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Quantification of bisphenol A and its selected analogs in serum using pre-column derivatization with high-performance liquid chromatography and tandem mass spectrometry

Dongqin Tan[1,2*] | Jing Jin[1*] | Longxing Wang[1] | Xiaolin He[3] | Cuicui Guo[1,2] | Dhanjai [1] | Xianbo Lu[1] | Jiping Chen[1]

[1]CAS Key Laboratory of Separation Science for Analytical Chemistry, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China

[2]University of Chinese Academy of Sciences, Beijing, China

[3]The Second Hospital of Dalian Medical University, Dalian, China

Correspondence
Prof. Jiping Chen, CAS Key Laboratory of Separation Science for Analytical Chemistry, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China.
Email: chenjp@dicp.ac.cn

*The authors contribute equally to this work.

Due to regulation of the use of bisphenol A, several analogs serving as bisphenol A replacements have drawn substantial attention for their adverse health effects. To investigate their occurrence in humans and identify possible pollution sources, it is necessary to develop a sensitive method for total bisphenols detection. Thus, a method based on enzymolysis and liquid-liquid extraction followed by molecularly imprinted polymer solid-phase extraction and pre-column derivatization with high-performance liquid chromatography and tandem mass spectrometry was proposed. The developed method exhibited superior selectivity and sensitivity. The matrix effect can be eliminated to a great extent. The method detection limits for eight bisphenols were 0.05~0.19 ng/mL. Satisfactory recoveries (71~119%) were obtained by spiking bovine serum at three levels (0.8, 8 and, 20 ng/mL). The method was successfully applied to determine total bisphenols in the serum samples of children. Bisphenol A, bisphenol F, bisphenol S, bisphenol B and bisphenol F were detected with concentrations from below the method detection limit to 1.65, 0.45, 0.79, 2.04 and 0.17 ng/mL, respectively. These results indicate that bisphenol A remains the major pollutant among the studied bisphenols in children, whereas threats from bisphenol A analogs should also be monitored.

KEYWORDS
bisphenol, derivatization, high-performance liquid chromatography, serum tandem mass spectrometry

1 | INTRODUCTION

Bisphenol A (BPA) is a synthetic chemical used to manufacture polycarbonate plastic and epoxy resins, which are commonly used to produce food packaging containers and can linings. BPA is suspected of being associated with human and animal health problems [1,2]. Accumulating evidence suggests that BPA exposure might cause endocrine and reproductive systems disruptions in adults, children and newborns [3–5]. In addition, BPA interferes with the normal functions of various hormones including sex hormones, leptin, insulin, and thyroxin causing a wide range of adverse health effects, i.e., hepatotoxic, immunotoxic, mutagenic and carcinogenic effects [6,7]. Considering the spontaneous migration of BPA to the human body, many countries have proposed legislation to prohibit the manufacture or sale of baby bottles containing BPA [8]. Consequently, several bisphenol analogs such as bisphenol S (BPS), bisphenol F (BPF),

Article Related Abbreviations: ACN, acetonitrile; BPA, Bisphenol A; BPAF, Bisphenol AF; BPAP, Bisphenol AP; BPB, Bisphenol B; BPE, Bisphenol E; BPF, Bisphenol F; BPS, Bisphenol S; BPZ, Bisphenol Z; MIP, molecularly imprinted polymer

bisphenol B (BPB) and bisphenol AF (BPAF) have gradually been applied as substitutes to BPA in plastic manufacturing [9]. Likewise, other structural analogs such as bisphenol E (BPE) and bisphenol AP (BPAP) are also potential substitutes, although their purpose and the dosage remain unclear [10].

However, many of these substitutes were not fully evaluated regarding their health effects before entering the market. Numerous studies indicate that these BPA alternatives show similar toxicities or an even greater deleterious effect than BPA itself [11–13]. For example, BPS and BPF have an endocrine-disrupting effect and possess hormonal activity similar to that of BPA [12]. The potency of BPAF was 47.6-fold higher than that of BPA due to its strong antagonism to 17 β-estradiol [13]. Therefore, screening the levels of BPA and its analogs to evaluate human exposure, especially for children, is of great significance. Nevertheless, studies on the occurrence of bisphenol analogs in the human body remain deficient, primarily due to the lack of sensitive methods for trace-level detection in complex matrices such as blood [14,15], urine [14], breast milk [16], solid tissue [16] and placenta [16]. As reported, BPA can be ingested into the human body and then metabolized primarily to BPA-glucuronide and BPA-sulfate, whereas, the free BPA residual in serum accounts for less than 1% of the total bisphenol content [17]. To identify the pollution source and evaluate the health risk, analysis of the total bisphenol content via a selective and sensitive method is essential.

BPA has been extensively studied in the past few years, but efforts to detect BPA and its analogs simultaneously have been hampered by limitations in current instrumental analytical methods. Among these techniques, HPLC-MS/MS has gradually become the optimal choice due to its inherent advantages of high sensitivity and selectivity. However, the sensitivity for detection of BPA and its analogs using ESI in negative mode remains insufficient. Fortunately, a pre-column derivatization using dansyl chloride prior to LC-MS/MS analysis can greatly improve the detection sensitivity for BPA and estrogens [18]. It offers an effective pathway for derivatizing BPA analogs due to their similar structures, which bearing two hydroxyphenyl functionalities.

Thus, the present work is intended for developing a highly selective and sensitive method for analyzing total bisphenol content in blood serums using enzymolysis, molecularly imprinted polymer solid phase extraction (MIP-SPE) and pre-column derivatization HPLC-MS/MS. The optimized detection parameters of derivatization-HPLC-MS/MS and a full method validation protocol for bisphenol analogs detection in serum are presented. The developed method was successfully applied to the determination of eight bisphenols in serum samples.

2 | MATERIALS AND METHODS

2.1 | Materials and chemicals

HPLC-MS grade methanol (MeOH), acetonitrile (ACN) and water were purchased from Merck (Merck & Co. USA). Pesticide-residue grade *n*-hexane was obtained from J.T. Baker (Phillipsburg, NJ, USA). HPLC-grade ethyl acetate and TFA were procured from Sigma–Aldrich (Shanghai, China). BPA (purity > 99%), BPS (purity > 98%), BPF (purity > 99%), BPE (purity > 99%), BPB (purity > 98%), BPAF (purity > 99%), BPAP (purity > 98%) and bisphenol Z (BPZ, purity > 98%) and dansyl chloride (purity > 99%) were procured from J&K Chemical (Beijing, China). The β-glucuronidase enzyme from Helix pomatia (Type H-2) was a product of Sigma–Aldrich (Shanghai, China) and was prepared in ammonium acetate solution (1 M, pH 4.7) with a concentration of 300 units/mL. Stock solution of each bisphenol compound with a concentration of 1000 ng/ml was prepared in ACN. $^{13}C_{12}$-BPS, $^{13}C_{12}$-BPA and $^{13}C_{12}$-BPAF (Cambridge Isotope Laboratories, Andover, MA, USA) were prepared in ACN with a concentration of 1000, 1000 and 100 ng/mL, respectively. To prepare the calibration curve, solutions involving targets (0.05 ∼100 ng/mL) and surrogates (10 ng/mL) were prepared.

MIPs were prepared according to our previous work [19] using 1,1,1-tris(4-hydroxyphenyl)ethane (THPE) as the template, 4-vinylpridine as the functional monomer and ACN as the polymerization solvent. Glass cartridges (3 mL) were used to reduce possible contamination during solid-phase extraction.

2.2 | Sample preparation

In this study, blood samples were collected from the Second Hospital of Dalian Medical University (Dalian, China). The blood was obtained through venipuncture and clotted in a vacuum tube (Becton Dickinson, NJ), followed by centrifugation at 3500 rpm for 10 min. The obtained serum was separated and transferred to polypropylene tubes with caps and finally stored at −80°C for later use. Samples were stored in glass or polypropylene tubes to avoid possible contamination.

The commercially available β-glucuronidase from Helix pomatia usually contains a small amount of aryl-sulfatase. Therefore, it can deconjugate the glucuronidated and sulfated forms of BPA simultaneously [20]. In our work, 0.5 mL of thawing serum was transferred to a 10 mL glass tube and spiked with 4 ng of surrogate standards ($^{13}C_{12}$−BPS, $^{13}C_{12}$−BPA and $^{13}C_{12}$−BPAF). Then, 1 mL of 1 M ammonium acetate buffer (pH 4.7) containing 300 units of β-glucuronidase was added. The mixture was then gently mixed and incubated for 12 h at 37°C.

After incubation, 1 mL water was added into the solution. The mixture was then extracted three times with 3×3 mL of ethyl acetate by vortexing for a few minutes and centrifuged (4000 rpm, 5 min) for each suspension. The organic phase was evaporated to dryness under a gentle stream of nitrogen and was re-dissolved with 1 mL ACN. The obtained solution was then loaded onto a MIP-SPE column pre-packed with 100 mg MIPs and preconditioned with 3 mL MeOH and ACN, successively. After rinsing with 1 mL ACN, the column was eluted with 5 mL MeOH. The obtained eluent was evaporated to dryness under a gentle stream of nitrogen.

The eluent residue was reconstituted in 200 μL sodium bicarbonate buffer (100 mM, pH 10) and derivatized with 200 μL dansyl chloride (1 mg/mL in acetone) by vortex-mixing for 1 min, followed by incubation at 60°C for 80 min. After cooling to room temperature, 1 mL water was added to the solution. The mixture was then extracted three times with 3×3 mL hexane. The obtained supernatant was separated and evaporated to dryness under gentle nitrogen, followed by reconstituting with 400 μL ACN/H_2O (50:50, v/v) before HPLC–MS/MS analysis.

2.3 | HPLC–MS/MS analysis

BPA and its selected analogs were determined using a HPLC coupled to a triple quadrupole mass spectrometer (Thermo Fisher Scientific TSQ Quantum Access MAX, USA) operating in positive ESI mode with selective reaction monitoring (see Supporting Information Table S1 for transitions). The ion source and MS/MS conditions are listed in the supporting information. Chromatographic separation was achieved on a Hypersil GOLD C18 column (150 mm × 2.1 mm, 5 μm) (Beijing, MA, USA) with a flow rate of 200 μL/min at 30°C. Gradient elution using ACN (solvent A) and water (solvent B) as the mobile phase followed the program: 0 min, 65:35 (A:B); 20 min, 100:0; 25 min, 100:0, 25.2 min, 65:35; 35 min, 65:35.

3 | RESULTS AND DISCUSSION

3.1 | Optimization of HPLC–MS/MS conditions

Dansyl chloride has often been applied to increase the ionization efficiency of estrogens and BPA in LC–MS analysis due to its high reactivity with a phenolic hydroxyl group [13,21]. Due to the similar molecular structure, BPA analogs can also be derivatized with dansyl chloride to enhance response intensity. To optimize the ionization efficiency of BPA and its analogs, the derivatization conditions were carefully investigated, including the mass of dansyl chloride (0, 10, 100, 500, 1000, 2000 μg/mL), pH of sodium bicarbonate solution (8.5, 9.5, 10, 10.5, 11 and 12), reaction time (5, 30, 60, 80 and 120 min), and temperature (40, 60 and 80°C) (Figure 1).

The signal intensity of all targets increases significantly with the concentration of dansyl chloride and achieves satisfactory results above 500 mg/mL (Figure 1A). Therefore, excess dansyl chloride (1000 mg/mL) was used in the following experiments to ensure sufficient derivatization in a complex matrix. It was found that the derivatization efficiency does not change continuously as the pH varies from 8.5 to 12 (Figure 1B). Generally, the reaction system reaches the optimal derivatization efficiency in a basic environment at pH 10. However, the highly alkaline condition (pH 12) led to undesirable hydrolysis of sulfonic esters [22]. Similarly, the reaction time has an obvious effect on the derivatization (Figure 1C). For BPS, the optimal efficiency was achieved within 5 min. The efficiency for BPA and other bisphenols increased with the duration of the derivatization and reached the maximum at 80 min, followed by a decrease with excess time (120 min). Thus, 80 min was chosen as optimum for the derivatization to obtain high efficiency for all bisphenols. As shown in Figure 1D, most bisphenols except BPF exhibited a similar variation effect of temperature. In detail, the peak area for BPS, BPE, BPA, BPB, BPAP, BPAF, and BPZ increased as the reaction temperature increased from 40 to 60°C and then decreased at 80°C. Therefore, 60°C was selected as the optimum temperature for dansyl chloride derivatization.

The chromatograms showed the presence of major peaks corresponding to di-derivatized forms of bisphenols. The full scan MS spectrum shows the fragmentation of the isolated dansyl derivatives resulting from protonated molecular ions $[MH]^+$, and the major product ions at m/z 171 (Table S1), which were derived from the cleavage of a C–S bond in the dansyl portion [18]. Abundant ions of $[MH]^+$-234 were also obtained and possibly originated from the cleavage of an S–O bond in the residual fragment ion of $[MH]^+$-171 [22]. Hence, $[MH]^+ \rightarrow 171$ and $[MH]^+ \rightarrow [MH]^+$-234 were used as the transitions (Supporting Information Table S1). Under optimum conditions, the ionization efficiency was greatly improved through derivatization with dansyl chloride (Figure 2). The S/N of dansyl derivatives for most of the bisphenols increased 6- to 373-fold compared with that of the underivatized targets in a negative ESI mode (ESI(-)). In other words, the sensitivity of bisphenols detection in biological samples can be greatly improved by adopting dansyl chloride as the post-column derivatization reagent, which would guarantee a high detection rate for performing their exposure and risk assessment successfully.

3.2 | Optimization of extraction conditions

Developing a selective extraction method and minimizing matrix interferences is imperative for trace analysis in a complex matrix. BPA was previously quantified using

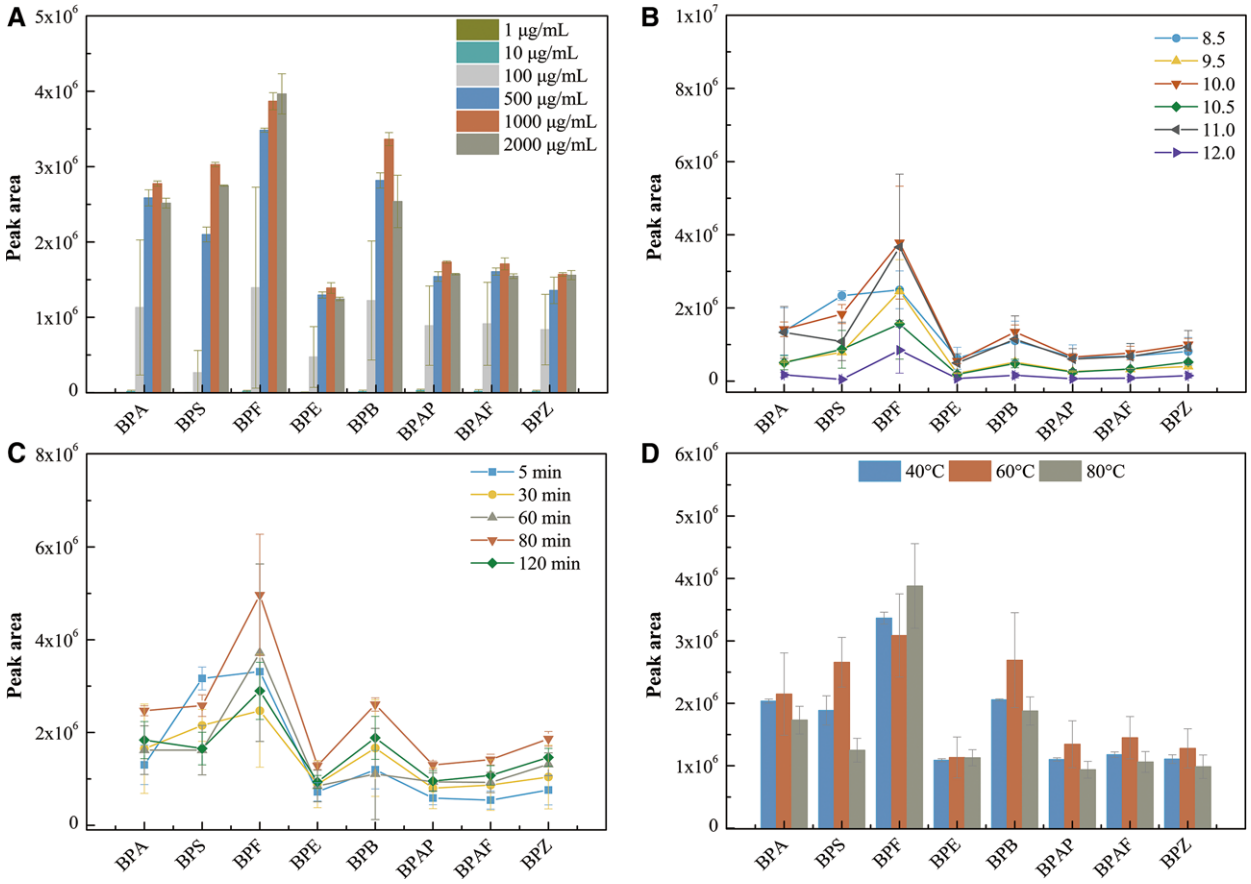

FIGURE 1 Optimization for derivatization conditions: (A) Concentration of dansyl chloride; (B) pH of NaHCO3 solution; (C) reaction time; (D) reaction temperature

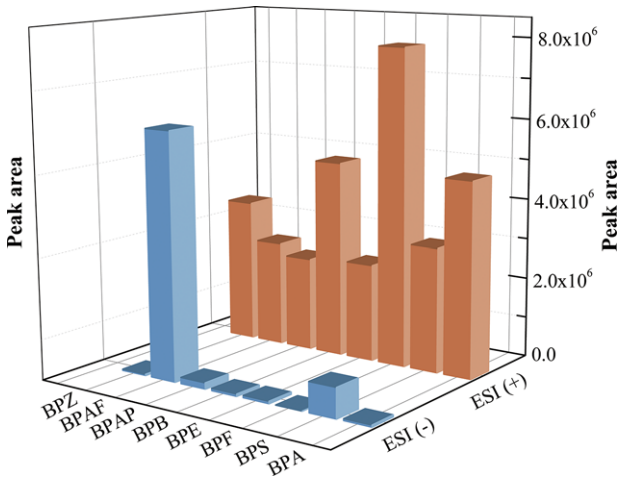

FIGURE 2 Signal-to-noise ratio of BPA and its analogs (20 ng/mL for each compound) using HPLC-MS/MS in negative mode (ESI(-)) and positive mode (ESI(+)). ESI(-): analyzing bisphenols standards directly. ESI(+): analyzing derivatives of bisphenols standards

derivatization-LC-MS/MS by analyzing the crude extracts of serum after ethyl acetate extraction [20]. However, LLE was inadequate for complex samples and would sometimes yield a severe matrix effect in MS detection. Therefore, an efficacious cleaning procedure was essential to some extent. Molecularly imprinted polymers (MIPs) have been reported to possess a very high selectivity [23]. Well-designed dummy MIPs using 1,1,1-tris(4-hydroxyphenyl)ethane as dummy templates can exhibit class-selectivity towards bisphenol compounds in milk, sediment and human urine samples [19].

To achieve a better cleanup of serum extracts in the SPE procedure, the rinsing and elution conditions were carefully optimized. After optimization, 1 mL of ACN acts as a rinsing solvent to remove the residual analytes and matrix components. To gain a high elution efficiency, MeOH, MeOH/TFA (98:2, v/v) and MeOH: NH_3 (98:2, v/v) were selected as the elution solvent. As shown in Supporting Information Figure S1, MeOH/TFA (98:2, v/v) showed poor elution with recoveries below 13.8%, possibly due to the reaction between TFA and dansyl chloride, which subsequently reduced the derived efficiency. In contrast, 5 mL of MeOH/NH_3 (98:2, v/v) and MeOH had a higher elution efficiency for bisphenols. For BPA elution, a better result was achieved with MeOH (Supporting Information Figure S1). Therefore, 5 mL of MeOH was selected as the elution solvent.

3.3 | Validation of the developed method

To avoid possible contamination, all glass containers used in this study were carefully washed with chromic acid lotion and dried at 450°C for 5 h, followed by washing with ACN and then MeOH before use. Blanks of pure water were analyzed to determine the background contributed during the entire procedure. Only BPS and BPA were detected and all blank values were less than 10% of the average concentrations in serum samples.

To correct for the potential losses of analytes during sample preparation, and to compensate for the variations in MS response between injections, surrogate standards of $^{13}C_{12}$-BPS, $^{13}C_{12}$-BPA and $^{13}C_{12}$-BPAF were used in this study. Calibration curves in the range of 0.05∼100 ng/mL (six levels in duplicate) were developed by plotting the peak area ratios of the analyte derivative to its surrogate derivative versus the analyte concentrations and fitting these data with the linear regression. As shown in Table 1, squared correlation coefficients (R^2) for BPA and its analogs were in the range of 0.991∼0.997, exhibiting a good linearity over a wide concentration range.

Fetal bovine serum was applied as a QC samples due to its similar matrix with human serum. The mean recoveries for target bisphenols spiking at low, medium, and high levels (0.8, 8 and 20 ng/mL) were in the range of 71∼119, 82∼100, and 84%∼118%, respectively (Table 1). The precision of the method, expressed as the RSD%, was evaluated by the interday (n = 5) and intraday (n = 3) repeatability, which was 0.4∼12.1 and 4.3∼14.2%, respectively. The method detection limits for BPS, BPF, BPE, BPA, BPB, BPAP, BPAF and BPZ were estimated as 0.05∼0.19 ng/mL (Table 1). The MDL of BPA was much lower than the reported

TABLE 1 Correlation coefficient, precision, recovery, method detection limits (MDLs) and LOQs achieved by the proposed method

		Precision (%)						Recovery (%)				
		Intraday (n = 3)			Interday (n = 5)							
Analytes	Linearity (R^2)	Low[a]	Med[a]	High[a]	Low[a]	Med[a]	High[a]	Low[a]	Med[a]	High[a]	MDL[b] S/N = 3	LOQ[c] S/N = 10
BPA	0.9932	8.3	3.4	2.1	10.8	6.7	9.8	81.5	85.6	94.6	0.12	0.4
BPS	0.9936	3.6	2.9	1.1	8.8	4.7	5.3	72.6	99.8	92.5	0.06	0.19
BPF	0.9914	9.9	4.4	0.4	13.2	5.4	5.1	97.2	84.6	99.3	0.19	0.63
BPE	0.9906	7.7	3.3	4.9	12.0	10.3	7.7	106.3	82.4	117.7	0.07	0.25
BPB	0.9969	10.2	3.5	4.0	14.2	6.4	9.8	71.2	82.8	93.9	0.05	0.18
BPAP	0.9974	12.1	2.6	0.8	12.4	4.3	8.9	72.2	86.0	98.3	0.09	0.3
BPAF	0.9968	2.8	3.2	4.3	5.0	7.0	4.5	118.9	94.8	108.6	0.07	0.2
BPZ	0.9945	6.3	4.8	1.2	8.5	9.5	6.3	76.4	84.1	84.8	0.06	0.2

[a]Spiking level. Low: 0.8 ng/mL; Med: 8 ng/mL; High: 20 ng/mL.
[b]Method detection limit (ng/mL).
[c]LOQ (ng/mL).

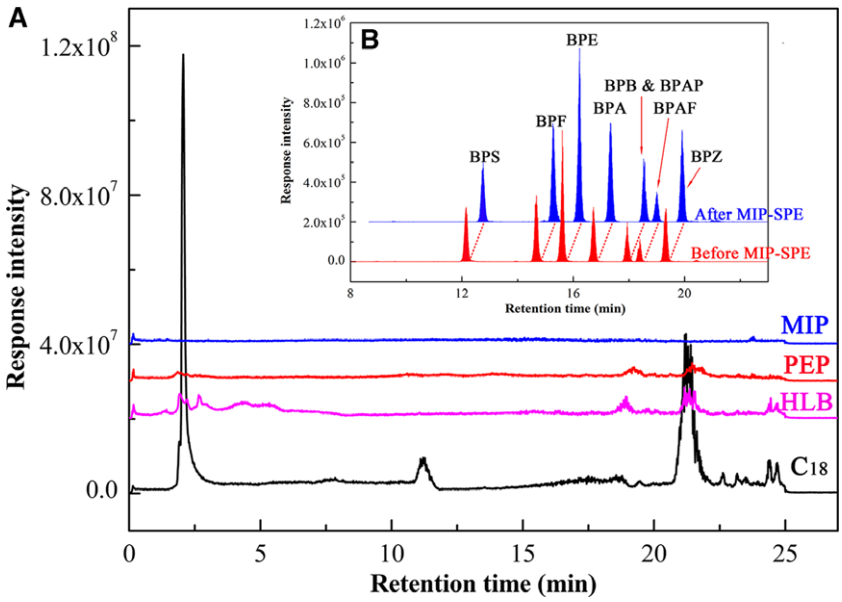

FIGURE 3 (A) Full scan spectra (m/z: 100∼1000) of the extracts of blank bovine serum with different sorbents (MIP, PEP, HLB and C18) and (B) total ion chromatogram in SIM mode of spiked bovine serum (8 ng/mL) before and after using MIP-SPE according to section 2.2

results (0.28~5 ng/mL) (Supporting Information Table S2). This comparison indicated that the proposed method is efficient for improving the detection sensitivity of BPA and its analogs, resulting in a determination in the magnitude of pg/mL.

The occurrence of the matrix effect originating from the co-eluting, undetected matrix components can affect the reproducibility and accuracy of the analysis of small molecules in biological fluids [24]. The matrix effect was calculated as: ME (%) = (B−C)/A × 100 [25], where A is the peak area of the neat analytes, B is the peak area of the extracted analytes spiked into serum and C is the peak area of target bisphenols in blank serum. The efficiency for reducing the matrix effect using MIPs and LLE was compared. Significant ion suppression (ME: 34~77%) was observed for all targets using the LLE method (Supporting Information Figure S2), whereas the matrix effect was greatly lowered (65~111%) for BPF, BPE, BPB, BPAP and BPAF through further extraction and purification with MIPs-SPE. In contrast to the effect of commonly used sorbents, such as C_{18}, HLB and PEP [15,22,26], bisphenols can be greatly recovered with MIP-SPE (Figure 3 (A), 3(B)). Moreover, the extracts of bovine serum had a cleaner chromatogram after cleanup with MIPs than with C_{18}, HLB and PEP (Figure 3A), indicating a higher selectivity possessed by MIPs. Therefore, the use of MIPs was beneficial for selective quantification of bisphenols in serum samples.

3.4 | Method application

The developed method was applied to analyze BPA and its analogs in 20 children's serum samples. As shown in Table 2, BPA has the highest (70%) detectable frequency, followed by BPF (25%), BPS (15%), BPB (10%) and BPAF (10%). However, BPE and BPZ were not detected in all samples.

TABLE 2 Concentrations of eight bisphenols in 20 serum samples of children

Analytes	Detection frequency[a] (%)	GM[b]	Concentrations (ng/mL)
BPA	70	0.85	<LOD~1.65
BPS	15	0.06	<LOD~0.79
BPF	25	0.41	<LOD~0.45
BPE	0	0	nd[c]
BPB	10	1.1	<LOD~2.04
BPAP	0	0	nd[c]
BPAF	10	0.16	<LOD~0.17
BPZ	0	0	nd[c]

[a]Values > LOD.
[b]The abbreviation of geometric mean.
[c]Not detected.

The high detection rate of BPA reveals its omnipresence in the environment and the human body through migration from products containing BPA [27]. The concentration of BPA in children's serum can reach < LOD~1.65 ng/mL, which agreed with the previous results [28,29]. Similarly, BPF, BPS, BPB and BPAF were below 0.45, 0.79, 2.04 and 0.17 ng/mL, respectively. The above results indicate that BPA can still be a dominant pollutant in children due to its extensive application in plastic products. Meanwhile, other bisphenol analogs that serve as BPA alternatives, may also become potential threats to human health. Therefore, more investigations are required to accurately assess the level and source of these bisphenol compounds.

4 | CONCLUDING REMARKS

In this work, a highly selective and sensitive method was established to simultaneously determine the total BPA content and its analogs in blood serum using MIP-SPE and derivatization with dansyl chloride prior to LC–MS/MS analysis. After extraction and derivatization, the detection sensitivity of bisphenol compounds in serum was greatly improved. The proposed method was validated with acceptable accuracy, high recoveries and low detection limits, which is adequate for the accurate quantification of trace-level bisphenols in serum. BPA was detected most serum samples, whereas BPF, BPS, BPB and BPAF had a low detection rate. These results indicate the wide presence of BPA and the potential emergence of some analogs as BPA alternatives in plastic products. Therefore, it is necessary to pay more attention to the human exposure level and pollution source of bisphenol analogs, especially for children and newborns.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

ORCID

Dongqin Tan https://orcid.org/0000-0002-0007-3213

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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