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RAPID, COST-EFFECTIVE AND ACCURATE QUANTIFICATION OF DIPHENYLMETHANE DERIVATIVES BISPHENOL A USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

High performance liquid chromatographic method with isocratic elution was developed for the determination of Bisphenol A in canned food and drinking water bottle samples. The method was validated according to international conference on harmonization guidelines. The BPA was separated using C_{18} Hypersil BDS column with flow rate 1.0 ml/min. The sample was detected at 254 nm applying photo diode array detector. The linearity of the proposed was in the range of 3.5 – 25.0 μg/ml. The LOD and LOQ value were found to be 0.76 and 2.53 μg/ml respectively. The method can be used for routine quality control samples as well as for research purposes for the determination of BPA.

KEYWORDS: Bisphenol A; HPLC; Validation; Column; ICH guidelines; Canned food; Drinking water bottles.

INTRODUCTION

Bisphenol A is a member of diphenylmethane and biphenols that can be produced by synthetic pathway. The colorless compound has two hydroxyphenyl group, $(CH_3)_2$ C $(C_6H_4OH)_2$ (Figure 1) is freely soluble in different organic solvent but less solubility with water.
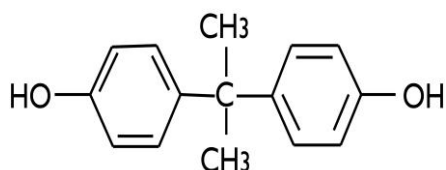
Figure 1: Structure of Bisphenol A (BPA).

The BPA chemical was utilized to make only plastics since 1940. Now enormous quantity of BPA is produced worldwide. The advantage of BPA can be used as an intermediate for the manufacturing of unsaturated polyesters, polycarbonate, styrene resins and epoxy resins.[1–5] The BPA has typical demand as coating material for cans, paper, antioxidants, dental filling for teeth and additives for powder paints. It is observed that the plastics like water bottles, pipes, milk bottles, caps, food storage container and bags contain BPA.[6] The receptors estrogen, androgen, peroxisome proliferator, aryl hydrocarbon are incorporating with endocrine system mainly hormone and other body system. The BPA has the quality to bind with the receptors easily.[7–9] It has potentially multidirectional toxic effects in animals and humans. It is regularly effect on endocrine system that dominates the cause of birth defects, growth, development disorder and cancerous tumor.[6,10]

In the current scenario, the water is polluted with BPA by different sources namely through sewage, drainage, landfills and manufacturing industry. The developed countries are not bothering about the toxicity of the hazardous chemical and without following the rules, regulations dumping in the form liquid and solid in the environment.[11–13]

Due to the importance of BPA, it is necessary to identify as well as quantify it in each of application. The literature survey pointed out some analytical methods for determination of BPA using UV–Visible spectrophotometry,[14–18] X–ray diffraction,[17] flow injection chemiluminescence,[19] capillary electrophoresis,[20–22] Raman spectroscopy,[17] Nuclear magnetic resonance,[23] micellar liquid chromatography,[24] fourier transform infrared spectroscopy,[17,25] voltammetry,[26] high performance liquid chromatography (HPLC),[27–43] ultra pressure liquid chromatography,[44] gas chromatography[45] liquid chromatography–mass spectrophotometry,[46–50] ultra pressure liquid chromatography–mass spectrophotometry [51–54] and gas chromatography–mass spectrophotometry.[55–60] The determination of BPA in the previous studied are required lots of clean up procedure and long analysis time using HPLC. The mass

spectrophotometry combined with liquid chromatography and gas chromatography's are sensitive techniques for the determination but instruments are not easily available everywhere due to its cost. The present work is simple and sensitive for the quantification of BPA in canned food and drinking water bottle samples. The method was validated according to international conference on harmonization guidelines,[61–62] This method can be applied for routine work in the industry as well as in the academic, hospitals for research purposes due to low cost and shorter analysis time.

Experimental
Chemicals and materials
All reagents and solvents are HPLC grade.
- Double distilled water (Laboratory, Jubail Industrial College, Saudi Arabia).
- Acetonitrile (Carlo Erba Reagents, France).
- n-hexane (Fisher Scientific, UK).
- Acetone (Fisher Scientific, UK).
- Silica gel (Fisher Scientific, UK).
- Anhydrous sodium sulfate (Carlo Erba Reagents, France).
- Bisphenol A (Sigma Aldrich, UK).

Instrumentation
The HPLC model LC – 2010 CHT was used for the determination of BPA. The instrument is belonging to Shimadzu Company, Kyoto, Japan. The pump, degassing unit, auto sampler, column oven and photo diode array detector model are LC – 20 AD, DGU – 20 A $_{5R}$, SIL - 20 AC, CTO - 20 AC and SPD - 20 A respectively. The HPLC was connected with HP – 5502 and processing system run with LC solution.

Chromatographic Conditions
The mobile phase is prepared by mixing acetonitrile and distilled water (40: 60, v/v). The mobile phase was prepared daily and degassed by passing through a 0.45 μm ultipor filter with ultra sonication for at least 10 minutes. The investigation method is isocratic with flow rate 1 ml/min. The column for the separation used BDS Hypersil C_{18} (250 mm×4.6 mm, 5 μm). All separations were performed at 25°C. The run time for the analysis 10 minutes and detected at 254 nm.

Standard sample preparation
The BPA standard corresponding to 50 mg was transferred into 500 ml volumetric flask and dissolved with distilled water. The final volume was diluted with water and kept in room temperature. The stock solution was further diluted to prepare calibration concentrations during the analysis.

Determination of BPA in canned foods
Twenty grams food content that purchased from the local market was transferred into 500 ml beaker. Acetonitrile (100 ml) as well as anhydrous sodium sulfate (25 gram) were added. The mixture was stirred at high speed 1300 rpm for 20 minutes. The homogeneous mixture was filtered using vacuum pump and residue cleaned with 50 ml acetonitrile two times. The filtrate was mixed with 100 ml n-hexane and continued stirring for 15 minutes with same speed. Then it was resettled on the separating funnel for half an hour. The lower acetonitrile layer was transferred into round bottom flask and added 100 ml with the hexane layer into the funnel, waited for 15 minutes. The acetonitrile layer was extracted and gently placed in the same RBF. Acetonitrile was collected after simple distillation. 150 ml acetone added with the residue and passed through column chromatography where silica gel powder used as stationary phase (conditioning with acetone) and collected. The extract was dried by evaporation and dissolved with distilled for the analysis.

Sample preparation from drinking water bottles
Commercial mineral waters varied with manufacturing date are purchased from local market in plastic bottles. Initially water bottles were stored in room temperature. After that some bottles were kept in the sunlight (45 to 50°C) for 6 hours. The analytical method didn't require any pretreatment, clean up procedure and filtration. The samples were injected directly into the HPLC for the determination. The samples temperature was maintained between 10 to 15°C before the analysis.

Validation study
The reported method was validated according to ICH guidelines parameters specificity, linearity, linear range, accuracy, precision, limit of detection, limit of quantitation, robustness and ruggedness. The stability of standard BPA sample was evaluated and quantified.

System suitability
The standard BPA solution (100 μg/ml) was prepared and diluted to make (8, 16, 24 μg/ml) for system suitability. This parameter like theoretical factors and tailing factor were determined for suitability of the proposed method.

Calibration and linearity
The calibration curve was constructed in the range of 3.5–25.0 μg/ml from a stock solution. This narrow concentration range was used throughout the analysis as a linearity range to overcome the problems in the column. The triplicate injections from each of the standard were injected to construct the calibration curve. The linearity of the proposed chromatographic method was investigated by applying a linear regression analysis and calibration data from the experiment were calculated at 95% confidence level. The importance of the calibration curve equation with coefficients was studied and calculated using t-test. The level of confidence was used to build the prediction intervals and confidence. All statistical analyses were carried out using the statistical software and Microsoft excel.

Detection (LOD) and quantification (LOQ) limits
The limits of detection (LOD) and quantification (LOQ) can be calculated according to
LOD = (3 × SD)/m
LOQ = (10 ×SD)/m
Where m is the slope of the calibration curve and SD is the standard deviation on the intercept of the calibration curve.

Precision
The precision was evaluated by repeatability and intermediate precision. In repeatability tests, three solutions (5, 15, 25 µg/ml) of each standard solution were prepared as described above and analyzed in the same day. Relative standard deviations (RSDs) were calculated from data in triplicate and were used to estimate the repeatability study. The samples are kept for 5 days and interday precision tests were carried out in the same way as the repeatability tests during five consecutive days. The RSDs were calculated from the obtained data and used as intermediate precision.

Accuracy
The accuracy values were calculated by using recovery results by injecting triplicate of each standard (10, 15, 20 µg/ml) in the chromatographic system. Sample solutions were prepared as described above and spiked with concentration (5, 10 and 15.0 µg/ml) with adequate volumes from stock solution (5 µg/ml). Recovery percentages (%), % RSD, standard analytical error (SAE) and confidence limit (CL) were calculated at 95% confidence level.

Application in real samples
The analytical method was validated according to international conference on harmonization guidelines and verifies the applicability of the proposed developed chromatographic method for canned food samples and drinking water bottles to determine the presence of bisphenol A in the sample.

RESULTS AND DISCUSSION

Method development
The BPA separation is usually performed by C_{18} column and mobile phases containing acetonitrile and water as solvents with isocratic elution mode. It was observed by several analytical researchers that acetonitrile gives better results compared to methanol in terms of high resolution, better peak shape as well as with shorter analysis time. Therefore, the acetonitrile with different aqueous mobile phases and ratios are studied to verify the better separation of BPA. The investigation continued with C_8 column and retention time was found 6.4 minutes. After performing all trials, BDS C_{18} (25 cm×4.6 mm ID, 5 µm) column and acetonitrile, water (40:60, v/v) were the best combination for better separation and peak shape. Thus, this column and solvent composition was selected for the rest of the studies. The flow rate was varied from 1.0 to 0.5 ml/min using the same mobile phase. Flow rate of 1.0 ml/min with

separation time 3.5 min gave higher sensitivity and was therefore selected for further analysis. Besides, sharper peaks and better reproducibility were obtained when 25°C was utilized as column temperature.

Validation study
The validation study was performed according to recommendations from guidelines [61-62]. In the validation study, parameters as selectivity, linearity, measuring range, limit of detection, limit of quantitation, precision and accuracy were evaluated.

System suitability
System suitability of the proposed method was investigated by injecting standard solution before the start of analysis. Number of theoretical plate and tailing factor were determined from the obtained result. Three different concentrations were selected and each one injected five times. The percent relative standard deviations were calculated and tabulated (Table 1). The results were acceptable within the international conference on harmonization limit (2%).

Linearity, LOD and LOQ
The linearity graph was constructed using standard solution of BPA in the range of 3.5 – 25.0 µg/ml. A linear model was regulated with the help of experimental results of the calibration in terms of peak area and concentration and utilizing the linear regression technique at 95% confidence level (Figure 2). Therefore, the importance of the analytical curve coefficients with respect to slope and intercept was determined by a t-test (Table 2). The linearity introduced by analytical curve within the proposed concentration range that can be represented by equation y = 1888.2x + 2543.2 with r^2 = 0.999.

The LOD and LOQ value of proposed method were evaluated and found to be 0.76 and 2.53 µg/ml respectively from the obtained result. Therefore, the results were indicated that the developed method can be used to determine BPA in low concentration level.

Precision and accuracy
The precision result was evaluated by the applying intraday and interday precision. The results were expressed in terms of % relative standard deviation (Table 3). The RSD ranged from 0.262% to 0.681% for three different concentration (5, 15, 25 µg/ml) of standard aqueous solution in the precision tests. The RSD (%) values for repeatability estimates were considered appropriate because they were smaller than those recommended by guidelines (2%).

Therefore, these results indicate that the method proposed presents good precision for the analysis of BPA. The accuracy was estimated by means of recovery tests at three different concentration levels (5, 15, 25 µg/ml) and demonstrated with percentage recoveries. The results were within acceptable limit (80 – 110 %)

and found to be 99.28 – 99.66 % for all concentrations of BPA used for the determination. The results executed that the chromatographic method has good accuracy for the analysis of BPA (Table 4).

Robustness
The standard solution (20μg/ml) was applied for robustness studies. The sample was injected with triplicate into the HPLC. The investigation was continued with changing column temperature, flow rate and mobile phase combination from the normal conditions (Table 5).

Application of proposed method to real samples
The validated chromatographic method was applied for the determination of BPA in canned food and drinking

water bottle samples of different origins and manufacturers. The results were tabulated in Table 6.

CONCLUSIONS

A simple and direct method of determination of BPA in canned food and drinking water bottle samples has been developed and validated. The chromatographic method can be applied to determine the quality of food for routine analysis due to its excellent analytical performance (good selectivity, linearity, precision and accuracy and low limits of detection and quantification). The proposed method was accurate to quantify BPA in the canned food and drinking water bottle samples.

Table 1: System suitability of the proposed method.

Concentration (μg/ml)	Found concentration (μg/ml)	SD	% RSD
8	7.88	0.08	1.00
	7.94		
	8.09		
	7.97		
	8.00		
16	15.86	0.07	0.44
	15.91		
	15.84		
	15.90		
	15.74		
24	24.07	0.12	0.51
	23.94		
	23.87		
	23.82		
	24.11		

Table 2: Summary of optical and regression characteristics of the proposed method.

Parameters	Bisphenol A
Linearity Range (μg/ml)	3.5 – 25.0
Linear Equation	$Y = 1888.2X + 2543.2$
Correlation Coefficient (r^2)	0.999
Standard Deviation (S_0)	478.42
Slope (b)	1888.2
LOD (μg/ml)	0.76
LOQ (μg/ml)	2.53

Table 3: Intraday and interday precision of standard BPA solution.

Precision	Concentration (μg/ml)	Found Concentration (μg/ml)	SD	% RSD	SAE	CL
Intraday	5	4.97	0.034	0.681	0.015	0.042
	5	4.99				
	5	4.98				
	5	4.95				
	5	4.91				
	15	14.92	0.087	0.584	0.039	0.108
	15	14.99				
	15	15.07				
	15	14.97				
	15	14.83				
	25	24.56	0.115	0.467	0.051	0.143
	25	24.55				
	25	24.71				
	25	24.78				
	25	24.79				
Interday	5	4.92	0.032	0.646	0.014	0.04
	5	4.96				
	5	4.93				
	5	5.00				
	5	4.94				
	15	15.01	0.081	0.541	0.036	0.101
	15	14.94				
	15	14.83				
	15	14.87				
	15	15.00				
	25	24.88	0.065	0.262	0.029	0.081
	25	24.80				
	25	24.71				
	25	24.77				
	25	24.85				

SD= Standard deviation; %RSD= Percent relative standard deviation.
SAE= Standard analytical error; CL= Confidence limit.

Table 4: Accuracy results of the proposed method for Bisphenol A.

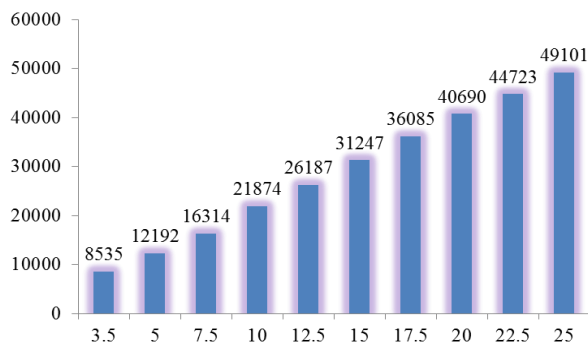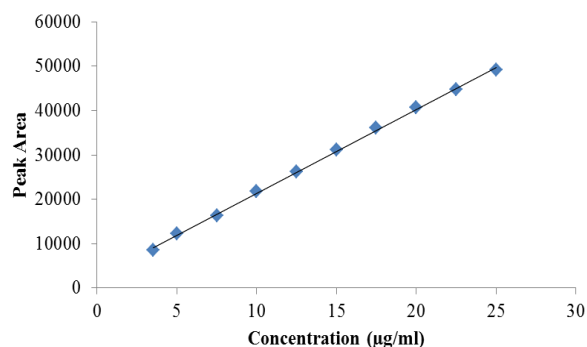| Concentration (μg/ml)	Found Concentration (μg/ml)	% Recovery	% RSD
5	4.98	99.28	0.905
5	4.95		
5	4.90		
5	5.02		
5	4.98		
15	14.78	99.34	0.639
15	14.89		
15	14.93		
15	14.86		
15	15.04		
25	24.97	99.66	0.260
25	24.87		
25	24.99		
25	24.84		
25	24.92		

%RSD= Percent relative standard deviation.

Table 5: Robustness data of the proposed analytical method for the determination of BPA.

Parameters	Concentration (µg/ml)	Found Concentration (µg/ml)	SD	%RSD	% Recovery
Flow rate (0.9 ml/min)	20	19.92	0.143	0.709	100.57
	20	20.29			
	20	20.09			
	20	20.21			
	20	20.06			
Flow rate (1.1 ml/min)	20	20.32	0.215	1.074	100.26
	20	20.08			
	20	20.01			
	20	20.13			
	20	19.72			
Column Temperature 26°C	20	20.03	0.124	0.619	100.57
	20	20.27			
	20	20.15			
	20	20.17			
	20	19.96			
Column Temperature 24°C	20	19.90	0.169	0.839	100.60
	20	20.17			
	20	19.99			
	20	20.23			
	20	20.32			
Mobile phase (38:62,v/v)	20	20.06	0.165	0.817	100.56
	20	20.22			
	20	20.01			
	20	20.34			
	20	19.94			
Mobile phase (42:58,v/v)	20	20.15	0.158	0.783	100.69
	20	20.02			
	20	20.20			
	20	19.96			
	20	20.36			

SD= Standard deviation; %RSD= Percent relative standard deviation.

Table 6: Application of the proposed method for canned food samples and drinking water bottles.

Samples	Concentration of BPA (µg/ml)
Green peas (Luna Co.)	Not detected
Light tuna (Goody Co.)	Not detected
Vienna sausage (American garden Co.)	Not detected
Hana Water (Hana Water-Hana Food Industries Co.)	Not detected

Figure 2.b: Linearity graph of BPA using standard solutions.

Figure 2.a: Linearity results (Concentration vs peak area).

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