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Optimization of gas chromatographic analysis of halogenated acids in drinking water using full factorial experimental design

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ABSTRACT

An analytical method based on gas chromatography–mass spectrometry (GC–MS) has been developed to determine non-volatile fraction of disinfection by-products (DBP) in drinking water. Solid phase extraction (SPE) with tri-methyl-ammonium chlorine (TMA-Cl) cartridges is followed by derivatization of desired analyte in the eluted extract. The studied factors are elution volume, methy-tertiary-butyl ether (MTBE) volume and derivatization time. Experimental design was used to investigate and subsequently used to optimize the elution volume of derivatizing agent (10% acidic methanol), MTBE volume and derivatization time for haloacetic acids (HAAs) extraction in the water sample. Regression models and desirability functions were applied to find an experimental setup for acquiring the highest global extraction yield of HAAs. The elution volume and derivatization time were the only statistically significant factors from this study. In the final optimized conditions, the procedure was applied to the SPE–GC–MS analysis of HAAs in water samples with better figures of merit. This modified method has advantage over the EPA method 552.1.

Keywords: Factorial design; Experimental design; SPE; Haloacetic acids

1. Introduction

Chlorination is commonly used for treating drinking water and it is the main chemical disinfection measure applied worldwide. However, a number of animal studies and epidemiological investigations have shown that many disinfection by-products (DBPs) could cause cancers or have adverse effects on the urinary organs, digestive system and reproductive system [1–3]. Natural organic matter (NOM) in water has been regarded as a precursor of DBPs [4,5]. Total organic carbon (TOC) is an aggregate parameter of various fraction of NOM. Since, the USEPA has anticipated the total TOC parameter as a measure of DBP precursors [6]. The major sources of NOM are either photosynthetic input from phytoplankton (autochthonous) or imported from terrestrial and wetland/littoral higher plant tissues (allochthonous).

DBP exposure may be also attributed with decreased birth weight, a public health risk that is under active investigation [7]. THMs have already received the most attention because of their carcinogenicity on humans and animals. In addition, HAAs has also increased our concerns of their acute effects on

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human health. There are nine species of HAAs; that are monochloroacetic acids (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA), dibromoacetic acid (DBAA), bromochloroacetic acid (BCAA), bromodichloroacetic acid (BDCAA), dibromochloroacetic acid (DBCAA) and tribromoacetic acids (TBAA), some of which have been found in drinking water, tap water [8].

According to the Drinking Water Standards and Health Advisories, the US Environmental Protection Agency (US EPA) has classified DCAA as likely to be a carcinogen to humans and TCAA as suggestive evidence of carcinogenicity [9]. The US EPA has regulated the maximum contamination level (MCL) under the Stage 1 disinfectants/disinfection by-products (D/DBPs) rule for the total of five HAAs (MCAA, DCAA, TCAA, MBAA and DBAA) in drinking water to be 60 μg/l, which is effective for all surface water public water systems and all groundwater public water systems [10]. The World Health Organization has published drinking water guidelines for DCAA, 0.05 mg/L and TCAA, 0.1 mg/L [11].

In order to monitor these halogenated acids in water samples, chromatographic methods are most commonly used, in particular gas chromatography (GC) [12] and reversed phase ion pair chromatography (RP-IPC). GC is a very efficient technique with high resolution and very good detection limits can be achieved using specific detectors. For the analysis of HAAs by GC, a prior derivatization step is necessary because of their low volatility, high solubility in water and high polarity. However, it is possible to determine HAAs without derivatization using RP-IPC, IC, LC–MS and HPLC but in this case, level of detection is higher [13].

Solid phase extraction (SPE) prior to separation has been studied for the determination of these compounds in water samples. A solid phase extraction (SPE)/gas chromatography/mass spectrometry (GC/MS) method was developed for quantifying several of the targeted HAAs for this study. SPE offers an alternative extraction means to conventional liquid–liquid extraction, and the use of a MS detector provides better sensitivity and improves identification capability. In analytical chemistry, multivariate techniques have been applied to the optimization of chemical factors during the development of analytical strategies involving pre-concentration systems using solid phase extraction [14,15], cloud point extraction [16,17] and liquid–liquid extraction [18,19].

The optimization of the main factors affecting the sample preparation was carried out by means of experimental design. The essential difference between classical one-factor-at-a-time method and the many factors at time, the values of all factors are varied in each experiment in a programmed and rational way. Many of the factors studied will probably have no influence, only few will act upon the response; thus, the influencing factors can be detected while keeping the number of experiments to a minimum [20].

Procedural optimization can be achieved in a traditional trial, studying each factor separately, or using chemometric approach based on the use of an optimum set of experiment which allows the simultaneous variation of all experimental factors studied, and the distinguishing of interactions among them that are not detectable with classical experimental methods [21,22]. The chemometric methodology also reduces the number of experiment required. All factors affecting on SPE experiment were optimized by two-level full factorial design. The evaluation and analysis of responses of nine HAA was done by statistical plots and tests.

The purpose of this study is to develop an efficient analytical method for the determination of HAAs at trace level in drinking water by SPE–GC–MS. Mass detection (MS) has been used to identify HAAs in chlorinated drinking waters. To this purpose, a two-level full factorial experimental design was applied in order to check the most influential factors and interactions, and try to improve the sensitivity of the method. SPE is widely used for sample extraction and analyte enrichment. Special attention was put on optimization of elution volume, MTBE volume and derivatization steps by using a two-level full-factorial experimental design. The calculated regression models were used to evaluate the response (extraction recoveries) acting the search for the optimal conditions (highest global SPE–GC–ECD recovery) by multicriteria decision method of the desirability functions.

After the method optimization, drinking water samples collected at different locations of treatment plant have been analyzed.

2. Material and methods

2.1. Chemicals and reagents

The acids studied were: MCAA, MBAA, DCAA, TCAA, BCAA, DBAA, DCBA, DBCA and TBAA. Individual standards were obtained from Supleco (Darmstadt, Germany). An individual standard solution of 1,000 mg/L of each compound was prepared with methyl-tert-butyl ether (MTBE, Supleco) because an initial study showed that if these compounds are prepared using methanol, spontaneous methylation is obtained [23]. Standard working solutions were prepared weekly or daily, depending on their concentra-

tion. All solutions were stored at 4°C in the refrigerator. A standard solution of 1,000 mg/L of each HAA was used in methylated form (methyl ester) to study the recovery of the process. Ultrapure water was prepared with a Milli-Q water purification system (Millipore, Bedford, MA, USA). Helium (99.995% quality) sodium sulphate (Probus, Badalona, Spain), anionic exchanger Silia*Bond* TMA chloride cartridge and HPLC gradient-grade methanol (Sharlau, Barcelona, Spain) were used for SPE.

2.2. Instrumentation

2.2.1. GC/MS analysis

A Hewlett–Packard (Palo Alto, CA, USA) 5890 gas chromatograph equipped with an HP5972 mass spectrometer and an HP7673 automatic injector was used. The GC system was equipped with a split/splitless injector. The fused silica capillary column DB-5.625 30 m × 0.25 mm I.D. × 0.25 μm film thickness fused silica was used.

2.3. Sample preparation

Silia*Bond* TMA chloride (or Silia*Bond* SAX, *Si*-TMA-Cl) is mainly used as a strong anion exchanger (SAX) in ion exchange SPE. The function bears a positive charge across the whole pH range as well as in organic solvents. Since the chloride ion is bound relatively strongly to the ammonium, it may be suited to activate the ion exchanger by changing the chloride for an acetate counter ion.

SPE is more efficient than LLE, yields quantitative extraction that is easy to perform, is rapid and can be automated. Solvent use and experiment time are reduced. In the SPE process, the sorbent used was TMA-chloride as the functional group (ISOLUTE-*Si*-TMA-Cl).

An amount of 3-mL SPE cartridges was conditioned by adding two 10 mL aliquots of methanol to the cartridge and allowing it to drain under vacuum, followed by 10 mL aliquots of deionized water. The samples were then attached to the vacuum manifold using the Teflon tubing and tube adapters. The flow rates were 1.5 mL/minute for all samples for complete passage of the water through the sorbent. In this whole process, constant flow rate was to be addressed specially in sample application and elution step. The vacuum lines were closed individually upon completion of the water transfer. To avoid loss of compounds, the vacuum was not applied to the sorbents any longer than necessary once the water had eluted. A clean-up step was made using 10 mL of methanol to remove possible contaminants sample in sorbent. The Teflon tubing from each sample cartridge was removed and the vial rack inserted with collection vials. A 10% H_2SO_4/MeOH solution was used as the elution solvent and placed at the top of the sorbent. Finally, the collected extracts were quantitatively methylated with MTBE at 50°C for hours to produce ester derivatives. After methylation, 7 mL of Na_2SO_4 solution was added to increase the extraction efficiency and drying the extract. The extracted samples were placed in amber vials prior to GC analysis. In the above sample preparation technique, elution volume, MTBE volume and derivatization time were selected as design factors. The TIC chromatograph of HAAs spiked in drinking water is shown in Fig. 1.

2.4. Experimental design

Factors that may influence the performance of a process or experiment can be classified as potential

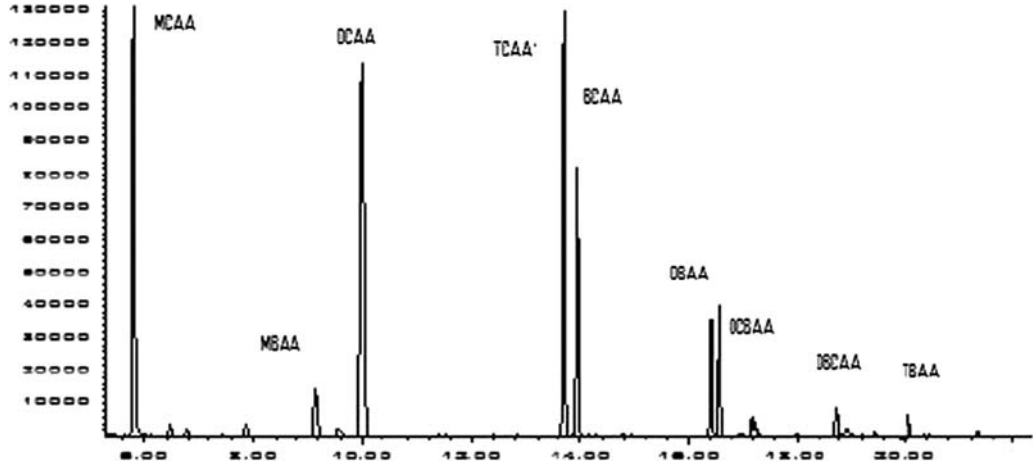

Fig. 1. TIC chromatograph of HAAs spiked in drinking water.

Table 1
Results of statistic analysis (*F*-test) at 95% confidence level

Compounds	SPE		LLME		F_{calc}	F_{tab}
	Standard deviation S_1	Variance S^2_a	Standard deviation S_2	Variance S^2_b		
MCAA	3.1	9.61	2.6	6.76	1.421	5.82
MBAA	3.2	10.24	2.2	4.84	2.115	5.82
DCAA	3	9	1.8	3.24	2.777	5.82
TCAA	3.9	15.2	1.7	2.82	5.391	5.82
BCAA	2.3	5.29	1.8	3.24	1.632	5.82
DBAA	4.9	24.01	2.4	5.74	4.181	5.82
DCBAA	3.8	14.4	3.5	12.25	1.175	5.82
DBCAA	2.9	8.41	2.8	7.89	1.065	5.82
TBAA	4	16	2.4	5.76	2.777	5.82

design factors. In this study, initially three factors were chosen with narrow range so finally design expert software could not calculate the main effect and interaction effect between factors involved in the experiment because the range of factors must be wider to watch out for the effect on response [24].

3. Results and discussion

SPE conditions were optimized using a constant sample concentration of 20 μg/L in all the design experiments. Response was evaluated in terms of HAA peak area. The analysis of results of the first design showed that all selected variables produced non-significant effect and that no significant interactions between factors were apparent due to selection of narrow range of two levels of the studied factors.

Here, a full 2^3 factorial experiment was investigated at two levels of the factors. This is done by performing a series of experiments in the laboratory with different high and low setting as outlined in Table 2. The designed experimental results are then statistically evaluated. This approach has the benefit over the often employed one-at-a-time optimization that it identifies the effect of each independent factor acting on its own, in addition to determining the interaction among two or more factors. The regression model determined that elution volume itself had no significance but the interaction with derivatization was quite significant which means the elution volume would be able to elute all compounds from the cartridge but recoveries would be low. In order to get high recovery of all nine HAAs, it needs to be heated to enhance derivatization of target compounds for complete quantification. So without derivatization time, elution volume alone would not be efficient. So, factorial

Table 2
Factor level in the design for HAAs SPE optimization with wide range

Factors	Low (−)	High (+)
Two-level full-factorial design (2^3)		
Elution volume (mL)	1	3
MTBE volume (mL)	0.5	2
Derivatization time (min)	30	120

design determined the optimal elution volume and derivatization time in order to achieve the highest global SPE–GC–MS recovery within the explored domain. Hence, more optimal reaction conditions could be investigated further by increasing derivatization time and elution volume, thus exceeding the chosen experimental domains. However, further investigations outside the chosen experimental domains were carried out. As can be seen, in the interaction plots the target compound response would be increased when the elution volume and derivatization time increase. The low level of derivatization time (30 min) and high level of derivatization time (120 min) were indicated by symbols in Fig. 2, same as for methylation volume.

In the case of TCAA. The recovery of this compound would not be affected by changing the levels of methylation and elution volume. As can be seen in the contour plot (Fig. 2), whether at low or high level, the recovery would be same and that was an interesting conclusion which was drawn, TCAA will not pose a significant interaction. As can be observed in Table 3, the contour plot was explaining about methylation volume for one of HAA compound that was same for the rest of HAAs compounds. In that plot it was clearly observed that methylation volume either at low or high level does not have an effect on recovery

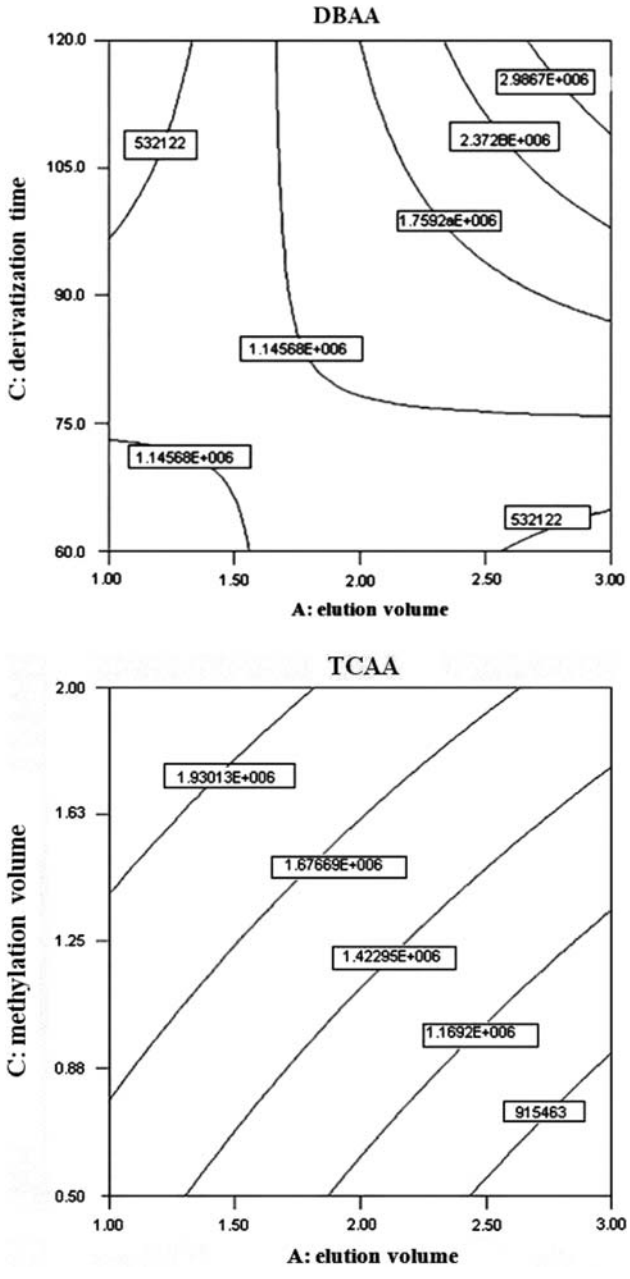

Fig. 2. The contour plots of two target compounds at optimal point projection (elution volume = 3 mL; methylation volume = 2 mL; derivatization time = 120 min).

of all nine HAAs with varying elution volumes. This would be only explained by chemiometric tool. In addition, non-significant and significant interactions were explained as a function of each experimental factor. As can be seen in Fig. 2, by observing the contour plot, optimal condition for DBAA was found to be around 3 mL elution volume and 120 min derivatization time; and significant interaction was detected as well.

Table 3
The *p*-value for the main effects and two-way interaction of each target compound

Compound	Main effect			Two–way interaction		
	A	B	C	AB	BC	AC
MCAA	0.56	0.15	0.09	0.70	0.68	0.02
MBAA	0.41	0.43	0.02	0.92	0.45	0.01
DCAA	0.68	0.52	0.04	0.91	0.78	0.02
TCAA	0.66	0.65	0.12	0.92	0.57	0.02
BCAA	0.59	0.64	0.14	0.93	0.57	0.02
DBAA	0.58	0.53	0.24	0.98	0.96	0.02
DCBAA	0.65	0.13	0.72	0.99	0.97	0.01
DBCAA	0.70	0.17	0.52	0.89	0.90	0.01
TBAA	0.13	0.26	0.94	0.05	0.02	0.06

$p < 0.05$ means significant.

HAA SPE was based on the two tested factors. Higher the elution volume and the methylation volume, better the response. Obviously, methylation volume impacts same yield when using different ranges of methylation volume. The main effect of MTBE volume on the response was not significant. So that constant MTBE volume was adopted, because the lower value and higher value of MTBE produce same response yield. No significant interaction was detected.

The data analysis of this matrix that produced the derivatization time only appeared statistically significant for all nine responses but elution volume was significant interaction with derivatization time as can be seen in Table 2. The % contribution of each factor is given in Table 4.

The regression models were then used to depict the response surfaces and to search for the highest global SPE–GC–MS recovery within the explored domain. As can be seen in the Fig. 3, a global desirability $D = 0.80$ was calculated and the optimal extraction conditions were found in correspondence to 3 mL elution volume, a 2 mL MTBE volume and 120 min derivatization time to the solution. The obtained value of the global desirability showed that the optimal extraction conditions were good for all the compounds with the exception of MCAA, DCBAA, DBCAA; in fact, these target compounds showed a desirability value lower than those calculated for the other compounds. This value has not much difference than those calculated for other target compounds. It means optimal extraction conditions would be suitable for them as well, but not as good as those for others.

Experiments performed in the optimized conditions showed high recoveries for all nine HAAs except

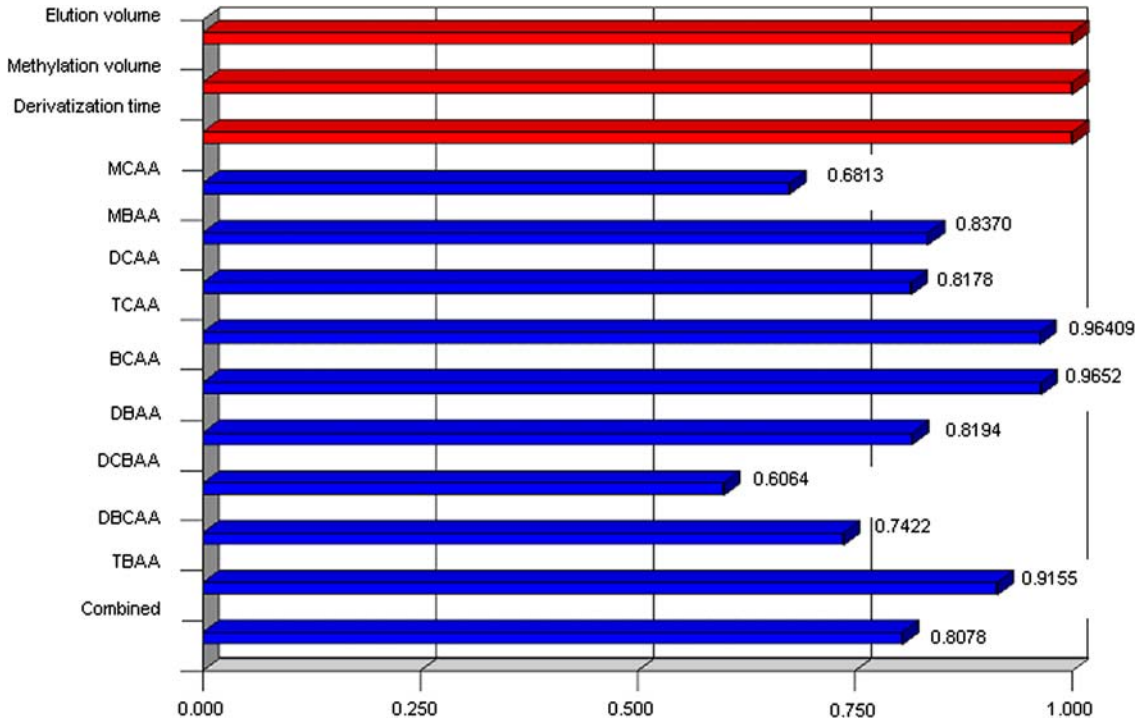

Fig. 3. Bar graph of desirability for all nine target compounds (HAAs).

Table 4
The % contribution effect of each factor on HAAs extraction efficiency

Compound	Quantitation ion (m/z)	Percent of effect (%)		
		A: Elution volume	B: MTBE volume	C: Derivatization time
MCAA	59	4.6	12.4	18.8
MBAA	59	2.2	6.5	39.6
DCAA	59	0.7	8.8	33.4
TCAA	59	4.1	4.1	17.4
BCAA	59	6.5	1.1	16.7
DBAA	59	1.4	8.2	7.7
DCBAA	59	4.8	12.7	2.6
DBCAA	59	2.5	9.2	5.3
TBAA	59	9.1	2.1	3.6×10^{-3}

MCAA, MBAA and TBAA. This behaviour could be explained taking into account the possibility of 3-mL elution volume might not be sufficient for complete elution of these compounds from sorbent, thus requiring different elution volume than those utilized for the other compounds. In the further step, the method was validated operating under these conditions. The method was validated in terms of detection limits, quantitation limits, linearity and precision.

The analytical errors of developed method were investigated using *F*-test in order to evaluate the random error between SPE and LLME. The data were shown in Table 1.

The method validated was then applied to analyzed drinking water samples. Full scan TIC chromatograms were recorded for identification and confirmation purposes. Operating under SIM conditions, DCAA, TCAA and BCAA were detected and quantified in drinking water samples.

4. Conclusion

The optimal extraction conditions corresponding to the highest global SPE–GC–MS recovery were calculated by the multicriteria decision method of the desirability functions. This set-up was found in correspondence with an elution volume of 3 mL, MTBE volume of 2 mL and 120 min derivatization time. The application of optimal condition to the extraction of HAAs from water sample produces better detection and quantification limits. The experimental design approach assists the process for the suitability for determination of HAAs in the framework of established legal guideline. One interesting conclusion can be pointed out from this study, either 2 mL MTBE volume or 0.5 mL give maximum extraction yield of nine responses. So with application of experimental design

tool, organic solvent volume could be reduced to 0.5 mL instead of 2 mL. In this research, 2^3 design was used with unreplicated for locating optimal region for all nine responses. Linearity of the regression models for all nine compounds was confirmed by introducing centre point in the factorial. There was no significant curvature in the response which means that there was no quadric effect in the response, resulting in a first-order model. The method application potential was evaluated by drinking water sample taken from local treatment plant.

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