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Micro-QuEChERS extraction coupled to GC–MS for a fast determination of Bisphenol A in human urine

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ABSTRACT

Bisphenol A (BPA) is considered an endocrine disruptor and public concern over BPA exposure has been raised. Several studies have assessed human exposure to this plasticizer, confirming its ubiquitous presence and highlighting children as a public of special concern. A simple, efficient, cheap and green analytical procedure is reported within this paper. This paper reports, for the first time, the development of a modified Micro-QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) method coupled to gas chromatography-mass spectrometry (GC–MS) as a new strategy for the efficient extraction and determination of Bisphenol A in human urine samples. Several parameters that are known to influence extraction were optimized. Good linearity was achieved at the studied concentration range (1–50 μg/L), with a correlation coefficient (R^2) of 0.998. The optimized method proved to be accurate (≥74% recovery), reproducible (< 11% relative standard deviation) and sensitive for BPA determination (detection limit of 0.13 μg/L and quantification limit of 0.43 μg/L). The analytical procedure was applied to the analyses of 12 urine samples collected from children living in the North/Center region of Portugal. BPA was detected in all the analyzed samples in concentrations ranging from 1.5 μg/L to 48.9 μg/L. The proposed methodology is suitable for the determination of BPA in urine samples in the framework of biomonitoring studies and bioanalytical analyses, applying GC–MS detection.

1. Introduction

In the last decades, environmental exposure to certain industrial chemical substances has caused apprehension due to their potential toxicity and widespread use [1]. Bisphenol A (BPA), common name for 2,2-bis(4-hydroxyphenyl) propane is one of the major industrial chemicals of emerging concern [1].

Due to its cross-linking properties BPA has been widely used in the manufacture of polycarbonate plastics and epoxy resins, in the production of several products, such as food containers, food and beverage can linings, food packaging materials, CDs, medical equipment, bottles, plastic bags, etc [2]. Bisphenol A has been found to leach and migrate rather easily [2–13]. According to the available studies, BPA exposure from dietary sources is generally considered higher than exposure from non-food sources. Nevertheless, not all sources and routes of exposure contributing to the omnipresent BPA body burden are thoroughly understood [6,14,15].

BPA is considered an endocrine disruptor [2,5,16] and consequently, public concern has been raised by several studies suggesting a link between BPA exposure with several health outcomes, namely obesity [17–25]. However, nowadays these human health effects from low-level exposures to BPA are being debated [4,16,26–32]. In 2015, the European Food and Safety Authority (EFSA) has lowered the Tolerable Daily Intake (TDI) for BPA to a temporary TDI (t-TDI) of 4 μg/kg body weight/day, based on new data and the uncertainties surrounding health effects in regard to mammary gland, reproductive, metabolic, neurobehavioral and immune systems [28]. Moreover, according to several studies, children seem to be a population of special concern as their exposure levels are higher when compared to adolescents and adults [33–35].

Pharmacokinetic studies showed that BPA is rapidly metabolized and conjugated predominantly with the glucuronic acid to the BPA-glucuronide in the gut wall and liver [36–41]. Since most of the BPA taken up orally is excreted in urine within less than 24 h, urine is the preferred matrix for estimating human exposure [38,42–44].

The identification and quantification of BPA is challenging, due to

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the low concentrations at which this compound is typically present in human matrices and due to a possible background contamination. Therefore, biomonitoring should be performed through highly sensitive analytical methods and exposure assessment based on the conjugates [45].

Common sample preparation techniques for BPA human biomonitoring methods include solid phase extraction (SPE) and liquid–liquid extraction (LLE) [5,46,47]. The demand of high-throughput methods in biomonitoring programs has led to the development of automated off-line and on-line SPE methods. These on-line SPE methods tend to reduce significantly the sample volume required and procedure time [48,49]. Generally, liquid chromatography coupled to mass spectrometry is the most common analytical technique for BPA determination, not requiring a derivatization step [38]. However, several studies have reported the use of gas chromatography with a prior derivatization step frequently associated with SPE as the extraction technique [5,38]. Additionally, some authors have addressed the comparison between GC and LC for the determination and quantification of a broad range of compounds, concluding that both techniques are comparable [50–52].

The QuEChERS (quick, effective, cheap, rugged and safe) methodology was initially developed in 2003 for the determination and measurement of pesticides residues in vegetables and fruits, combining the extraction/isolation of pesticides and extract clean-up [53]. This technique comprises extraction using commonly acetonitrile (ACN), as extraction solvent, and purifying the extract by dispersive solid-phase extraction (dSPE) [54]. Since then the QuEChERS technique has become the method of choice for food analysis and has suffered various modifications and improvements over the years. Therefore, nowadays this method is applied to other analytes and matrices [54,55].

This methodology has been applied for BPA determination in food matrices and animal organs, namely in seafood, canned food (seafood, vegetables and fruits), packed food, honey and rat testis [56–65]. In these studies, different compositions of QuEChERS salts were tested such as the original composition (NaCl and MgSO4), citrate buffer (additional citrate buffers) and acetate buffer (additional acetate buffer). Nonetheless, the extraction solvent was always set to the ACN. The QuEChERS has also been used, in few occasions for the determination of pesticides [66–68], diverse environmental contaminants [46], pharmaceuticals [69,70] and lipids [71] in urine samples. For this matrix, different salt compositions were also tested and used, still ACN was once more the chosen extraction solvent, except for the lipids determination [71].

The present work displays a novel methodology based on QuEChERS technique coupled to GC–MS for BPA determination in human urine samples. As far as the authors know this is the first time this method has been applied with this aim. The developed method, based on miniaturized QuEChERS method presents several advantages when compared with more traditional extraction techniques (namely manually-operated SPE) as it is less laborious, time consuming, cheaper and greener (less solvent consumption). The present work is therefore relevant for human biomonitoring studies and biomedical analysis in GC–MS field.

2. Material and methods

2.1. Reagents and chemicals

GC-grade Hexane and Methanol, Acetonitrile (ACN) HPLC-grade (purity ≥99.9%) were purchased from Merck (Darmstadt, Germany). Commercially available bisphenol A (BPA, 2,2-(4,4-dihidroxydiphenyl) propane) (99% purity), and the isotope labeled internal standard $^{13}C_{12}$-BPA (99%) were provided by Sigma (St. Louis, MO, USA). The derivatization reagent was BSTFA + TMCS (99:1) (GC/GC–MS) from Supelco (Bellefonte, PA, USA). Three different types of QuEChERS and two dSPE were tested: QuEChERS A ((4 g magnesium sulfate ($MgSO_4$) and 1 g sodium chloride (NaCl)); QuEChERS B (6 g $MgSO_4$ and 1.5 g anhydrous sodium acetate (CH_3COONa)); and QuEChERS C (6 g $MgSO_4$, 1.5 g NaCl, 1.5 g of sodium citrate dihydrate ($Na3Cit{\cdot}2H_2O$) and 0.750 g sodium citrate sesquihydrate ($Na_2HCit.1.5H_2O$)). The two tested dSPE had the following composition: dSPE 1) was composed of 25 mg of C18 ((octadecyl sorbent (C18)) and 150 mg of $MgSO_4$; and dSPE 2) was composed by 50 mg of primary and secondary amine (PSA) exchange material, 50 mg of C18 and 150 mg $MgSO_4$. The QuEChERS and the dSPE were supplied by Agilent technologies (Bond Elut Sample preparation solutions) (Lake Forest, CA, USA). For enzymatic hydrolysis was used the enzyme β-glucuronidase/arylsulfatase from *Helix pomatia* (EC 3.2.1.31/EC3.1.6.1; 5.5/2.6 U/mL) purchased from Roche Diagnostics (Indianapolis, USA).

2.2. Standard solutions

Stock solutions (100 mg/L) were prepared in methanol. Working solutions were prepared daily from these stocks by appropriate dilution. The solutions were stored at −20 °C. Two five-concentration-level calibration curves within the 1–50 μg/L concentration range in methanol and urine (matrix-matching calibration, spiked after extraction) were prepared. Deuterated internal standard ($^{13}C_{12}$BPA) was employed to compensate for possible matrix effects and analyte losses.

2.3. Instrumentation

Chromatographic analysis was carried out in a TRACE GC Ultra gas chromatograph Polaris Q coupled with ion trap mass spectrometer (Thermo Fisher Scientific) operated in the electron impact ionization (EI) mode at 70 eV and controlled by Xcalibur 1.3. The helium carrier gas (Linde Sógas purity ≥99.999%) was maintained at a constant flow of 1 mL/min. Injection (2 μL) was carried in splitless mode. A Phenomenex column ZB-XLB (30 m x 0.25 mm I.D, 0.25 μm film thickness) was used. The GC oven temperature was programmed from an initial temperature of 90 °C (1 min hold), ramped at 15 °C/min up to 250 °C (1 min hold), increased to 255 °C at 20 °C/min (5 min hold) and finally to 270 °C at 10 °C/min (1 min hold). This program resulted in a total run time of 23.42 min. The other optimized parameters included a transfer line temperature of 250 °C and an ion source of 250 °C. The BPA was quantified in the selected ion monitoring (SIM). The selected ions for BPA were 357 and 372, for $^{13}C_{12}$BPA were 364 and 383, and the retention time of the compounds was 12.85 min. The identification was confirmed by retention times and ion ratios. To homogenize the samples a VWR vortex mixer (Radnor, Delaware, USA) was used. For centrifugation, a Thermo Scientific™ Heraeus™ Megafuge™ 16 Centrifuge (Germany) was applied.

2.4. Urine samples

Urine samples were obtained from voluntary children that were normal and obese/overweight. The study was approved by the ethics committee of the Centro Hospitalar S. João/FMUP (Medicine Faculty of Oporto University ref. 163.13) and all the parents provided written consent. All samples were stored in glass material at −20 °C until analysis. Urinary creatinine concentration was measured through a modified Jaffe method [72] with an Olympus AU5400® (Beckman–Coulter®, Porto, Portugal) at São João Hospital, Department of Clinical Pathology.

2.5. Micro-QuEChERS optimization

Different composition of QuEChERS (Original, AOAC and EN methods) salts as well as two dSPE (dSPE 1 and dSPE 2) were tested through preliminary recovery studies. Additionally, several parameters that can affect the extraction efficiency were analyzed. During method optimization, the following parameters were evaluated: urine (1.0 and 1.5 mL) and ACN (1.0, 1.5 and 3 mL) volumes; ACN acidification (1%

acetic acid); different masses of the selected QuEChERS (500 and 750 mg); ideal volume of the final extract (100, 200, 400 and 500 µL) used prior to derivatization.

After optimization, the samples were analyzed according to the following procedure. An aliquot of 1.5 mL of homogenized urine was mixed into an 8 mL glass vial with 25 µL of β-glucuronidase/aryl sulfatase enzyme (to hydrolyze glucuronide- or sulfate-conjugated metabolites), and the internal standard. The samples were incubated overnight at 37 °C. After the enzymatic hydrolysis took place, an optimized Micro-QuEChERS procedure was employed to extract BPA from urine samples. To the hydrolyzed sample were added 750 mg of QuEChERS B (AOAC method) and 3 mL of ACN. The mixture was strongly shaken in a vortex for 1 min and then centrifuged during 10 min at 4500 rpm. The obtained ACN layer was immediately transferred into the 2 mL dSPE 1, mixed for 1 min and centrifuged for 10 min at 4500 rpm. Later, 200 µL of the extract were transfer to a GC vial and evaporated to dryness under a gentle stream of nitrogen. The dry residue was then dissolved in 100 µL of derivatization reagent (BSTFA + 1% TMCS). This mixture was put in a bath at 80 °C for 30 min, following the derivatization conditions (time and temperature) previously reported by Kuo and Ding [73]. The final extract was transferred into a glass insert (into a GC Vial) and analyzed using the GC–MS system.

2.6. Method validation

The method was validated for linearity, detection and quantification limits (LOD and LOQ, respectively), selectivity, accuracy, recovery and precision, according to international guidelines [74–76].

The selectivity of the method was analyzed by comparing the chromatograms of several blank urine samples with those of the spiked (BPA) urine samples.

A five point matrix-matched calibration curve was obtained using human urine samples fortified, after extraction, with BPA at concentrations from 1 to 50 µg/L (three replicates of each). The calibration curve was constructed using analyte/internal standard peak area ($^{13}C_{12}$ BPA) ratio versus concentration of the analyte in urine matrix. A calibration curve was also constructed with standard solutions in the same linear range for the evaluation of possible matrix effects. In this study, the LOD and LOQ were calculated with S/N 3 and 10 of the lowest analyzed concentration, respectively.

Generally, the term Accuracy refers to the trueness and precision of the method. Concerning trueness, several approaches can be applied. In the present study accuracy is expressed as recovery and was calculated through the spiking recovery method (%) [76]. Recovery studies were performed at spiking levels of 10, 20, 50 µg/L. The mean peak areas of the urine samples spiked before and after extraction were compared. The interday precision and the intraday precision of the method were evaluated at two concentration levels, of 20 and 50 µg/L. For the intraday precision, three replicates were analyzed on one day (n = 3), whereas for the interday precision, three replicates were analyzed on three consecutive days (n = 9). The results were expressed as the percent relative standard deviation (RSD).

3. Results and discussion

3.1. Modified QuEChERS optimization

During method optimization, background contamination was addressed, as exogenous sources of contamination are reported to be problematic when measuring this compound [77,78]. Glassware was used whenever possible and cleaned with hexane to eliminate any potential background contamination.

3.1.1. Micro-QuEChERS and dispersive SPE content

In the initial optimization tests a urine volume of 1 mL was used as other authors [67,71] reported good recoveries using similar amounts of sample. Additionally, the original method (10 g or mL sample per 10 mL of extraction solvent) was scaled by using 1 mL of urine, 500 mg from each tested QuEChERS content (weighted into a glass flask) and 1 mL of ACN. The extraction solvent was set to ACN as this solvent is known to be more efficient than others, such as acetone and methanol [53,79]. Moreover, ACN has been used successfully in the extraction of several compounds [46,66–70] from urine matrix.

As described in Section 2.1 (from material and methods), in the present study three different QuEChERS (A, B and C) and two dSPE (1 and 2) compositions were tested. In a preliminary test, to select the best possible composition and combination, the obtained peak areas from urine samples fortified before extraction were compared with the peak area of a standard solution, all at concentration level of 50 µg/L. Concerning the QuEChERS content, the AOAC composition (B) gave the best recoveries (from 92 to 120%). This composition was also successfully applied to the determination of disulfoton and its oxidative metabolites in human whole blood and urine samples (recoveries ranging from 87 to 112%) [67].

For the clean-up step, the dSPE 1, constantly, presented higher recoveries (≥100%) than the dSPE 2 (from 69 to 92%), when combined with all the tested QuEChERS. Therefore, dSPE 1 composed of 25 mg of C18 and 150 mg of $MgSO_4$ was selected.

In a second approach to perform a more precise recovery experiment, accounting for the matrix effects, only the combination of the QuEChERS A, B and C with the dSPE 1 was evaluated. For analyzing recoveries, the obtained extracts peak areas (spiked pre-extraction) were compared with the peak area of a spiked matrix extract (spiked post-extraction) also at concentration of 50 µg/L (Fig. 1).

Finally, ACN, as extraction solvent, QuEChERS B with the AOAC salts (MgSO4, CH3COONa) and the dSPE 1 (25 mg of C18 and 150 mg of MgSO4) were selected for sample preparation, as this combination presented higher recoveries (102%) with good peak shapes and removal of matrix interferences.

3.1.2. Acidification of the extraction solvent

As pointed out previously the original QuEChERS composition has suffered modifications to improve the extraction of pH sensitive compounds and in addition to minimize their degradation [80,81]. According to the AOAC 2007.01 method, an acidification of the extraction solvent occurs (ACN with 1% of acetic acid) [80]. Consequently, the ACN acidification was tested and evaluated. We believe that is the first time an acidification of the ACN was also tested for the EN 15562 method and the Original composition for urine samples. A signal

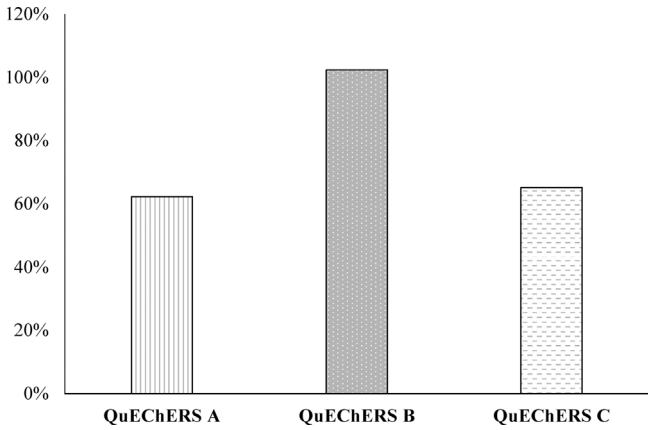

Fig. 1. Recoveries obtained with the three composition of QuEChERS salts combined with dSPE 1 clean-up (comparison between a matrix sample spiked before and after extraction at concentration level of 50 µg/L) (n = 1).
QuEChERS A ((4 g magnesium sulfate ($MgSO_4$) and 1 g sodium chloride (NaCl)); QuEChERS B (6 g $MgSO_4$ and 1.5 g anhydrous sodium acetate (CH_3COONa)); and QuEChERS C (6 g $MgSO_4$, 1.5 g NaCl, 1.5 g of sodium citrate dihydrate ($Na3Cit{\cdot}2H_2O$) and 0.750 g sodium citrate sesquihydrate ($Na_2HCit.1.5H_2O$)).

Table 1
Recoveries obtained during the experiments with the modified micro AOAC 2007.01 (ACN without acidification) QuEChERS method.

Experiments	Urine (mL)	QuEChERS B (mg)	ACN (mL)	Recoveries (%)
A	1.0	500	1.0	102
B	1.5	500	1.0	73
C		750	1.5	119
D		750	3.0	107

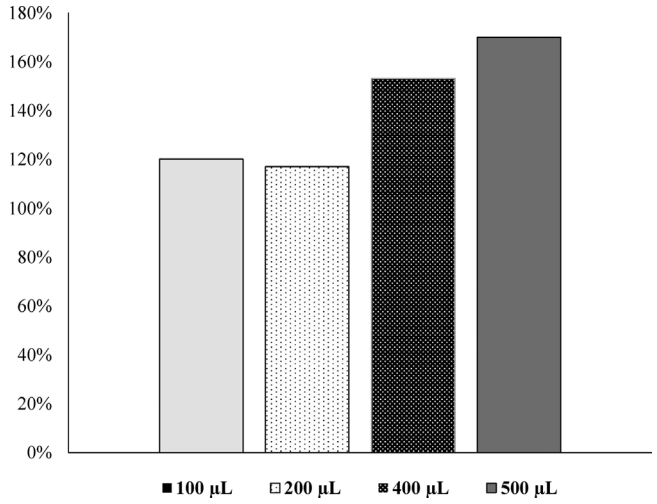

Fig. 2. Obtained matrix effects with the different extract volumes (matrix sample spiked before extraction compared with a standard at concentration level of 50 µg/L) (n = 1).

enhancement for these experiments could not be avoided, probably due to the presence of acetic acid as referred by other authors [82]. Furthermore, the chromatogram with AOAC salt composition and extraction with ACN without acidification, besides giving a good recovery (102%) also shown less matrix interferences. Therefore, the AOAC salt composition combined with the non-acidified ACN was chosen for further optimization studies.

3.1.3. Ratio of mass of QuEChERS content per volume of solvent and sample

After the QuEChERS and dSPE selection, different amounts of the selected QuEChERS and different ACN and urine volumes were tested in four experiments. The results of these tests are depicted in Table 1.

Overall, good recoveries were obtained with all the tested experiments. However, experiment D was chosen since it better separated the organic phase from the aqueous which allowed an easier removal of 2 mL to the clean-up (dSPE).

3.1.4. Selection of the volume of matrix extract

Optimizing the method further, the ideal volume of extract (removed after the dSPE), to be employed in the derivatization, was evaluated. Four extract volumes (according to experiment D), namely 100, 200, 400 and 500 µL were tested. After derivatization, the peak areas obtained from the analyzed extracts were divided by the peak area of a standard, all at concentration level of 50 µg/L. In Fig. 2 the observed matrix effects are shown.

The extract volume of 200 µL was selected as it showed a lower matrix effect (+10%) compared to other tested volumes. A possible explanation is that by concentrating more the presence of matrix components increased leading to higher matrix effects. For the volumes of 400 and 500 µL, dried and re-dissolved in 100 µL of the derivatization reagent (concentration factor of 4 and 5) the observed matrix effects were of +50 and +70%, respectively. The optimized procedure is shown in Fig. 3.

3.2. Method validation

A complete method validation, comprising linearity, selectivity, sensitivity, accuracy, precision (within day) and ruggedness (between days), was performed. In addition, matrix effects were also studied.

At BPA retention time, no interferences from endogenous substances were detected. Consequently, a good separation was obtained under the described GC–MS conditions. A chromatogram of a urine sample spiked with 50 µg/L of BPA is depicted in Fig. 4.

The capacity to quantify levels of target analytes in biological samples accurately and precisely involves the use of highly sensitive and selective instrumentation, namely through tandem mass

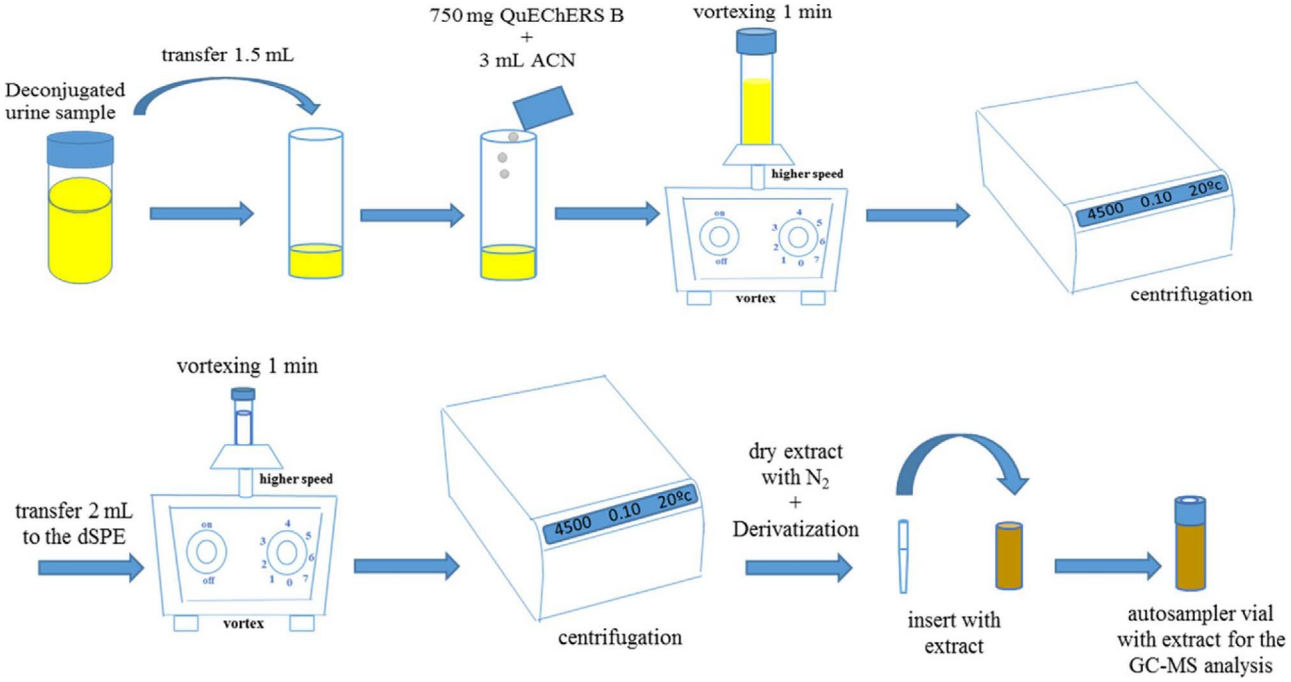

Fig. 3. Scheme of the optimized Micro-QuEChERS extraction for BPA analysis in urine.

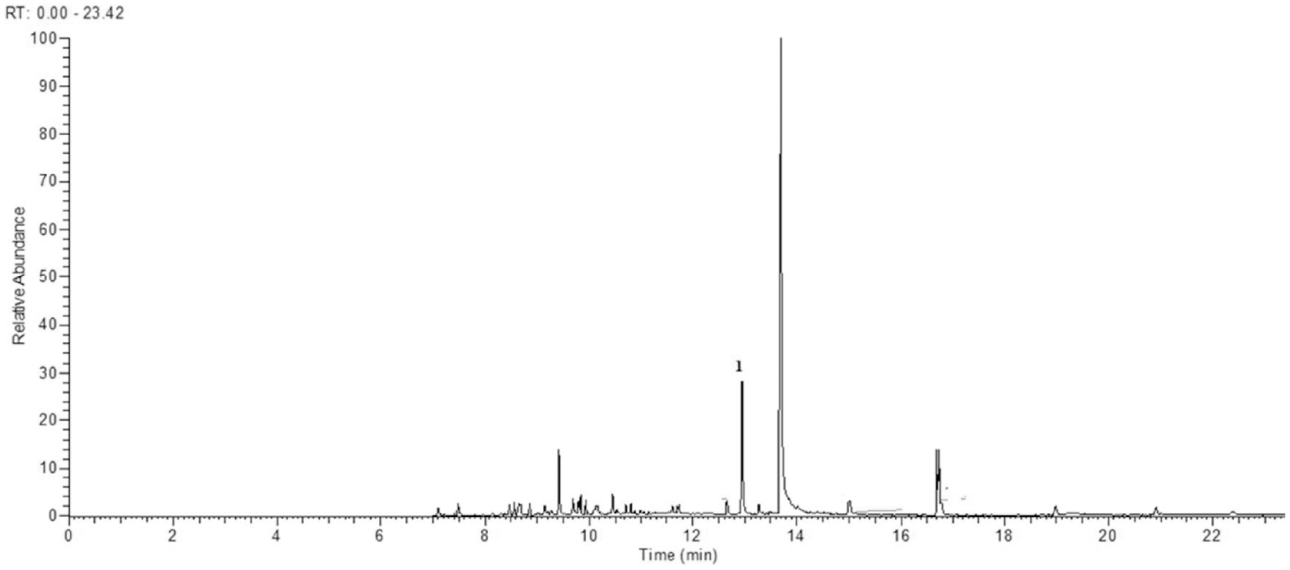

Fig. 4. Gas chromatography–tandem mass spectrometry separation profile of Bisphenol A at a spiking level of 50 µg/L in human urine (1-Bisphenol A).

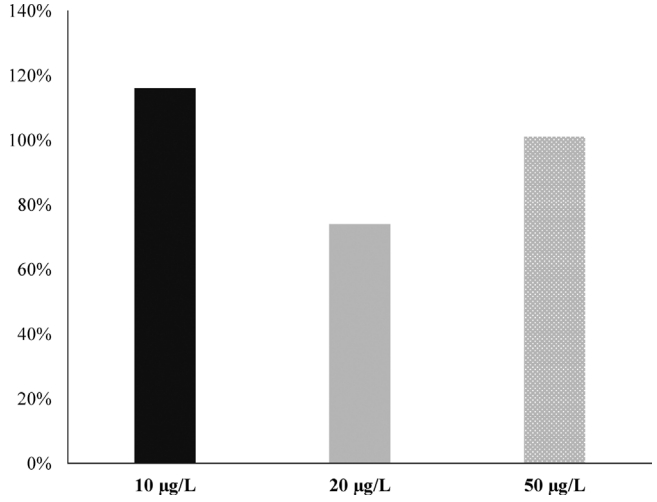

Fig. 5. BPA recoveries percentages from three spiked urine samples at concentration level of 10, 20 and 50 µg/L.

spectrometry and a comprehensive understanding of extremely variable matrix effects. Usually, matrix effects are caused by the co-elution of matrix components that modify the ionization as well as the chromatographic response of target analytes, leading to reduced or increased sensitivity of the analysis. Therefore, before accuracy and precision are evaluated, these effects should be characterized and controlled. The term, "matrix effects," was first discussed by Tang and Kebarle [83] and it generally refers to a difference in mass spectrometric response for an analyte in standard solution versus the response for the same analyte in matrix [83].

Several approaches can be applied to determine the matrix effect in biological samples such as flow-based evaluation, post-extraction spike matrix comparison, and some alternative methods such as adding known amounts of target compounds to biological matrices obtained from at least ten donors [84].

Each biological matrix has a unique composition, urine is a complex sample with a general composition that includes salts, organic molecules (e.g., urea and amino acids), proteins (e.g., albumin and immunoglobulins), crystals (e.g., calcium phosphate and uric acid) and cells (white blood cells and transitional cells) [85]. Additionally, according to the diet and hydration status of the donors the amount of the matrix components can change [85].

To evaluate the matrix effect, the slopes obtained in the calibration with matrix matched-standards (spiked after extraction) were compared with those obtained with standard solutions according to other reports [84,86]. In general, a signal enhancement was observed (+44%).

Common strategies can be used to minimize or compensate for matrix effects in GC–MS method. A combination of these approaches is recommended to successfully manage matrix effects so that they will not alter method accuracy and precision [84]. Therefore, matrix-matched calibration was used for quantification purposes and additionally we used an isotopically labeled analogue of the target analyte as an

Table 2
Total BPA obtained in children's' urine (µg/L and µg/g creatinine).

Sample	Gender	Age	Weight group	Creatinine (g/L)	Total BPA (µg/L)	Total BPA (µg/g creatinine)
1	M	7	Obese/overweight	0.90	15.9	17.67
2	F	14	Obese/overweight	1.09	7.9	7.25
3	F	15	Obese/overweight	2.28	7.5	3.29
4	M	12	Normal	2.43	19.0	7.82
5	M	16	Normal	2.58	48.9	18.95
6	M	4	Normal	0.83	9.1	10.96
7	F	8	Obese/overweight	0.28	5.8	20.71
8	F	6	Obese/overweight	0.86	4.9	5.70
9	M	10	Obese/overweight	0.73	2.5	3.42
10	M	9	Obese/overweight	1.05	1.7	1.62
11	M	8	Obese/overweight	1.33	3.0	2.26
12	F	10	Obese/overweight	0.57	1.5	2.63

internal standard. This last approach is considered one of the most effective ways to rectify or account for matrix effects [86]. We obtained a linear response, over the concentration range from 1 to 50 μg/L, a slope of 0.0048 μg/L, with a correlation coefficient of 0.998. The obtained LOD and LOQ were of 0.13 and 0.43 μg/L, respectively. The methods LOD and LOQ were in the same range [87] (limit of detection of 0.1 ng/mL, applying UPLC–MS/MS) or even lower [88] (lower limit of quantification of 50 ng/mL, applying GC–MS) than other recently reported methods for BPA determination in urine samples.

The mean recoveries (n = 3 for each spiking level) and RSD for BPA, obtained with urine samples spiked at 10, 20 and 50 μg/L, measured by GC–MS (SIM mode), are shown in Fig. 5. Overall, good recoveries (from 70 to 120%) were obtained, and the percent relative standard deviations for recovery at different spiking levels ranged from 3 to 11%. The intraday precision and the interday precision of the method ranged from 3% to 10% and from 4% to 9%, respectively. Therefore, the developed method can be regarded as useful and appropriated for the quantification of BPA in urine samples.

3.3. Application to urine samples

The developed and optimized method was applied for the determination of total BPA in 12 randomly selected children, including both male and female subjects, with normal weight and obese/overweight. The samples were collected in 2014/2016. The age range was from 4 to 16 years old, with an average of 10 years old. The results obtained with the human urine samples are summarized in Table 2. The results showed that total BPA was detected in all the participant subjects at various degrees of concentrations, ranging from the lowest level at 1.5 μg/L to the highest at 48.9 μg/L. Values for total BPA were adjusted to the total creatinine content in the urine sample (Table 2).

4. Conclusions

With this study, for the first time, a new sample preparation method based on a miniaturized QuEChERS for BPA determination in human urine samples was presented. The optimized Micro-QuEChERS coupled to GC–MS, with derivatization, can be regarded as a sensitive and specific method for the quantification of total BPA in urine samples. Excellent recoveries were obtained, calibration was linear up to 50 μg/L with a LOQ of 0.43 and LOD of 0.13 μg/L, respectively. Traditionally GC–MS based methods (namely applying manually-operated SPE) for BPA determination in urine sample are laborious, time consuming and include numerous steps that can lead to background contamination. The proposed method is quick (can be performed in less than 1 h), easy, cheap and rugged. Additionally, it can be regarded as a greener alternative to traditional methods requiring smaller sample and extraction solvent volumes. The QuEChERS technique proved once more its versatility and may be a possible value tool for the biomedical analysis and biomonitoring studies in GC–MS field.

Conflict of interest statement

The authors declared no conflict of interest.

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