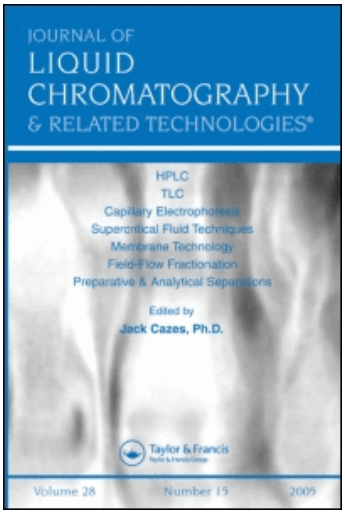

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Analysis of Dichloroacetic Acid in Drinking Water by Ion Exchange HILIC-LC/MS/MS

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ABSTRACT

Dichloroacetic acid (DCA) is a small, polar compound that individuals are exposed to as a result of drinking water consumption. The occurrence of DCA in drinking water is of concern because DCA has been shown to cause cancer in laboratory animals. To date, no validated LC/MS/MS methods are available for quantitative analysis of DCA. In addition, most methods use a derivatizing reagent that can artificially inflate the levels of DCA. Presented in this paper, is a validated LC/MS/MS method for the analysis of DCA in drinking water. An amino column

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was used with ion-exchange hydrophilic interaction chromatography (HILIC).

Key Words: Dichloroacetic acid; HILIC; Ion exchange; Drinking water.

INTRODUCTION

Dichloroacetic acid (DCA) is a compound that has been recently receiving close attention from the United States Environmental Protection Agency (USEPA), due to its potential to adversely affect individuals who consume it in drinking water. There are two main sources of exposure to DCA. DCA is found in drinking water as a disinfection by-product of chlorination. A second source of exposure is from solvents that are metabolized to DCA. One such solvent is trichloroethylene (TCE), another common contaminant in drinking water. TCE has been used extensively as a metal degreaser, in dry cleaning, and as a general-purpose solvent. As a result of its widespread use and the fact that it is soluble to some extent in water, TCE is a common contaminant of water supplies nationwide.[1] DCA is formed from metabolic conversion of TCE via the cytochrome p450 pathway.[2,3]

Chlorination of drinking water containing tannins (natural organic matter) produces haloacetic acids (HAAs). The maximum contaminant level (MCL) issued for a total of 5 HAAs (HAA5) by the USEPA is 60 ng/mL in drinking water for the following acids: DCA, TCA (trichloroacetic acid), MCA (monochloroacetic acid), MBA (monobromoacetic acid), and DBA (dibromoacetic acid). DCA and TCA have been found to make up the majority of HAAs in drinking water.[4,5]

In the past, it was believed that TCE itself was the cause of liver cancer in mice exposed to TCE in drinking water. More recently, it has been found that the metabolites of TCE are actually causing the observed carcinogenic effects.[6–9] Among the metabolites shown to cause cancer are DCA, TCA, and chloral hydrate.[6–9] One of the criteria for a compound to be a suspected human carcinogen is that the chemical causes cancer in more than one species of laboratory animal. DCA is the only one of the above-mentioned TCE metabolites shown to cause liver cancer in both rat and mouse.[6–8] This indicates that the DCA may be more of a threat than the other metabolites in causing cancer. The USEPA recognizes DCA as the most potentially harmful HAA in drinking water, as this is the only HAA5 with a maximum contaminant goal level (MCGL) of zero in drinking water, and is the only HAA5 with the classification of probable human carcinogen.[10]

Analyzing DCA has been quite problematic in environmental and biological samples. The most common method for analyzing DCA and other HAAs has been derivatization followed by gas chromatography (GC) analysis.[3,11–14] Two capillary electrophoresis (CE) methods also exist in which HAA samples are derivatized prior to analysis.[15,16] It has been found, however, that the strong acids used with the derivatizing reagents can convert TCA into DCA.[17] This results in artificially high levels of DCA being reported. Several mass spectrometry methods have been reported for DCA.[18–24] However, many of these methods do not use HPLC.[19–22] Therefore, DCA was not isolated from the sample, resulting in a greater possibility of other chemicals in solution interfering with DCA analysis. Two of the LC/MS methods use sulfuric acid for pH adjustment of samples in order to protonate DCA. Also, two methods use ion pairing agents, which suppress ionization in the mass spectrometer. An HPLC method utilizing a conductivity detector has been described for the analysis of DCA in tap water.[25] Unfortunately, the limit of detection (LOD) of this method is 50 ng/mL which is much higher than the levels of DCA that would be expected in drinking water. The USEPA is currently in the process of creating a new draft of the risk assessment for TCE which should take into account the impacts that DCA and TCA have on carcinogenicity. Therefore, it is important to have a sensitive, validated analytical method for quantitation of DCA. The use of LC/MS/MS allows DCA to be analyzed without derivatization.

Polar molecules in general, produce sharp, reproducible peaks when run by HPLC. Reversed phase chromatography (RP-HPLC) using a C18 or C8 column is the most widely used procedure for the analysis of non-volatile compounds. However, small charged polar compounds, such as DCA, often elute in the solvent front when run by RP-HPLC, because they lack affinity for the non-polar stationary phase of most RP columns. Therefore, other columns must be used for the analysis of such compounds.

Hydrophilic interaction chromatography (HILIC) is a method by which the aqueous solvent, rather than the organic, determines how quickly the compound elutes. Columns containing a polar end group, such as an amino or silica column, can be used in either HILIC or mixed HILIC-ion exchange chromatography.[26] In HILIC-ion exchange chromatography, retention is based on the affinity of the polar analyte for the charged end group on the column stationary phase. HILIC-ion exchange chromatography has been successfully utilized for many applications and is used in the method presented in this paper.[26] This paper describes the first HILIC-ion exchange chromatography method and the first LC/MS/MS method for the analysis of DCA.

EXPERIMENTAL

Chemicals and Reagents

HPLC grade ACN and HPLC grade Optima Water were purchased from Fisher Scientific Company (Milwaukee, WI). Ammonium formate salt and DCA, 99% were purchased from Aldrich (Fair Lawn, NJ).

Method Development

The final method for DCA reported in this paper was determined after varying several experimental parameters. Several columns were investigated for use with this method. These included a Waters Xterra C18 column, a Phenomenex Synergi Max column, a Keystone Prizm column, and a Phenomenex Luna Amino column. Mobile phases investigated during method development included methanol/formic acid, methyl-tertbutyl ether (MTBE)/water, methanol/ammonium acetate, and acetonitrile (ACN)/ammonium formate. A range of buffer concentrations (0–40 mM) was tested for the mobile phases listed. Two ion-pairing agents (tetraethylammonium hydroxide and triethylamine) and Dowex cation exchange resin were also investigated for use in this study.

Flow injection analysis of DCA was performed in order to optimize the mass spectrometer settings. All spectra obtained were in electrospray negative ionization (ESI^-) mode. The molecular ions $(M\text{-}H)^-$ of DCA with mass to charge ratio (m/z) 127 and 129 (chlorine isotopes) were observed, and source conditions were optimized to maximize these ions. Upon collisionally induced dissociation, major fragment peaks at m/z 83 and 85 were observed corresponding to the neutral loss of CO_2 (loss of 44). The collision energy, as well as collision cell entrance and exit lenses, were optimized to maximize this transition. The transition from m/z 127 to 83 was chosen as the transition to monitor because of its greater abundance. The ion at m/z 127 represents the more favored Cl^{35} isotopic species.

Liquid Chromatography

An Agilent 1100 Series HPLC (Palo Alto, CA) was employed for this study. The HPLC was equipped with the following components: a degasser, a quaternary pump, an autosampler, and a thermostated column compartment. The HPLC column used in this study was a Phenomenex (Torrance, CA) Luna Amino ($150 \times 2.1\,mm^2$, $5\,\mu m$ particle size). A $4.0 \times 2.0\,mm^2$ Phenomenex Security Guard Amino guard column was also used. The column was

kept at 25°C for all experiments. The flow rate was 0.7 mL/min. Two mobile phases were utilized with the gradient run. The two components of the mobile phase were A (ACN) and B (40 mM of ammonium formate made in HPLC grade water). The gradient run was as follows: 90% A at time 0, 30% A at 5 min, and 90% A at 6 min. A re-equilibration period of 9 min then followed, making the total run time 15 min long. The injection volume was 10 μL, and the autosampler needle was rinsed with ACN between samples.

Mass Spectrometry

The mass spectrometer used in this study was a Micromass Quattro LC triple quadrupole mass spectrometer fitted with a Z-spray source (Manchester, UK). The mass spectrometer was run in ESI^- using the MRM mode to monitor the transition from m/z 127 to 83. Settings for the capillary, cone, and extractor were, respectively, 0.50 kV, 15 V, and 2 V. The source temperature was set at 150°C and the desolvation gas temperature was 350°C. Gas flow rates were 1170 L/hr for the desolvation gas and 70 L/hr for the cone gas. The collision energy for dissociation was 9 eV and the entrance and exit lenses of the collision cell were set at −5 and 35 V, respectively.

Sample Preparation

A 1 mg/mL stock solution of DCA was made in water each day samples were run. From this stock solution, a 10 μg/mL DCA solution was prepared by adding 10 μL of the 1 mg/mL stock solution to 990 μL of water. Samples for the calibration curves were made up in 60 : 40 ACN : water, the approximate percentages of ACN and water, just prior to the time of DCA elution. A solution of 500 ng/mL was made by adding 300 μL of 10 μg/mL DCA into 5.7 mL of 60 : 40 ACN : water. This solution was used to spike all but three of the calibration curve samples. A 50 ng/mL solution was made by adding 100 μL of the 500 ng/mL solution to 900 μL of 60 : 40 ACN : water. This solution was used to spike the three lowest calibration curve samples in order to decrease variability due to pipetting small sample volumes. An appropriate amount of either 50 or 500 ng/mL DCA solution was added to 60 : 40 ACN to yield samples with DCA concentrations of 5, 10, 25, 50, 75, 150, 200, 250, 300, 400, and 500 ng/mL for use in a calibration curve. Samples for validation were made in the same way and had concentrations of 5, 10, 15, 30, 100, and 500 ng/mL. Tap water samples (volume = 500 μL) were dried under vacuum and reconstituted in 100 μL of 60 : 40 ACN : water. This was done to have the tap water samples dissolved in the mobile phase composition, and to concentrate the samples in order to improve sensitivity of the method.

Validation

On three separate days, an 11-point calibration curve was run along with 6 validation points ($n = 5$ for each validation point for one day, $n = 15$ for each validation point for all three days). In order to obtain the best fit for the data, a comparison was made between the linear calibration curves with no weighting and linear calibration curves with the following weightings: $1/x$, $1/x^2$, $1/y$, and $1/y^2$. Precision (% RSD) and accuracy (% Error) were calculated for the six calibration points. In order for a validation point to pass, both the precision and accuracy had to be less than 20% for the lower limit of quantitation (LLOQ) and less than 15% for all other points. The LLOQ was the lowest concentration sample, which would pass validation. A 3 : 1 signal to noise ratio was the criteria used to determine the LOD.

Stability Studies

Autosampler stability was determined by pipetting a sample from the same solution into several autosampler vials. The samples were then injected every hour for 15 hr. Freeze/thaw stability was performed over three cycles.

Tap Water Samples

Drinking water samples were run to determine whether the method would give reliable results for a practical application. Tap water samples were obtained from several locations in Athens, GA, and areas surrounding Atlanta, GA. Three comparisons were made between samples: (1) amount of DCA in tap water vs. bottled water, (2) amount of DCA present in homes with a home filtration device vs. those without a water filtration device, and (3) amount of DCA present in drinking water treated by different disinfection processes. Each sample had an $n = 5$.

RESULTS AND DISCUSSION

Results of Method Development

The Xterra and Synergi columns investigated for use in the analysis of DCA were found to be very sensitive to salt in samples. This was true to the extent that minute amounts of salt in samples (such as in tap water samples) shifted the peak for DCA to an earlier retention time and distorted the peak, resulting in area

counts that were not reproducible. Higher salt concentrations greatly distorted the peak, such that the peak was not recognizable and eluted with the solvent front. Initial tests indicated that sodium was the main ion responsible for shifting the peak. A cation exchange resin was then used in an attempt to help improve the peak shape by replacing sodium ions with hydrogen ions. While this did help to some extent, too much salt remained in the samples. A Keystone Prism column was investigated, as this column had worked for the analysis of TCA, a compound that has similar problems with salt in samples.[27] However, this column was not capable of analyzing for DCA in the presence of sodium. A Phenomenex Luna Amino column was then chosen, because the amino column could be used in ion exchange mode, since the negatively charged DCA has an affinity for the positively charged amino groups. Sodium has no affinity for the amino groups, as both are positively charged, and, therefore, sodium should not be retained. An ACN : aqueous buffer mobile phase was chosen, because this combination of mobile phase has been shown to work well for HILIC separations of small polar compounds on amino columns.[26] Formate buffer was used because it is volatile. A 40 mM buffer was the optimum concentration of ammonium formate, because this concentration resulted in the best peak shape with minimal ion suppression. Generally, as the concentration of buffer increased, the peak shape improved. However, high concentrations of buffer can result in ion suppression in the mass spectrometer. The optimum flow rate was determined to be 0.7 mL/min, because this resulted in the best peak shape, as well as a faster run time. A chromatogram of DCA at the LLOQ and a blank chromatogram (60 : 40 ACN : HPLC grade water) are shown in Fig. 1.

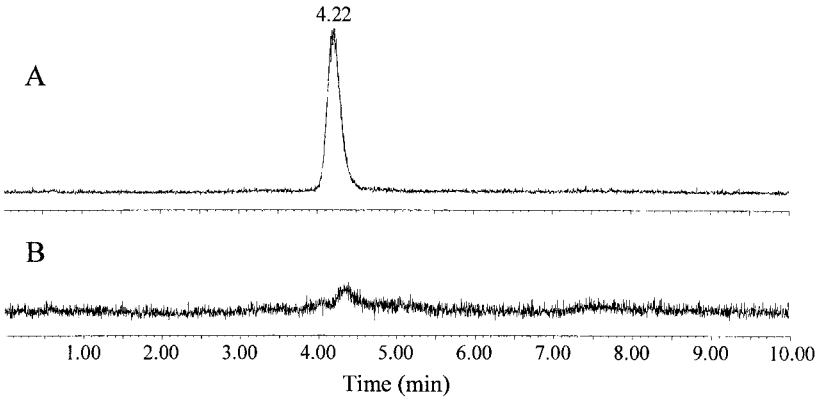

Figure 1. Chromatogram of DCA at (A) LLOQ (5 ng/mL) and (B) blank (60 : 40 ACN : water).

Validation

$1/y^2$ weighting was chosen because this type of weighting minimized the sum of the percent residuals, indicating the best fit. This type of weighting was also chosen because it gave more emphasis to the points at the lower end of the calibration curve, where the %Error is often the highest. All calibration curves used in the validation of DCA had an R^2 value of greater than 0.99. For all 3-validation days, the calculated values for all six-validation points corresponded well to the actual concentrations (Table 1). As shown in Tables 2 and 3, precision and accuracy values were less than 7.7 (% RSD) and 8.2 (% Error), respectively. Both of these values are well below 15%, the value required by the FDA for successful validation. The LLOQ was found to be 5 ng/mL, and the LOD was 1 ng/mL.

Stability Studies

DCA was stable in the autosampler over the duration of the stability study (15 hr). The compound was also stable over three-freeze/thaw cycles.

Tap Water Samples

Calculated concentrations of DCA in tap water and bottled water samples are shown in Table 4. For water samples taken from an individual's residence, concentrations for both unfiltered tap water and tap water treated by a home filtration device are provided. All of the calculated DCA concentrations

Table 1. Actual vs. calculated DCA concentrations on validation days 1–3.

Actual DCA concentration (ng/mL)	Calculated DCA concentration[a]			
	Day 1 ($n = 5$)	Day 2 ($n = 5$)	Day 3 ($n = 5$)	Days 1–3 ($n = 15$)
5	4.6 ± 0.3	5.1 ± 0.2	5.1 ± 0.3	4.9 ± 0.4
10	10.3 ± 0.3	9.2 ± 0.2	10.0 ± 0.3	9.8 ± 0.5
15	15.3 ± 0.1	15.7 ± 0.4	15.9 ± 0.4	15.6 ± 0.4
30	29.8 ± 2.3	29.7 ± 0.7	30.9 ± 0.8	30.1 ± 1.4
100	107.2 ± 1.5	106.6 ± 2.1	104.6 ± 1.3	106.1 ± 6.1
500	460.0 ± 13.0	466.5 ± 3.3	460.0 ± 16.2	462.2 ± 11.7

[a]All concentrations reported as $x \pm s$. x, mean; s, standard deviation.

Table 2. Accuracy data for method validation.

DCA concentration (ng/mL)	% Error[a]			
	Day 1 ($n = 5$)	Day 2 ($n = 5$)	Day 3 ($n = 5$)	Days 1–3 ($n = 15$)
5	8.23	4.49	3.64	5.45
10	2.54	2.83	7.51	4.30
15	1.96	5.38	4.56	3.97
30	5.54	2.84	1.94	3.44
100	7.21	4.56	6.62	6.13
500	7.99	7.80	6.69	7.56

[a]% Error = absolute value $[(A - O)/A]*100$. A, actual concentration; O, observed concentration.

were shown to be reasonable, as tap water samples all showed agreement with levels of DCA reported in the EPA's Safe Drinking Water Information System.[28] Bottled water samples contained much less DCA than tap water samples. This is not surprising, as DCA is commonly found in tap water as a disinfection by-product of chlorination. Bottled water may either not be treated with chlorine or there are so few tannins that DCA is not formed upon chlorination. It is interesting to note that in all the cases except one (Covington, GA,), household water filtration devices decreased the amount of DCA in the water sample. The one filter that did not remove DCA from tap water was old and in need of changing. Old filters can concentrate pollutants and when used too long can leach these pollutants into the water to be consumed.

Table 3. Precision data for method validation.

DCA concentration (ng/mL)	% RSD[a]			
	Day 1 ($n = 5$)	Day 2 ($n = 5$)	Day 3 ($n = 5$)	Days 1–3 ($n = 15$)
5	5.57	4.77	5.56	5.30
10	3.13	2.52	3.48	3.05
15	0.96	2.87	2.46	2.10
30	7.68	2.28	0.89	3.61
100	1.41	2.00	1.23	1.55
500	2.82	0.71	3.52	2.34

[a]% RSD = $(s/x)*100$. s, standard deviation; x, mean.

Table 4. Calculated Concentrations of DCA in tap and bottled water.

Drinking water source	Filtered[a] (ng/mL) ($n = 5$)	Unfiltered[a] (ng/mL) ($n = 5$)	Water[a] treatment type
East Athens, GA, home	8.24 ± 0.01	14.2 ± 0.29	Chlorination
East Athens, GA, apartment	ND[b]	25.2 ± 0.99	Chlorination
South Athens, GA, apartment	ND[b]	12.2 ± 0.13	Chlorination
Covington, GA, home	30.3 ± 1.08	28.1 ± 0.26	Chlorination
Vinings, GA, business		13.3 ± 0.20	Chlorine dioxide
Duluth, GA, business		17.8 ± 0.29	Ozonation
Bottled water sample 1		ND[b]	
Bottled water sample 2		ND[b]	
Bottled water sample 3		ND[b]	
Bottled water sample 4		ND[b]	

[a]All concentrations reported as $x \pm s$. x, mean; s, standard deviation.
[b]ND, not detected because signal response was below LLOQ.

Also interesting to note, is the fact that the filters used with the Covington, GA and East Athens, GA home samples were pitcher-type water filtration devices and removed less than half of the DCA present in the tap water. In contrast, the South Athens apartment and East Athens apartment filtered water samples were both collected from home filtration devices that fit directly onto the water faucet. These filters removed the greatest percentage of DCA from the drinking water.

Concentrations of DCA were also compared among drinking water samples treated by each of the following disinfectant processes: chlorination, chlorine dioxide, and ozonation followed by chlorination. Concentrations for drinking water disinfected by each of the treatment processes can also be found in Table 4. There appeared to be no difference in DCA levels among the different drinking water treatments, based on limited sampling.

CONCLUSIONS

The method presented is the first LC/MS/MS analytical method for the determination of DCA and one of few for quantitation of small organic anions. The use of an amino column and ion exchange-HILIC chromatography allowed the small polar compound DCA to be analyzed without peak shifting due to salts in the sample. This method does not require the

use of derivatization reagents shown to give inaccurate results for the analysis of DCA. The method uses small volumes (500 μL) of drinking water to detect low levels of DCA (LOQ = 5 ng/mL). This method is also the only known method for DCA analysis that has been validated using the criteria recommended by the US FDA. All precision and accuracy numbers for validation points were below 15%. The method was applied to a number of drinking water samples, and the levels of DCA were determined to be between 12 and 28 ng/mL (ppb). Samples from bottled water contained low levels of DCA that were above the LOD, but below the LOQ of this method (roughly 1–1.5 ng/mL). Finally, the levels of DCA did not appear different, when different water treatment strategies were employed.

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