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An indirect method for the analysis of bisphenol A, as a Mn(III)–chelate complex, in milk samples by ultrasound assisted-cloud point extraction/flame atomic absorption spectrometry

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A method for indirect determination of bisphenol A (BPA), as a Mn(III)–chelate complex, in milk samples by flame atomic absorption spectrometry (FAAS) was developed. The method was based on cloud point extraction with ultrasound assistance (UA-CPE). In the pre-concentration step by UA-CPE, the ternary complex selectively formed between BPA and Mn(III)–oxalate at pH 5.0 was extracted into the mixed micellar phase of ionic and nonionic surfactants, cetyltrimethylammonium bromide (CTABr) and polyethylene glycol tert-octylphenyl ether (Triton X-114) as a sensitivity enhancer and extractant. After phase separation by centrifugation, the separated extract was diluted with acidic methanol and analyzed by FAAS. The reproducibility of the signal in the detection step especially at low concentrations was greatly improved by the use of polyvinyl alcohol (PVA) as a stabilizer. Using indirect Mn-responses by FAAS, the main variables affecting the extraction efficiency were evaluated and optimized. Under optimized conditions, the calibration graph was highly linear in the range of 0.8–130 μg L^{-1} with limits of detection and quantification of 0.23 and 0.76 μg L^{-1}, intra- and inter-day precisions in the range of 2.8–5.2% and 3.8–7.2%, and recovery in the range of 94.2–98.5% (10, 25, 100 μg L^{-1}, n: 5 and 3 × 5). From pre-concentration of a 35 mL sample by UA-CPE, the pre-concentration factor was found to be 70 with a 41-fold sensitivity improvement. The matrix effect was greatly reduced by deproteinization with trichloroacetic acid (TCA) and 20-fold dilution of milk samples before analysis. The method accuracy was checked by analysis of trace BPA in milk samples *via* a calibration curve in solvent and a matrix-matched calibration curve prepared from sample extracts. The results were in the range of 2.1–7.3 μg L^{-1} and 2.0–7.0 μg L^{-1} without any matrix effect. According to the Student's *t*-test, there is not a statistically significant difference between the results found by using the two calibration curves. Finally, it can be concluded that the method is suitable for detecting BPA in milk based products at concentrations far below the specific migration limit (SML) of 600 μg L^{-1}.

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1. Introduction

Food safety is one of the major concerns in research related to food toxicology and analytical chemistry. The contaminants present in beverages and food are the most attention-drawing subjects in the last decade. Among food contaminants, bisphenol A (BPA) is now attracting attention due to its negative ecological and human health effects. BPA is an organic compound and consists of two phenol molecules bonded by a methyl bridge and two methyl groups. As a synthetic monomer, BPA is widely used in many productions, including polycarbonate plastics, epoxy resin linings of canned foods and beverage containers.[1] BPA could be introduced into food and beverages through migration from polycarbonate tools and containers or epoxy coatings.[2] Owing to the massive use and emissions of BPA-based materials, BPA can be released into the environment and cause adverse ecological and human health effects. As a consequence of environmental contamination, BPA could be absorbed by crops, and then enter the food chain. Due to all these features, it is of great importance to develop accurate and reproducible methods to monitor the trace levels of BPA in food and beverages.

Regarding the acute oral toxicity of BPA, its adverse effect on human health has aroused extensive concern. Recent research indicates that BPA can disrupt the natural hormone balance in humans and can be particularly harmful to fetus, infants, and young children.[3,4] Furthermore, residues of BPA in milk and milk based products may pose a serious threat especially to the health of infants and children.[5,6] There is a tolerable daily intake (TDI) and reference dose (RfD) of 50 μg per kg per day estimated by the European Food Safety Authority (EFSA, 2007) and the US

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Environmental Protection Agency (EPA, 2009).[7] Also, for safety control of food products, a specific migration limit (SML) of 600 μg kg^{-1} was established by the European Food Safety Authority (EFSA).[8] So far, many analytical methods have been developed for monitoring trace levels of BPA in beverages and foods.[9–13] Owing to the complex matrices, tedious and time consuming sample preparation (extraction and cleanup) is required prior to the analysis by liquid chromatography (LC) coupled with ultraviolet (UV) absorbance, fluorescence(FL) and photodiode array detection (PDA) in normal and/or reverse phase (RP) modes including micellar LC and immune-affinity chromatography. Compared with LC coupled with UV, FL and PDA detection, gas chromatography mass spectrometry (GC-MS) offers a higher degree of selectivity and sensitivity. However, GC-MS is not capable of directly analyzing contaminants like BPA that are nonvolatile, polar, or thermally labile. Derivatization is required to increase their volatility and thermal stability.[12] LC-MS or LC-tandem MS has disadvantages such as higher operational cost; more limited sample throughput; and less favorable concentration sensitivity. Generally, the main drawbacks of the chromatographic methods, which are often used in analysis of BPA in the literature,[14–22] are related to the process of pre- or post-column derivatization leading to long analysis times, low reproducibility, interferences and problems connected to the stability of derivatization products including the solvent, pH and temperature gradient program in suitable elution mode. To get rid of the matrix effect, they also require tedious and time-consuming extraction or pre-concentration steps in the hands of well-trained technicians. To overcome the analytical problems such as poor precision, selectivity and detection limit, some separation/pre-concentration techniques with their own advantages and disadvantages were used in analysis of trace amounts of BPA in complex matrices.[12,23–31]

Unlike chromatographic techniques, flame atomic absorption spectrometry (FAAS) presents desirable characteristics, such as good selectivity, low cost, operational facilities and high analytical frequency. FAAS is used for food-sample analysis to avoid possible spectral or polyatomic interferences, which can appear in plasma techniques. However, the direct determination of trace metals by this technique is usually difficult because of the low concentration of metal ions in the samples and interference of matrix components. These problems can be overcome by using separation and or pre-concentration procedures before the analysis.

Cloud point extraction (CPE) has attracted great attention because it complies with the "Green Chemistry" principle.[32] CPE is simple, highly efficient, cheap, rapid and of lower toxicity than those procedures using organic solvents. CPE is based on the phase behavior of non-ionic surfactants in aqueous solutions. Non-ionic surfactants undergo phase separation upon increasing the temperature or the addition of a salting-out agent.[33] This procedure has been successfully employed to extract and pre-concentrate priority pollutants such as organophosphorus pesticides and poly aromatic hydrocarbons (PAHs) from different sample matrices before their detections by a suitable analytical technique.[34,35] To the best of our knowledge, there is only a report on the use of FAAS for indirect determination of BPA.[36] In this study reported by our research group, BPA was indirectly detected with limits of detection and quantification of 0.46 and 1.56 μg L^{-1} in a linear range of 1.5–130 μg L^{-1}. The method is based on charge transfer (CT), in which BPA reacts with Cu(II) in alkaline tartrate media at pH 8.0 to produce Cu(I), which reacts with an ion-pairing reagent, promethazine (PMZ) in the presence of cetyltrimethylammonium bromide (CTABr) with sensitivity enhancement and pre-concentration factors of 135- and 150-fold, respectively. After CPE with ultrasound assistance, the method was successfully applied to the indirect analysis of BPA in beverages with and without alcohol by FAAS.

In this sense, the main purpose of the study is to develop a simple, easy to use, low cost, fast, sensitive, and reliable UA-CPE procedure for separation, extraction and pre-concentration of BPA from a milk matrix as a ternary complex formed between BPA and Mn(III)-oxalate at pH 5.0, which is linearly related to the BPA concentration, prior to indirect analysis by FAAS. To further improve detection sensitivity, selectivity and reproducibility of analysis by FAAS, another objective of the present work is efficiently to use CTABr and polyvinyl alcohol (PVA) as a sensitivity enhancer and stabilizer, respectively.

2. Experimental

2.1. Instrumentation

An AAS-6300 atomic absorption spectrometer (Shimadzu, Kyoto, Japan) equipped with D_2-background correction, a Mn hollow cathode lamp and an air-acetylene flame atomizer were used for the indirect detection of BPA in surfactant-rich phases. The spectral resonance line, lamp current, spectral bandwidth, burner height, and acetylene and air flow rates used for the detection of the Mn were: 279.5 nm, 10 mA, 0.2 nm, 7.0 mm, 2.0 and 15.0 L min^{-1}, respectively. A centrifuge (Hettich Universal, Universal-320, Hettich Centrifuges, UK) was used to speed up the phase-separation process. An ultrasonic bath operating with an ultrasound frequency of 40 kHz at 300 W (UCS-10 model, Seoul, Korea) was used to maintain the temperature for UA-CPE. A VM-96B model vortex mixer with a frequency of 60 Hz at 12 W (Jeio Tech, Co., Ltd, Seoul, Korea) was used to thoroughly mix the solutions. A digital pH meter equipped with a glass-calomel electrode (pH-2005, JP Selecta, Barcelona, Spain) was used for pH measurements. Adjustable Eppendorf vary-pipettes (10–100 and 200–1000 μL) were used to deliver accurate volumes. The selected liquid milk products were kept fresh and cool in a refrigerator till analysis.

2.2. Reagents and materials

All chemicals and reagents used were of analytical-reagent grade or higher purity. Ultra-pure water with a resistivity of 18.2 MΩ cm was prepared using a Labconco (Kansas City, USA) water purification system. A stock solution of BPA (1000 mg L^{-1}) was prepared by dissolving the required amount (≥98%, Sigma-Aldrich) in methanol and stored under dark conditions at 4 °C. The standard working solutions were obtained daily by

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appropriate dilution of the stock solution with methanol. The oxidant solution, Mn(III)-oxalate at 16.5 mg L^{-1}, was prepared by mixing 3.0×10^{-4} mol L^{-1} MnO_4^- solution with 1.2×10^{-3} mol L^{-1} of Mn(II)-acetate solution in the presence of excess oxalate solution at pH 5.0, so as to be a minimum 16-fold excess compared to those of Mn(III). The solution was freshly prepared daily before analysis. The cationic surfactant, a CTABr solution of 1.0×10^{-3} mol L^{-1} was also prepared by dissolving and diluting a suitable amount of the pure solid surfactant (≥95%, Sigma-Aldrich) in water. The solutions of 5.0% (w/v) of polyethyleneglycol tert-octylphenylether (Triton X-114) and polyoxyethylene(7.5)nonylphenylether (PONPE 7.5) (Sigma-Aldrich) were independently prepared in water and an ethanol–water mixture (1 : 3, v/v), respectively. The acetate buffer was used to maintain the pH of the solutions at 5.0. The buffer solution (100 mL of 0.5 mol L^{-1}, pH 5.0) was prepared by adding 0.866 g $CH_3COONa \cdot 3H_2O$ (≥98%, Sigma-Aldrich) and 0.218 g glacial CH_3COOH to the solution and adjusting the solution to the desired pH using 5.0 mol L^{-1} HCl. The vessels and pipettes used for trace analysis were kept in 10% (w/v) HNO_3 for at least 24 h and subsequently washed five times with water.

2.3. Extraction of BPA from the sample matrix

The milk samples packed in polyethylene packing and produced by different companies were purchased from local open-markets and from a Turkish store in Sivas, Turkey. Sample preparation is a crucial step for obtaining reliable results. For reducing time and possible errors in the sample preparation step, a green extraction approach based on the ultrasonic effect was adopted. All samples were independently subjected to ultrasonic assisted extraction as an easy, convenient, and fast way of extraction to ensure complete dissolution before analysis.

5 mL of milk samples in contact with polycarbonate (PC) or polyvinyl chloride (PVC) containers was placed in a 50 mL centrifuge tube, homogenized by vortexing for 2 min at 1200 rpm, and 20 mL of acetonitrile containing 0.05 g NaCl/mL was added to this. The mixture was kept at 40 °C for 20 min in an ultrasonic bath so as to obtain a clear solution, and then centrifuged for 5 min at 4000 rpm. After centrifugation, the supernatant was withdrawn and 2 mL of methanol was added to it and then diluted to a total volume of 25 mL with water. 5 mL of the pre-treated sample solutions were obtained, after adding three different standard concentrations of BPA under optimal conditions, so as to fall into the calibration range; their BPA contents were indirectly analyzed by FAAS. An analyte blank including one quality control sample spiked before pretreatment was also submitted to the procedure in a similar way.

In this work two calibration methods were used: the (i) standard calibration curve and (ii) matrix-matched calibration curve. The standard calibration curve was built by using triplicate injections of a serial standard solutions containing BPA in the solvent at increasing concentrations ranging from 1.0 to 130 μg L^{-1} in a 50 mL centrifugation tube, so as to evaluate analytical features of the method. To mimic the environment where the analyte must be determined and the interactions between the analyte and other components in the matrix (altering the observed signal), a matrix-matched calibration curve was also prepared using the matrix extracts. For this purpose, the pre-treated sample extracts were used as the matrix and, after three-point standard addition, were processed in the enrichment step. Standard solutions of 5, 10, 15, 30, 60, 90 and 120 μg L^{-1} (depending on the BPA) falling in the range of 1–140 μg L^{-1} were externally added to the sample extracts. To evaluate matrix effects, the slopes of the two calibration curves prepared using solvent and sample extracts were calculated and compared for enhancement and/or suppression in the signal. Two calibration curve equations had comparable slopes (within −10.1% as shown in Table 1). Therefore, after ultrasonic sample preparation, it is reasonable to assume that no signal suppression or enhancement occurs in indirect analysis by

Table 1 The analytical features of the proposed pre-concentration method

	Without pre-concentration	With pre-concentration	
Analytical parameters[a]	By using the calibration curve	By using the calibration curve in solvent	By using the matrix-matched calibration curve
Linear working range, μg L^{-1}	300–12 000	0.8–130	1–140
Slope, m	-3.36×10^{-5}	-1.38×10^{-3}	-1.24×10^{-3}
Intercept, b	0.042	0.185	0.179
Correlation coefficient, r^2	0.9961	0.9936	0.9954
LOD and LOQ, μg L^{-1} (from blank measurements, n: 10)	107.1, 357	0.23, 0.76	0.43, 1.42
Intra-day precision RSD % (10, 25 and 100 μg L^{-1}, n: 5)	3.5[c]	2.8–5.2	3.2–5.7
Inter-day precision RSD % (10, 25 and 100 μg L^{-1}, n: 3 × 5)	5.3[c]	3.8–7.2	4.2–8.5
Recovery % (10, 25 and 100 μg L^{-1}, n: 5)	96.1[c]	94.2–98.5	92.5–96.5
Pre-concentration factor, PF	—	70	70
Sensitivity enhancement factor, EF	—	41	37
Matrix effect (ME), %[b]	—	—	−10.1

[a] In the presence of 1.0 mL of 2.0% (w/v) PVA as the stabilizer. [b] The matrix effect is calculated by using the formula, $ME\% = (m_A - m_B)/m_A \times 100$ where m_A and m_B are slopes of the calibration curve in the solvent and matrix-matched calibration curves prepared from the sample extracts before-pre-concentration by UA-CPE. [c] The accuracy and precision data of the method based on spiking with 100 μg L^{-1} of BPA (n: 5) before pre-concentration.

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FAAS, possibly caused by interfering components in the matrix. Without pre-concentration, the six-point calibration curve was indirectly constructed using the absorbance of the ternary complex against the BPA concentration in the range of 0.3–12 mg L^{-1} under optimal reagent conditions where the sample blank is Mn-oxalate plus other reagents without BPA.

2.4. The UA-CPE procedure

For the UA-CPE experiments, aliquots (5.0 and 35 mL) of sample solutions (for analysis of the samples and establishing the pre-concentration factor) or a suitable portion of standard solutions containing BPA in the range of 0.8–130 μg L^{-1}, 0.03 mol L^{-1} of acetate buffer at pH 5.0, 0.33 mg L^{-1} of Mn(III)-oxalate, 150 μmol L^{-1} of CTAB, 0.08% (w/v) PVA, 0.06% (w/v) of non-ionic surfactant, Triton X-114 as the extractant and 0.125% (w/v) Na_2SO_4 as a salting-out agent were placed in a 50 mL centrifuge. To facilitate ternary complex formation and mass transfer at the micellar interface, the solution was shaken vigorously and homogenized for 1 min at 3200 rpm using a vortex mixer, which was then filled with water up to the mark. After complexation, the mixture was left to stand in an ultrasonic bath at 40 °C for 10 min in order to provide clouding of the non-ionic surfactant. After a turbid solution is obtained, the separation of the phases was carried out by centrifugation for 5 min at 3750 rpm. The aqueous phase was carefully removed using a Pasteur pipette, and the surfactant-rich phase (~0.2 mL) was diluted to 0.5 mL with acidic methanol (containing 0.1 mol L^{-1} HNO_3) to reduce its viscosity. After UA-CPE, the diluted phase was introduced into a flame by conventional aspiration for indirect analysis of BPA.

2.5. Statistical analysis

Data processing and all statistical calculations (ANOVA) were performed using Excel 2010 (Microsoft Office®). Due to the lack of a CRM compatible with the sample matrix, for method validation, the Student's *t*-test, including recoveries and RSDs as a measure of accuracy and precision with and without spiking, was used for the comparison of results found by using two different calibration curves. The results are expressed as mean ± SD and 95% confidence intervals. The level of significance was set at 0.05; *p*-values >0.05 were assumed to be non-significant for all comparisons. Each point in the optimization step and calibration curves after pre-concentration was run in triplicate, and the results were indicated with error bars. The one- and two-paired ANOVA tests (*t*) in the optimization step and analysis step of the samples were conducted for statistical comparisons.

3. Results and discussion

Initially, it was observed in our first study[37] that when trace amounts of BPA are added to solutions containing Mn(III) and oxalate in the presence of CPC and CTAB as ion-pairing reagents at pH 5.5 and 6.0, there is a linear gradual decrease in the absorbance of the ternary complex for the fixed-time method of 5 min at a characteristic absorption wavelength, 447 nm with increasing BPA concentration. Also, it has been observed that the absorbance, which is corrected against the analyte blank, can be kinetically controlled and stabilized by adding PVA at optimal amounts into the reaction medium. In the present study, in order to reduce a possible matrix effect in analysis of the samples in the name of improving selectivity, a pre-concentration study was performed in the presence of non-ionic surfactants, Triton X-114 and PONPE 7.5 at pH 5.0. From the results, with a significant sensitivity difference, it was observed that the ternary complex, which is linearly correlated with the BPA concentration, could be extracted into the micellar phase of Triton X-114 in an ultrasonic bath and easily monitored by FAAS after dilution of the surfactant-rich phase with acidic methanol. Based on this observation, a new UA-CPE/FAAS method for separation, pre-concentration, accurate and reproducible determination of trace BPA from an aqueous sample matrix was designed, and various parameters affecting the extraction efficiency were evaluated and optimized.

3.1. Optimization step

The effect of the analytical variables such as pH, buffer, an anionic oxalate stabilized Mn(III) chelate, ionic/nonionic surfactants and PVA concentrations, including incubation temperature and time, centrifugation rate and time, on the absorbance of Mn at a resonance line of 279.5 nm, which is linearly related to the BPA concentration, was investigated by the univariate method, varying each parameter one-by-one while holding fixed the remaining, in order to take into account the sensitivity and precision of the measurements. Due to familiarity and ease to use, the univariate method is widely used in the optimization step to obtain maximum efficiency of analytical methods. The concentration of BPA, so as to fall in the linear working range, was fixed at a level of 25 μg L^{-1} during the optimization.

3.1.1. Effect of pH on the analytical signal. The effect of pH on UA-CPE of the BPA-Mn(III)oxalate complex in the presence of CTAB and PVA as a sensitivity enhancer and stabilizer was investigated within the range of pH 3.5–8.0 using diluted HCl and/or NaOH. The results are shown in Fig. 1(a). As can be seen, the extraction efficiency (having a linear relationship with the analytical signal for 25 μg L^{-1} BPA) reaches a maximum value at pH 5.0, being constant between 5.0 and 6.0 and gradually decreasing at higher pH values than 6.0. Since the pK_a value for the hydrolysis of Mn(III) is 0.83 with a standard deviation of 0.08 at 20 °C from the results of a serial spectrophotometric measurement based on a stopped-flow instrument at 300 and 470 nm,[38] the decrease in absorbance in the pH range of 6.0–8.0, can be due to the fact that the Mn(III) ions exist mainly either in the form of $Mn(OH)^{2+}$ or hydroxy oligomers of Mn(II) or Mn(III) or colloidal MnO_2 as a result of disproportionation. Also, when the stability of Mn(III)-oxalate complexes as a function of pH with K_f values of 9.5×10^9, 3.9×10^6 and 7.1×10^2 for $MnOx^+$, $MnOx_2^-$ and $MnOx_3^{3-}$ are considered in acidic pH, it is clear that $MnOx^+$ or Mn(OH)Ox as a result of hydrolysis, is predominant in the medium.[39] Also, it is implied by the authors[40] that a similar case as a result of hydroxylation of BPA at pH 5.0 is

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observed in laccase-catalyzed enzymatic treatment (as a multicopper oxidase enzyme oxidizing a variety of phenolic substrates, performing one-electron oxidations, leading to crosslinking) and removal of BPA and its derivatives in the presence of polyethyleneglycol (PEG) as a stabilizer, and from the IR spectra of BPA with and without PEG, oligomer precipitation without H_2O_2 obtained at 40 °C, pH 5.0 and 7.0, respectively. In the presence of PEG, it was also observed that the aggregation of oligomers was enhanced by decreasing the pH value to 3.0. The lower extraction efficiency at lower pH values than 5.0 may be due to the fact that H^+ ions can also bind to polar polyoxyethylene groups of the surfactant or ternary complex formed by either cation–Π interactions or a chelate with tetrahedral geometry after pH-dependent hydroxylation of BPA can be gradually dissociated and decomposed by an acid-catalyzed reaction (1).

$$2Mn^{3+} + H_2C_2O_4 \rightarrow 2Mn^{2+} + 2H^+ + 2CO_2 \quad (1)$$

In fact, the unusually high Lewis acidity of Mn^{3+} ions may be due to a Jahn–Teller distortion effect. As a result, to obtain stable and reproducible signals, pH 5.0 was selected as the optimal value in further studies.

Two buffer agents such as formate and acetate were tested for pH adjustment. A suitable absorbance signal can be achieved using both the formate and acetate buffers, but the latter gives more stable and reproducible signals with a significant sensitivity difference. Therefore, acetate buffer solution was chosen for adjusting the pH. The effect of the acetate buffer concentration in the range of 0.01–0.04 mol L^{-1} was investigated while the other analytical variables remained constant. As can be seen in Fig. 1(b), the best performance was obtained at a concentration of 0.03 mol L^{-1}. Therefore, 0.03 mol L^{-1} buffer concentration was employed for further studies.

3.1.2. Effect of Mn(III) oxalate and CTABr concentrations. The effect of Mn(III) oxalate, $MnOx^+$ or Mn(OH)Ox was investigated in the range of 0.033–1.32 mg L^{-1} for measurement of 25 μg L^{-1} BPA at pH 5.0. As can be seen in Fig. 2(a), the best analytical signal was obtained at a concentration of 0.33 mg L^{-1} while it sharply increased with increasing Mn(III) oxalate concentration in the low concentration region of 0.033–0.33 mg L^{-1}. At higher concentrations than 0.33 mg L^{-1}, the absorbance gradually decreased. This decrease in absorbance may be due to the concentration dependent disproportionation of Mn(III) in the ternary complex to give Mn(II) ions and MnO_2 by intra-molecular charge transfer (ICT). Therefore, a Mn(III)-oxalate concentration of 0.33 mg L^{-1} was considered to be sufficient for indirect detection of 25 μg L^{-1} BPA in further studies.

The effect of the ionic surfactant, CTABr, concentration on the analytical signal was investigated in the range of 6–1800 μmol L^{-1} in the presence of 25 μg L^{-1} BPA at pH 5.0. As can be seen in Fig. 2(b), the best analytical signal was obtained at a concentration of 150 μmol L^{-1}. At higher concentrations than 150 μmol L^{-1}, the absorbance was partly decreased depending on the surfactant volume. Therefore, a surfactant concentration of 150 mmol L^{-1} was considered to be sufficient for further studies. In fact, this value is 4-fold lower than the CMC of a cationic surfactant, CTABr, where the critical micelle

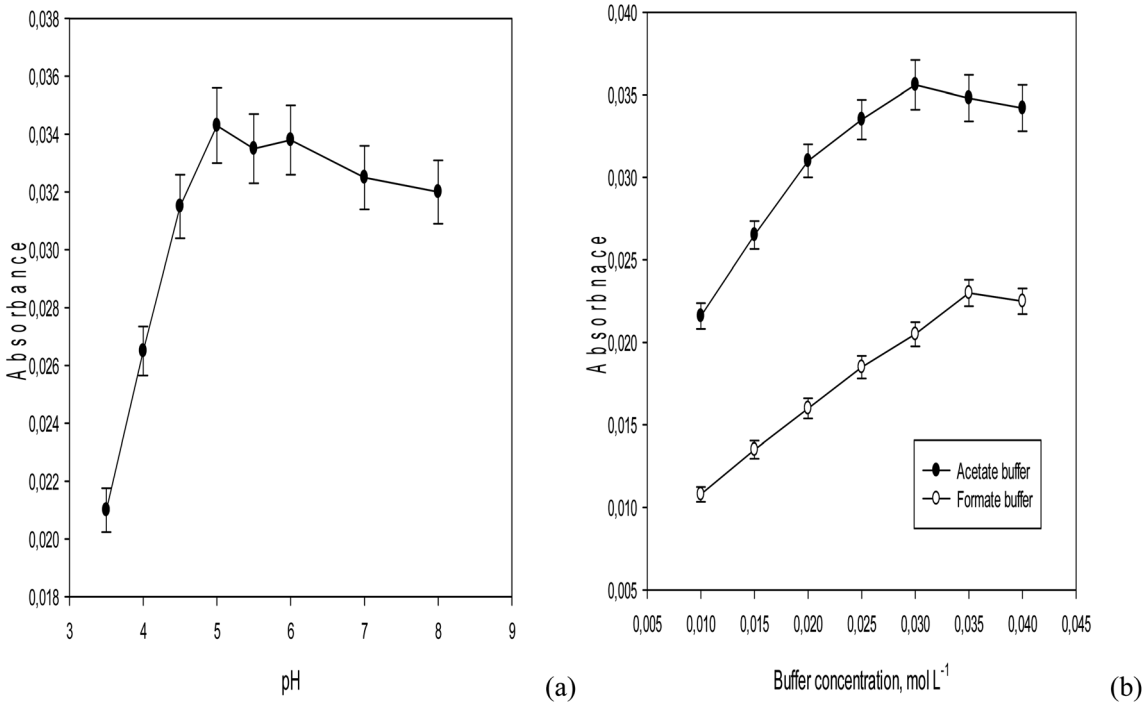

Fig. 1 The effect of (a) pH and (b) buffer concentration on the analytical signal. Conditions: 25 μg L^{-1} BPA, 0.33 mg L^{-1} of Mn(III)-oxalate, 150 μmol L^{-1} of CTABr, 0.08%(w/v) PVA, 0.06% (w/v) of Triton X-114 and 0.125% (w/v) Na_2SO_4 for incubation at 40 °C for 10 min.

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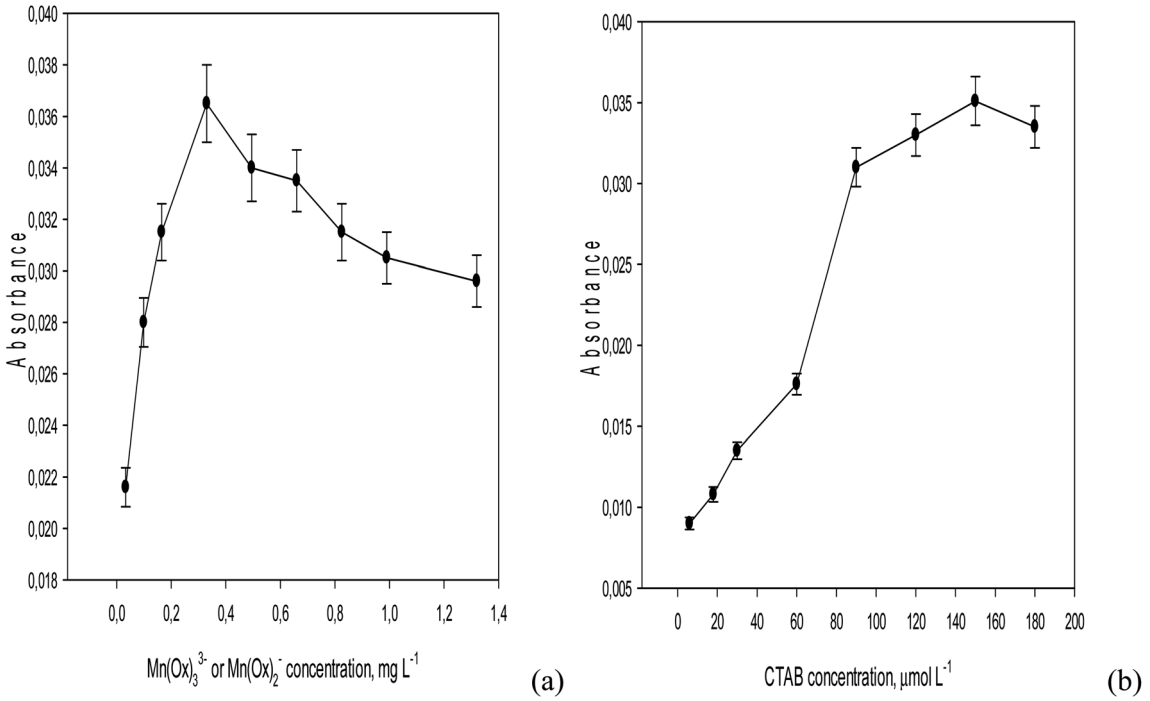

Fig. 2 The effect of (a) Mn(III)-oxalate and (b) the sensitivity enhancer, CTABr, concentration on the analytical signal. Conditions: 25 μg L^{-1} BPA, 0.03 mol L^{-1} of acetate buffer at pH 5.0, 0.08% (w/v) PVA, 0.06% (w/v) of Triton X-114 and 0.125% (w/v) Na_2SO_4 for incubation at 40 °C for 10 min.

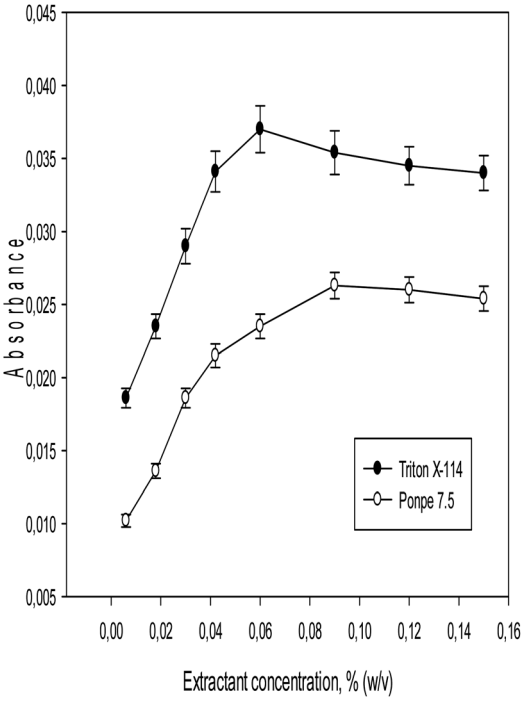

Fig. 3 The effect of the nonionic surfactant concentrations as extractants on the analytical signal. Conditions: 25 μg L^{-1} BPA, 0.03 mol L^{-1} of acetate buffer at pH 5.0, 0.33 mg L^{-1} of Mn(III)-oxalate, 150 μmol L^{-1} of CTABr, 0.08% (w/v) PVA and 0.125% (w/v) Na_2SO_4 for incubation at 40 °C for 10 min.

concentration (CMC) of CTABr is determined to be 0.6 mmol L^{-1} by cyclic voltammetry.[41] In this sense, for accurate and reliable measurements of BPA by FAAS, it is clear that the ionic surfactant, CTABr in the premicellar region acts as a sensitivity enhancer to facilitate the acid ionization of BPA by cation–Π and hydrophobic interactions, so as to form an extractable hydrophobic ternary complex.

3.1.3. Effect of the extractant concentration. The extraction efficiency was evaluated using two extracting nonionic surfactants, Triton X-114 and PONPE 7.5, with concentrations ranging from 0.006% to 0.15% (w/v). They were chosen as an extraction solvent due to their low toxicities and low costs, as well as easy phase separation by centrifugation.[42] The results are shown in Fig. 3. As can be seen, the best analytical signal was obtained with 0.06% (w/v) Triton X-114 with a significant sensitivity difference. At higher concentrations than 0.06% (w/v) the absorbance gradually reduced. This result might be related to the presence of high amounts of surfactant, resulting in an increase in the volume of the surfactant-rich phase. In addition, the viscosity of the surfactant-rich phase increases, leading to poor sensitivity. At lower Triton X-114 concentrations (below 0.06%, w/v), the extraction efficiency of the complex was very low, probably due to inability for the quantitative entrapment of a hydrophobic complex. So, a Triton X-114 concentration of 0.06% (w/v) was found to be enough.

3.1.4. Effect of the PVA concentration. To provide lower detection limits, increased selectivity and signal stability in indirect analysis of BPA by FAAS, the effect of the PVA concentration as a stabilizer for the analytical signal was investigated in the range of 0.004–0.12% (w/v) for the measurement of 25 μg

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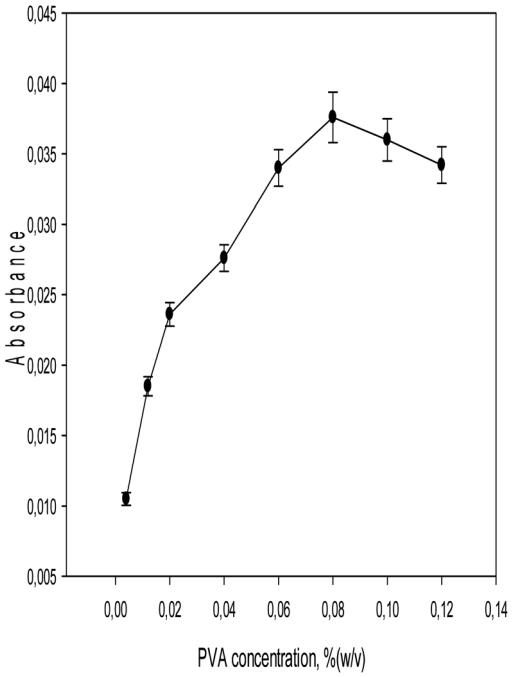

Fig. 4 The effect of the PVA concentration as a stabilizer on the analytical signal. Conditions: 25 μg L^{-1} BPA, 0.03 mol L^{-1} of acetate buffer at pH 5.0, 0.33 mg L^{-1} of Mn(III)-oxalate, 150 μmol L^{-1} of CTABr, 0.06% (w/v) of Triton X-114 and 0.125% (w/v) Na_2SO_4 for incubation at 40 °C for 10 min.

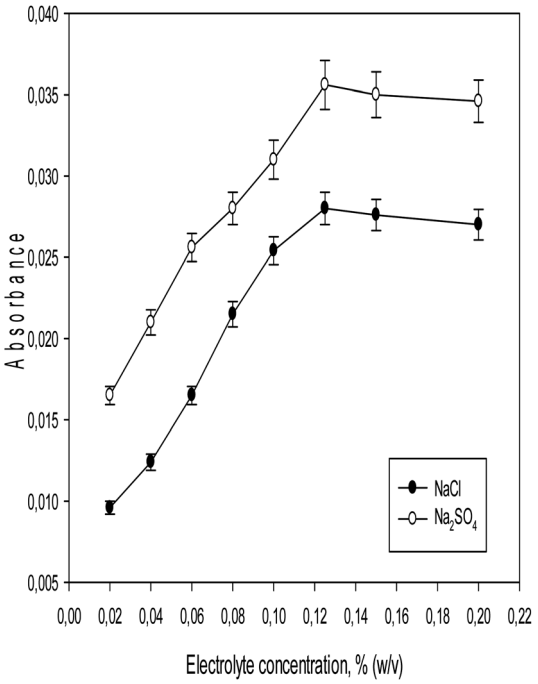

Fig. 5 The effect of the electrolyte concentration on the analytical signal. Conditions: 25 μg L^{-1} BPA, 0.03 mol L^{-1} of acetate buffer at pH 5.0, 0.33 mg L^{-1} of Mn(III)-oxalate, 150 μmol L^{-1} of CTABr, 0.08% (w/v) PVA and 0.06% (w/v) of Triton X-114 for incubation at 40 °C for 10 min.

L^{-1} BPA at pH 5.0. As can be seen in Fig. 4, the best analytical signal was obtained at a concentration of 0.08% (w/v). The performance of analysis is greatly improved because the mixed micellar medium shields the analyte from matrix components or because inclusion of PVA in the medium increases the efficiency of CT sensitive interaction between the analyte and redox sensitive Mn(III) oxalate.[43] At higher concentrations than 0.08% (w/v), the absorbance gradually decreased due to an increase in the viscosity of the solution, so as to lead to a decrease of the indirect aspiration efficiency of BPA in analysis by FAAS. Therefore, a PVA concentration of 0.08% (w/v) was found to be sufficient for further studies.

3.1.5. Effect of the electrolyte concentration. The cloud point of micellar solutions can be controlled by the addition of salts, alcohols, nonionic surfactants and some organic compounds (salting-out effects). An increase in the ionic strength of the medium in the UA-CPE process does not seriously alter the efficiency of extraction of the chelate complex. Also, the addition of salt can markedly facilitate the phase separation process, as demonstrated with some nonionic surfactant systems, since it alters the density of the bulk aqueous phase.[44] It is clear that the addition of Na_2SO_4 in the range of 0.02–0.2% (w/v) (Fig. 5) has a more positive effect than that of NaCl at a concentration of 0.12% (w/v) on the CPE efficiency with a significant sensitivity difference. So, 0.12% (w/v) of Na_2SO_4 was considered optimal in further experiments.

3.1.6. Effect of the diluent volume. Since the surfactant-rich phase obtained after pre-concentration contains a high concentration of Triton X-114 and, also, the extract volume obtained is rather small (~0.2 mL), a serial diluent such as acetone, acetonitrile, methanol, ethanol, methanol and ethanol acidified with 0.1 mol L^{-1} HNO_3, as shown in Fig. 6, was independently added to the surfactant-rich phase after phase separation. Moreover, it was necessary to decrease its viscosity without excessive dilution of the micellar phase to facilitate the introduction of the sample into the atomizer of FAAS. An extract volume of 0.5 mL after dilution was concluded to be optimal as a measure of analytical sensitivity with respect to the recovery of the Mn(III) chelate complex, which is linearly related to the BPA concentration at three different concentration levels. The pre-concentration capability of the UA-CPE system was further considered by studying the effect of the aqueous sample volume on the recovery of 0.2 μg of BPA from different sample volumes (5–35 mL). The results showed that the extraction was quantitative with the aqueous phase volume up to 35 mL. Due to the limitation in the size of our centrifuge tubes, extraction from higher aqueous volumes was not considered. Based on the final extract volume (0.5 mL) and the maximum sample volume where the extraction was quantitative (35 mL), a pre-concentration factor of ~70-fold was determined.

3.1.7. Effect of equilibrium temperature and incubation time. Two important factors in CPE are equilibration temperature and incubation time. It is known that when CPE is conducted using equilibration temperatures that are well above the cloud point temperature of the surfactant, the best extraction efficiency will be obtained.[33] It is desirable to employ the shortest incubation time and the lowest incubation

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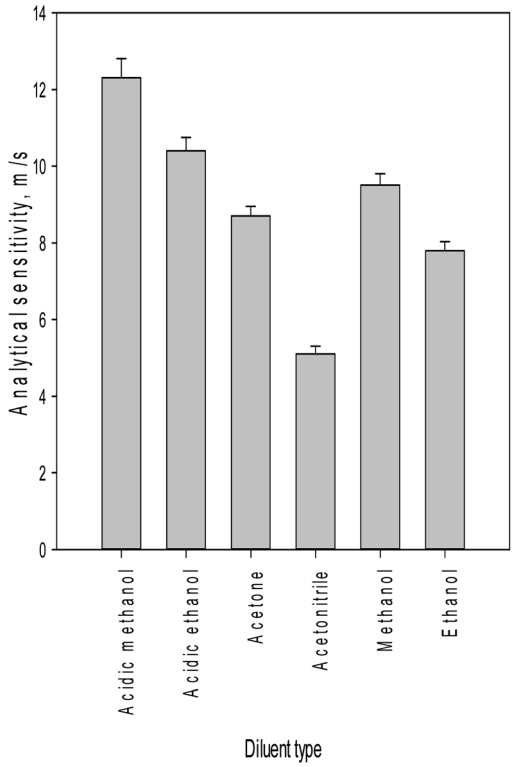

Fig. 6 The effect of the diluent type on analytical sensitivity. Conditions: 25 μg L^{-1} BPA, 0.03 mol L^{-1} of acetate buffer at pH 5.0, 0.33 mg L^{-1} of Mn(III)-oxalate, 150 μmol L^{-1} of CTABr, 0.08% (w/v) PVA, 0.06% (w/v) of Triton X-114 and 0.125% (w/v) Na_2SO_4 for incubation at 40 °C for 10 min.

temperature in order to ensure the completion of extraction and efficient separation of phases. Based on these reasons, the effects of equilibration temperature and time were examined. The dependence of the extraction efficiency upon equilibration temperature and time above the cloud point in the range of 20–60 °C and 1–30 min was thoroughly optimized, respectively. The results showed that an equilibration temperature of 40 °C and a time of 10 min were adequate to achieve quantitative extraction, and there were no appreciable improvements for a time longer than 10 min. Therefore, an equilibration temperature of 40 °C and an incubation time of 10 min were used.

3.1.8. Effect of the centrifuge rate and time. It is very necessary to pre-concentrate trace amounts of BPA with high extraction efficiency in a short time. Therefore, on the basis of the optimum conditions so far obtained, the effects of the centrifuge rate and time were studied. The results suggest that centrifugation for 5 min at 3750 rpm and cooling for 10 min in an ice-bath lead to the best signal and sensitivity for BPA.

3.2. Figure of merit of the method

The analytical features of the method were established using two different studies to control a possible matrix effect. Firstly, using calibration solutions in solvent, the method was used in the range of 0.8–130 μg L^{-1} for a serial aqueous standard solution of BPA under optimal conditions, and we tried to obtain the linear calibration graph. From triplicate measurements for each concentration level, the calibration graph was highly linear in the range of 0.8–130 μg L^{-1}. Some of the analytical features obtained from calibration solutions in solvent were given below. The limits of detection (LOD) and quantification (LOQ) were calculated as the ratio of three and ten times the signal standard deviation of the ten replicate blank measurements to the slope of the calibration curve, respectively. The LOD and LOQ were 0.228 μg L^{-1} and 0.76 μg L^{-1}, respectively. The sensitivity enhancement factor (EF), which was defined as the ratio of the slope of the calibration curves with and without pre-concentration, was 41. Secondly, in the sample preparation step, BPA was spiked to the sample extracts in the concentration range of 1–140 μg L^{-1} before extraction and pre-concentration, and we tried to obtain the calibration graph. In this study, our main purpose is to establish whether or not there is a matrix effect by matrix-matched calibration solutions according to calibration solutions in solvent. Some of the analytical results obtained from matrix matching are as follows: Linear working range, LOD, LOQ and EF values were 1–140 μg L^{-1}, 0.43 μg L^{-1}, 1.42 μg L^{-1} and 37, respectively. The slopes of both calibration curves are close to each other with a sensitivity difference of −10.1% as a suppression in the signal, so as not to show any matrix effect. More detailed results for both studies are given in Table 1.

3.3. Matrix effect

The interfering effects of the potential matrix components on triplicate measurements of 25 μg L^{-1} of BPA at the tolerance level, [interferent]/[BPA], ranging from 10 to 1500 were

Table 2 The effect of the matrix components on three replicate measurements of BPA at a level of 25 μg L^{-1} (*n*: 3)

Coexisting ions	Tolerance ratio	Mean recovery ± SD[a] (%)
NH_4^+, Na^+, K^+, Ca^{2+}, Mg^{2+}	1500 : 1	98.0 ± 2.0
Zn^{2+}	1250 : 1	101.0 ± 2.0
Cl^-, Br^-, Pb^{2+}	1000 : 1	(98.0–101.5) ± 2.0
HCO_3^-	750 : 1	97.0 ± 2.0
Fe^{2+}, Cd^{2+}, Ag^+	600 : 1	(95.0–96.5) ± 2.0
Bromobenzaldehyde, Ni^{2+}	500 : 1	(97.0–102.5) ± 3.0
Cu^{2+}	400 : 1	96.5 ± 2.5
2-Chlorobenzaldehyde, phenol, 2-aminophenol	350 : 1	(94.0–95.0) ± 2.0
NO_3^-, F^-, ethanol	300 : 1	98.0 ± 2.0
Co^{2+}, Cr^{3+}	250 : 1	(98.0–101.5) ± 2.5
2-Nitrophenol, 4-nitrophenol	200 : 1	(95.0–96.5) ± 2.0
HSO_3^-, NO_2^-	150 : 1	(94.0–95.5) ± 2.5
HPO_4^{2-}	100 : 1	101.0 ± 2.0
Benzaldehyde, 2,4-dinitrophenol	75 : 1	(101.0–103.5)±3.0
Formaldehyde, acetaldehyde	50 : 1	95.0 ± 2.5
MnO_4^-, MnO_4^{2-}	35 : 1	(95.5–97.0) ± 2.0
Fe^{3+}, VO^{2+}, VO_2^+, MoO_2^{2+}	25 : 1	(92.5–95.5) ± 2.5
Ascorbic acid	10 : 1 (150 : 1[b])	90.2 ± 2.5

[a] The percent recoveries and their standard deviations obtained from three replicate measurements of binary mixtures. [b] The tolerance ratio, after improvement using 1.5 mL of 25 mg L^{-1} Pb^{2+} as a chelating metal ion at pH 5.5.

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investigated. As can be seen from the results in Table 2, there is no interference effect of foreign interfering species other than the analyte in the sample matrix since a deviation of less than ±5.0% with a recovery higher than 90.2% is observed. It is clear that only ascorbic acid with a tolerance ratio higher than 10 forms an interference effect. However, this interference effect can be greatly suppressed and improved up to a tolerance ratio of 150-fold by using 1.5 mL of 25 mg L^{-1} Pb^{2+} as a chelating metal ion in the extraction step. At the given mole ratios, no significant serious interference was observed, and the recovery of BPA was quantitative with a recovery ranging from 90.2% to 103.5% in the presence of all the remaining interfering species.

3.4. Accuracy and analytical applications of the method

We have explored the feasibility of the method using pre-concentration with BPA in mixed micellar media for the indirect quantification of trace BPA in milk based matrices treated according to the experimental section. The method was applied to the determination of low levels of BPA in some milk based samples by means of a matrix-matched calibration approach for the control of a possible matrix effect. Due to the lack of a certified sample compatible with the sample matrix, the developed method was validated by intra- and inter-day accuracy (as the recovery rate) and precision (repeatability, for replicate studies conducted in one day, and reproducibility, for replicate studies conducted on three consecutive days) studies in the quality control sample spiked with 5, 10 and 15 μg L^{-1}. The results are presented in Table 3. The recoveries of the spiked samples were satisfactory with a recovery rate higher than 90% and a lower RSD than 8.8%, and were confirmed using the standard addition method, indicating the capability of the pre-concentration process in the indirect determination of BPA in the quality control sample.

Table 3 The validation studies for the replicate measurements of BPA in the quality control sample spiked with 5, 10 and 15 μg L^{-1}

Samples	Spiked concentration μg kg^{-1}	Intra-day precision, n: 5			Inter-day precision, n: 3 × 5		
		Found	Recovery%	RSD %	Found	Recovery%	RSD%
Semi-skimmed milk	—	3.4 ± 0.2	—	5.9	3.4 ± 0.3	—	8.8
	5	8.0 ± 0.4	92.0	5.0	7.9 ± 0.6	90.0	7.6
	10	12.7 ± 0.6	93.0	4.7	12.6 ± 0.8	92.0	6.3
	15	17.6 ± 0.8	94.7	4.5	17.5 ± 1.0	94.0	5.7

Table 4 The analysis results of BPA in liquid milk samples in contact with PC and/or PVC plastic products by the proposed method (n: 5)

Samples	By using the calibration curve in solvent				By using the matrix-matched calibration curve				The student's paired t-test[b]
	Added, μg L^{-1}	Found, μg L^{-1}[a]	RSD%	Recovery%	Added, μg L^{-1}	Found, μg L^{-1}[a]	RSD%	Recovery%	
Semi-skimmed	—	3.1 ± 0.2	6.4	—	—	3.2 ± 0.2	6.2	—	0.79
milk	5	7.8 ± 0.4	5.1	94.0	5	7.7 ± 0.4	5.2	90.0	—
Skim milk	—	6.3 ± 0.3	4.8	—	—	6.4 ± 0.3	4.7	—	0.52
	5	11.0 ± 0.5	4.6	94.0	5	11.0 ± 0.5	4.5	92.0	—
Milk shake	—	5.4 ± 0.3	5.6	—	—	5.1 ± 0.3	5.9	—	1.57
	5	10.1 ± 0.5	5.0	94.0	5	9.8 ± 0.5	5.1	94.0	—
Functional milk[c]	—	3.8 ± 0.2	5.3	—	—	3.9 ± 0.2	5.1	—	0.79
	5	8.4 ± 0.4	4.8	92.0	5	8.6 ± 0.4	4.7	94.0	—
Banana	—	7.3 ± 0.4	5.5	—	—	7.0 ± 0.4	5.7	—	1.18
flavored milk	5	11.8 ± 0.5	4.2	90.0	5	11.7 ± 0.5	4.3	94.0	—
Strawberry	—	5.4 ± 0.3	5.5	—	—	5.3 ± 0.3	5.7	—	0.52
flavored milk	5	10.1 ± 0.5	5.0	94.0	5	10.0 ± 0.5	5.0	94.0	—
Chocolate milk	—	6.4 ± 0.3	4.7	—	—	6.3 ± 0.3	4.8	—	0.52
	5	11.0 ± 0.5	4.5	92.0	5	10.9 ± 0.5	4.6	92.0	—
Light milk	—	2.1 ± 0.1	4.8	—	—	2.0 ± 0.1	4.8	—	1.57
	5	6.8 ± 0.3	4.4	94.0	5	6.7 ± 0.3	4.5	94.0	—
Buttermilk	—	3.8 ± 0.2	5.3	—	—	3.6 ± 0.2	5.5	—	1.57
	5	8.5 ± 0.4	4.7	94.0	5	8.2 ± 0.4	4.9	92.0	—
Whole milk	—	3.4 ± 0.2	5.9	—	—	3.2 ± 0.2	6.2	—	1.57
	5	8.1 ± 0.4	4.9	94.0	5	7.8 ± 0.4	5.1	92.0	—
Organic milk	—	2.6 ± 0.2	7.7	—	—	2.7 ± 0.2	7.4	—	0.79
	5	7.2 ± 0.3	4.2	92.0	5	7.2 ± 0.3	4.2	90.0	—

[a] The mean value plus its standard deviation for five replicate measurements of each sample by using two calibration approaches. [b] Based on the statistical comparison of the mean values obtained by using two calibration approaches, in which the tabulated t-value is 2.31 for a degree of freedom of 8 at a 95% confidence level. [c] Enriched milk with vitamins A, D and E.

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After validation, to assess the applicability of the method for real time samples, an attempt was made to determine BPA levels in milk based samples by means of the calibration curve in the solvent and matrix-matched calibration curves prepared from the sample extracts. A good agreement was statistically obtained between the BPA concentrations found by means of both approaches in terms of applicability of the two calibration curves to the BPA analysis in samples, so as not to show any matrix effect. From the results (ranging from 2.1 to 7.3 μg L^{-1} or 2.0–7.0 μg L^{-1}), it can be seen that the calculated t-values are lower than a critical value of 2.31 for a degree of freedom of 8 at a 95% confidence level, indicating that there is not any significant difference between the results found by using the two calibration curves. According to the EU's risk assessment report on BPA, these values are lower than the temporary tolerable daily intake of BPA of 10 μg kg^{-1} from food set in 2002,[45] in such a way as not to present a serious problem in the short term. In addition, for reliability of the results, recovery studies were performed by adding 5 μg L^{-1} of BPA into the samples prior to analysis. The recoveries were in the range of 90–94%. These values are clearly quantitative, and it shows that the method can be applied for the extraction, pre-concentration and determination of BPA in selected milk samples. The precision (as RSD%, *n*: 5) for selected samples was lower than 6.4%. The low RSDs represent the high reproducibility in these measurements. The detailed results are shown in Table 4.

3.5. Comparison with other methods

A comparison of the proposed method with other methods[24–31,46] is presented in Table 5 in terms of some analytical parameters including the linear working range, LODs, LOQs, the pre-concentration factor, the recovery% and the RSD% as a measure of accuracy and precision with sensitivity enhancements of 41- and 37-fold from pre-concentration of the 35 mL sample. The method has a reasonable pre-concentration factor, low RSD, comparable LOD and linear working range according to other methods. Moreover, the UA-CPE procedure has been evaluated as eco-friendly because it uses low volume non-toxic organic solvents, and shows more favorable properties such as simplicity, quickness and relatively low cost compared to coacervative microextraction (CME), pressurised liquid extraction (PLE), and solid phase microextraction (SPME). The higher sensitivity of other LC or GC techniques must be due to fluorescence, MS and/or tandem MS detection, including the use of further separation and pre-concentration tools at the micro- and nano-scale. However, these sensitive techniques are complex and expensive, and require tedious and time-consuming separation, pre-concentration and cleaning up procedures at different elution modes as well as requiring an expert user in her/his area. In addition, the proposed indirect method gave comparably good results in terms of linearity, accuracy and precision, and provided evidence of FAAS feasibility as an alternative to routine quality control of foodstuffs at the BPA level.

Table 5 Comparison of analytical performance data obtained by using the proposed UA-CPE and other previously reported methods in the literature

Sample	Pre-concentration method	Detection technique	Linear range, μg L^{-1}	LOD, μg L^{-1}	RSD%	Recovery%	PF or EF	References
Canned fatty foods	CME	LC-FL	0.2–60 ng	9 μg kg^{-1}	2–7	87–103	—	24
Powdered milk and infant formulas	PLE	LC/MS-MS	—	5 μg kg^{-1}	9–11.4	89.01–92.25	—	25
Food and environmental samples	SPE-DLLM-SFOD	HPLC-FL	0.005–10 ng g^{-1}	0.002 ng g^{-1}	6.8–9.6	93.3–102.1	1940	26
Vegetable and juice samples	*m*-MISPE	HPLC	0.5–100 nmol L^{-1}	0.2 nmol L^{-1}	3.5–6.8	80.7–87.3	—	27
Milk	PAMAM and Fe_3O_4 mNPs modified GCE	Amperometry	0.01–3.07 μ mol L^{-1}	5 nmol L^{-1}	3.8–5.7	95.3–104	—	28
Milk	DMIPs-SB	HPLC-UV	0.0228–2.28	0.00684	3.8–8.9	89.5–107.9	—	29
Eggs and milk	mSPDE	LC/ESI-MS-MS	1–500	0.1	≤8.0	79–87	—	30
Milk	SPME	HPLC	1.5–200	0.2	6.6	93.1–102	—	31
Beverages and powdered infant formula	DLLME	GC-MS	1–1000	0.005	15	82–111, 68–114	—	46
Milk based products	UA-CPE	FAAS	0.8–130, 1–140	0.23, 0.43	2.8–5.2, 3.8–7.2	94.2–98.5	41/37, 70	The current study

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4. Conclusions

In this work, a robust and efficient pre-treatment with ultrasonic assistance and CPE was developed to measure BPA in milk based products. A satisfactory extraction efficiency was obtained under the optimum conditions. CPE with ultrasonic assistance was combined to FAAS for the indirect detection of BPA in selected sample matrices. The established method had good linearity with an r^2 more than 0.9936 and 0.9954 in the linear working range of 0.8–130 and 1–140 μg L^{-1} with detection limits of 0.23 and 0.43 μg L^{-1} for the two calibration curves, and the spiked recoveries ranging from 90 to 94% with an RSD of 2.8–8.5% were applied to test milk based products. The contents of BPA in the samples were statistically consistent with those analyzed by means of two calibration methods. The pre-treatment can be accomplished in 25 min with less than 20 plus 2 mL of the organic solvents. It was proved that the proposed method presented a simple, inexpensive, highly efficient, and eco-friendly pre-treatment, and can be reliably used for the quantitative analysis of BPA in milk based products. As expected, the proposed method affords promising potential for the quality control analysis of milk based products.

Author contributions

N. K. Temel: conceptualization, methodology, investigation, visualization, writing – original draft. R. Gürkan: conceptualization, supervision, methodology, investigation, writing – review & editing.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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