applicability of the proposed method. Among all the considered bisphenols, only BPA and the three BPF isomers were detected in any of the analyzed samples. BPA concentration ranged from <LOD to 1.26 ± 0.09 μg L^{-1}, whereas 4,4′-BPF varied from <LOD to 1.00 ± 0.08 μg L^{-1}. To the best of our knowledge, 2,2′-BPF and 2,4′-BPF were reported for the first time in beverages, at concentration levels up to 0.12 and 0.51 μg L^{-1}, respectively.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chroma.2015.10.046.

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