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Direct large volume injection ultra-high performance liquid chromatography-tandem mass spectrometry determination of artificial sweeteners sucralose and acesulfame in well water☆

Minghuo Wu, Yichao Qian, Jessica M. Boyd, Steve E. Hrudey, X. Chris Le, Xing-Fang Li*

Division of Analytical and Environmental Toxicology, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada T6G 2G3

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ABSTRACT

Acesulfame (ACE) and sucralose (SUC) have become recognized as ideal domestic wastewater contamination indicators. Liquid chromatography-electrospray ionization mass spectrometry (LC-ESI-MS) analysis is commonly used; however, the sensitivity of SUC is more than two orders of magnitude lower than that of ACE, limiting the routine monitoring of SUC. To address this issue, we examined the ESI behavior of both ACE and SUC under various conditions. ACE is ionic in aqueous solution and efficiently produces simple $[M-H]^-$ ions, but SUC produces multiple adduct ions, limiting its sensitivity. The formic acid (FA) adducts of SUC $[M+HCOO]^-$ are sensitively and reproducibly generated under the LC-MS conditions. When $[M+HCOO]^-$ is used as the precursor ion for SUC detection, the sensitivity increases approximately 20-fold compared to when $[M-H]^-$ is the precursor ion. To further improve the limit of detection (LOD), we integrated the large volume injection approach (500 μL injection) with ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS), which reduced the method detection limit (MDL) to 0.2 ng/L for ACE and 5 ng/L for SUC. To demonstrate the applicability of this method, we analyzed 100 well water samples collected in Alberta. ACE was detected in 24 wells at concentrations of 1–1534 ng/L and SUC in 8 wells at concentrations of 65–541 ng/L. These results suggest that wastewater is the most likely source of ACE and SUC impacts in these wells, suggesting the need for monitoring the quality of domestic well water.

1. Introduction

Artificial sweeteners are widely used in food and beverages because they provide greater sweetness with much fewer calories compared to sucrose (table sugar). Most artificial sweeteners are not metabolized but are excreted directly to the wastewater. For example, sucralose (SUC) is 600 times as sweet as sucrose and over 90% of the ingested amount of SUC is excreted unchanged [1,2]. No evidence of toxic effects of sweeteners on humans has been established; however, their metabolic derangements have recently caused concern [3]. Recently, sweeteners have been detected in high concentrations in wastewater-impacted water systems and in the environment, and therefore, they are now considered as a group of emerging pollutants [4–6]. Richardson and Terner's review presents the current state of analytical and environmental studies of sweeteners [6].

Six artificial sweeteners are the most widely used: acesulfame (ACE), aspartame (ASP), sucralose (SUC), saccharin (SAC), cyclamate (CYC), and neohesperidin dihydrochalcone (NHDC). These sweeteners are synthetic compounds and do not occur in nature. High concentrations of these compounds have been found in wastewater, resulting in their occurrence in the aquatic environment [7,8]. Among these six artificial sweeteners, SUC and ACE have been confirmed that they can escape from the wastewater treatment process, and they are very stable in the environment with a long half-life up to several months or even years [9–11]. There are no other discharge sources to the aquatic environment; therefore, SUC and ACE are ideal indicators for monitoring wastewater contamination in water supplies.

The concentrations of sweeteners differ among different regions or countries, up to micrograms per liter levels in the wastewater. ACE has been reported from 12 to 45 μg/L in treated or untreated wastewater [7,12], while SUC, the most studied sweetener, has been reported to range from 0.3 to 6 μg/L in wastewater and

☆ Invited paper for the Honor issue of Professor Peichang Lu's 90th birthday.

* Corresponding author. Tel.: +1 780 492 5094; fax: +1 780 492 7800.
E-mail address: xingfang.li@ualberta.ca (X.-F. Li).

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Table 1
MRM transitions and parameters for the sweeteners analyzed.

Name	Q1	Q3	DP	EP	CE	CXP
ACE	162	81.9	−60	−10	−18	−6
	162	77.9	−60	−10	−20	−6
ACE-d4	166	85.9	−60	−10	−18	−6
	166	77.9	−60	−10	−20	−6
SUC	395	359	−80	−10	−14	−8
	397	361	−80	−10	−14	−8
	431	395	−60	−10	−18	−12
	433	397	−60	−10	−18	−12
	441	395	−50	−10	−16	−12
	443	397	−50	−10	−16	−12
SUC-d6	401	365	−80	−10	−14	−8
	403	367	−80	−10	−14	−8
	437	401	−60	−10	−18	−12
	439	403	−60	−10	−18	−12
	447	401	−50	−10	−16	−12
	449	403	−50	−10	−16	−12

CE, Collision energy; DP, declustering potential; EP, entrance potential; CXP, cell exit potential.

surface water [7,12–14]. SUC was also found in some treated drinking water at concentrations of 0.11–0.17 μg/L, suggesting that SUC can also bypass the drinking water treatment process [14]. Because of decades of extensive usage, both ACE and SUC have been detected in groundwater in some regions at the considerable concentrations of 0.02–5 and 0.6–2.4 μg/L, respectively [7,13]. Especially in some urban areas, the occurrence of ACE in groundwater can reach 100% frequency at μg/L levels [8].

For the analysis of sweeteners, several methods have been developed, with specific effort on SUC, such as liquid chromatography (LC) with ultraviolet detection (LC-UV) or tandem mass spectrometry (LC-MS/MS), gas chromatography with flame ionization detection (GC-FID) or mass spectrometry (GC-MS) detection and thin-layer chromatography (TLC) [12–17]. Among these, LC-MS/MS methods have become the preferred choice because of their unique sensitivity and selectivity. ACE is ionized in water, thus its electrospray ionization (ESI) efficiency is high and its ESI scan and MS/MS spectra are simple with a clear isotopic distribution. LC-MS/MS analysis of ACE can reach an excellent limit of detection (LOD) as low as 10 ng/L with direct injection of 20 μL [8]. However, unlike ACE, SUC is a neutral compound and it has a complicated chlorine isotopic distribution (Table 1). Therefore, LC-MS/MS analysis of SUC is not as sensitive as of ACE. The LC-MS/MS sensitivity for SUC is at several μg/L in the negative multiple reaction monitoring (MRM) mode using the ion pair of m/z 395–359 [12]. Alternatively, the ion transition of m/z 395–35 was used for better sensitivity (LOD at approximately 200 ng/L) [14]. However, m/z 35 is not specific to SUC due to the widespread existence of chlorine containing compounds. In the positive mode for SUC analysis, sodium adducts $[M+Na]^+$ dominate the Q1 full scan mass spectrum [13,18,19]; thus the sodium adducts were adopted as the precursor ion in positive MRM mode to provide an LOD of 300 ng/L [18]. In ESI-MS analysis, salt effects reduce ionization efficiency, and Na^+ ions are not desirable. Because of the lack of a constant concentration of Na^+ in the ionization source, the sodium adducts of SUC do not provide reproducible signals for quantification.

The concentrations of SUC and ACE in wastewater-impacted water systems have been reported in a range of 0.1 to several μg/L [12,15,20,21], which requires a method detection limit (MDL) at the ng/L level. The sensitivity of the current LC-MS/MS methods for analysis of SUC is not sufficient for environmental water samples without preconcentration. Solid phase extraction (SPE) is required to concentrate SUC from water at an enrichment factor of 50–1000. Accordingly, these methods are time consuming and laborious, resulting in higher cost.

The objective of this study is to build a sensitive, fast, and robust UHPLC-MS/MS method for direct analysis of both SUC and ACE without the need for pre-concentration. To achieve this, we carefully examined the characteristics of SUC under various UHPLC and MS conditions to identify MRM transitions that can produce high sensitivity and reproducible signals for SUC analysis. To further increase the UHPLC-MS/MS sensitivity for SUC and ACE, we

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integrated a large volume injection (500 μL) approach with UHPLC-MS/MS. Here we report the method development and application to determine ACE and SUC in groundwater collected from 100 domestic wells in Alberta, Canada. The results will provide new information on the impact of domestic wastewater on domestic well water in Alberta.

2. Experimental

2.1. Materials

The ACE and SUC were purchased from Sigma-Aldrich (St. Louis, MO). ACE-d4 and SUC-d6 were purchased from Toronto Research Chemicals Inc. (Toronto, ON, Canada). Formic acid (FA, 49–51%) of LC-MS grade was purchased from Sigma-Aldrich. Methanol and water were Optima LC-MS grade purchased from Fisher Scientific Inc. (Fair Lawn, NJ). All other chemicals were of analytical grade.

2.2. UHPLC-MS/MS analysis and sample collection

The UHPLC separation was performed on an Agilent 1290 series liquid chromatograph with an autosampler. Separation was achieved using a Dikma C18 column (100 × 3 mm × 3 μm) (www.dikmatech.com) and gradient elution conditions (mobile phase A, water containing 0.1% FA; mobile phase B, methanol containing 0.1% FA). Gradient: 0–2 min, 2–95% B; 2–4 min, 95% B; 4–4.1 min, 95–2% B; 4.1–5 min, 2%, flow rate 0.6 mL/min).

The TOF-MS analysis was performed on a 5600 mass spectrometer (AB Sciex, Concord, ON, Canada) with direct infusion to generate accurate mass spectra of ACE and SUC for confirmation. An API 5500 QTrap mass spectrometer (AB Sciex) was used for the determination of the sweeteners using negative MRM mode. The MRM parameters were first optimized with the infusion (flow rate at 10 μL/min) of SUC (500 μg/L) and ACE (100 μg/L) solution dissolved in 50% methanol with 0.1% FA. The optimized ESI source conditions for LC-MS/MS are as follows: curtain gas 40 psi, ion source gas 1 at 50 psi; gas 2 at 30 psi, source temperature 400 °C, ion spray voltage −4500 V, and the collision gas was set at high.

All samples were collected in 2013 in Alberta, Canada, and stored at 4 °C. All the samples were filtered to remove the insoluble particles prior to the UHPLC-MS/MS analysis. Isotopic internal standards of ACE-d4 and SUC-d6 were used for quantification of ACE and SUC, respectively. Before sample injection, the internal standards were spiked into the samples at the concentration of 50 ng/L (ACE-d4) and 200 ng/L (SUC-d6).

3. Results and discussion

3.1. Identification of chlorine and formic acid adducts of SUC

The UHPLC-MS/MS analysis of ACE and SUC (Fig. S1) shows the detection limits of ACE (10 ng/L) and SUC (4 μg/L), a difference in sensitivity about 400 times (S/N = 3), which is consistent with the reported methods using the same MS (AB Sciex 5500) and the same MRM transitions [8]. This explains in part the reason why ACE is detected more often than SUC in addition to the difference in its usage and stability in the environment [8]. This led us to investigate how to improve the sensitivity for SUC analysis and to achieve low LOD for both sweeteners using UHPLC-MS/MS analysis without SPE.

Fig. 1 shows a typical full scan spectrum of SUC (200 μg/L) in 50% methanol containing 0.1% FA in water, when analyzed by high resolution mass spectrometry (AB Sciex 5600) under negative ESI. Besides the known $[M-H]^-$ peaks at m/z 395.0063 (and isotopic peaks of m/z 397.0036 and 398.9007), there are two other groups of peaks with higher m/z ratios. Based on the accurate masses and isotopic patterns of chlorine ($Cl^{35/37}$), one group at m/z 430.9831 (and the isotopic peaks of m/z 432.9803 and 434.9775) was identified as $[M+Cl]^-$ with a mass difference of less than 3 ppm compared to their theoretical m/z ratios. Similarly, the other group at m/z 441.0120 (and the isotopic peaks at m/z 443.0093 and 445.0068) was identified as FA adducts $[M+HCOO]^-$.

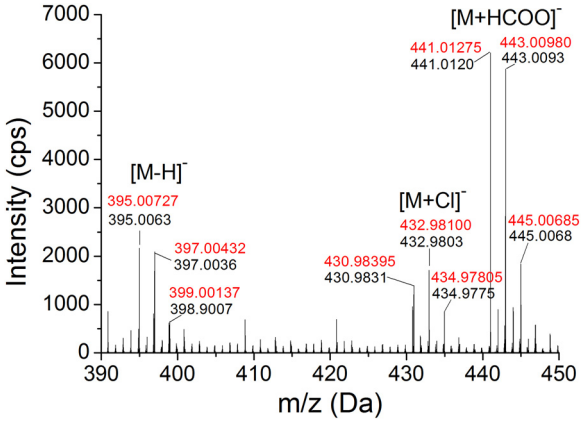

Fig. 1. Full TOF-MS scan of SUC (200 μg/L) in 50% methanol containing 0.1% FA at an infusion flow rate of 10 μL/min. Theoretical m/z shown in red. The peaks correspond to isotopic patterns of $Cl^{35/37}$ of $[M-H]^-$, $[M+Cl]^-$, and $[M+HCOO]^-$ (For interpretation of the color information in this figure legend, the reader is referred to the web version of the article.).

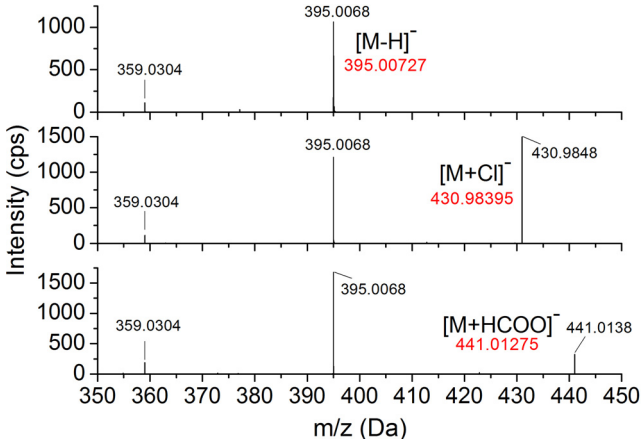

Fig. 2. The product ions of SUC and adducts (theoretical m/z shown in red). ESI conditions were the same as in Fig. 1 (For interpretation of the color information in this figure legend, the reader is referred to the web version of the article.).

To confirm the peak identities, we obtained the MS/MS spectra of $[M-H]^-$, $[M+Cl]^-$ and $[M+HCOO]^-$ ions, as shown in Fig. 2. The main product ion of m/z 395.0063 is m/z 359.0304, corresponding to the loss of HCl. This is consistent with the results reported by Ferrer et al. [18]. The product ions of m/z 430.9831 include m/z 395.0304 and 359.0068, corresponding to the sequential loss of two HCl molecules, supporting the identification of adducts $[M+Cl]^-$. Similarly, the product ion m/z 395.0304 is due to the loss of HCOOH from m/z 441.0120, and further loss of HCl results in m/z 359.0068 in the collision cell. The FA adducts ions can also be found in the spectra of SUC reported previously [22], but they were not characterized in detail. The chlorine adducts of SUC in negative ESI-MS were observed for the first time, and were observed even after the cleanup of the ionization source.

To further support our finding, we analyzed SUC-d6 under the same conditions used for SUC (Figs. S3 and S4). The spectra of SUC-d6 also show the formation of $[M+Cl]^-$, and $[M+HCOO]^-$ along with $[M-H]^-$ ions. In addition, we examined the ESI-MS

spectrum of SUC using acetic acid (AA) as the additive (200 μg/L in 50% methanol with 0.1% AA in water), and detected instead the adducts of $[M+CH_3COO]^-$ (Fig. S6). These results confirm that SUC can form these adducts under negative ESI-MS conditions. In UHPLC-MS/MS analysis of SUC, because FA is used in the mobile phase, the formation of FA adducts $[M+HCOO]^-$ is reproducible and consistent from day to day, whereas the reproducibility of $[M+Cl]^-$ is poor. Because no HCl is added in the mobile phase, the source of Cl^- for the formation of $[M+Cl]^-$ is likely due to the fragmentation of SUC in the ion source or the impurities in the SUC standards (SUC is prepared via selective chlorination of sucrose [23]). Fig. S5 describes the ionization pathways of SUC and its adducts.

3.2. UHPLC-MS/MS method development

Taking advantage of the reproducible and relatively higher intensity of the $[M+HCOO]^-$ ions, we used $[M+HCOO]^-$ as the precursor ion to develop a UHPLC-MS/MS method for the determination of SUC. Table 1 summarizes the MRM transitions and the optimized MRM parameters for analysis of both ACE and SUC including the internal standards ACE-d4 and SUC-d6. ACE and SUC are completely separated in 3 min with a gradient elution at a flow rate of 0.6 mL/min. The total UHPLC-MS/MS analysis including equilibration takes 5 min to complete. We compared the UHPLC-MRM chromatograms of SUC using $[M-H]^-$, $[M+Cl]^-$, and $[M+HCOO]^-$ as the precursor ions, under the optimized conditions with the injection volume of 20 μL. Fig. 3 clearly shows that $[M+HCOO]^-$ provides better peak intensity (S/N) compared to other ion transitions of $[M-H]^-$ and $[M+Cl]^-$ as the precursor ions. Based on the S/N = 3 in Fig. 3, the LODs of SUC are determined to be 5 μg/L (*m/z* 395–359), 2.1 μg/L (*m/z* 431–395), and 0.22 μg/L for the transition of *m/z* 441–395. Therefore, the sensitivity of *m/z* 441–395 transition of $[M+HCOO]^-$ is about a 20-fold improvement compared to *m/z* 395–359 of $[M-H]^-$ used in the previous methods. Fig. 4 shows the signal stability in MRM of *m/z* 441–395 transition from over 7 injections. The relative standard deviation (RSD) of the peak area is less than 4%.

The FA concentration (in mobile phase) is an important parameter for achieving high sensitivity. After a series of optimization experiments, we found that 0.02% FA provided better signal intensity than 0.1% and 0.05%, as shown in Fig. 4.

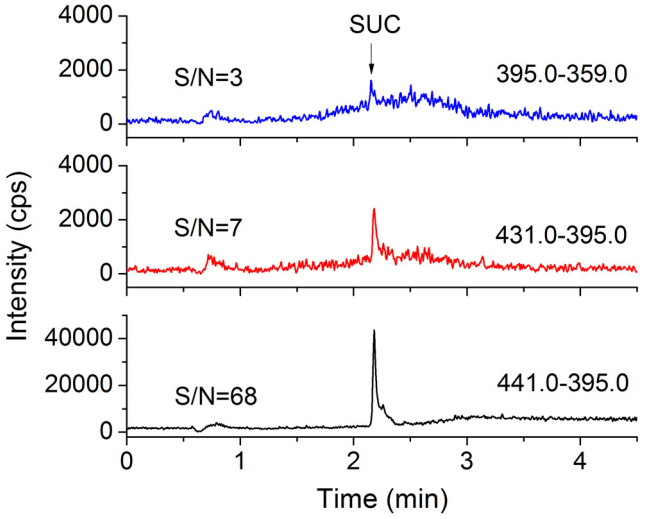

Fig. 3. UHPLC-MRM chromatograms of different precursor ions in ion transitions of SUC (5 μg/L), showing that the highest signal intensity was obtained from the ion transition of *m/z* 441.0–395.0. Mobile phase: (A) water containing 0.1% FA; (B) methanol containing 0.1% FA; gradient: 0–2 min, 2–95% B; 2–4 min, 95% B; 4–4.1 min, 95–2% B; 4.1–5 min, 2%; flow rate, 0.6 mL/min; injection volume, 20 μL.

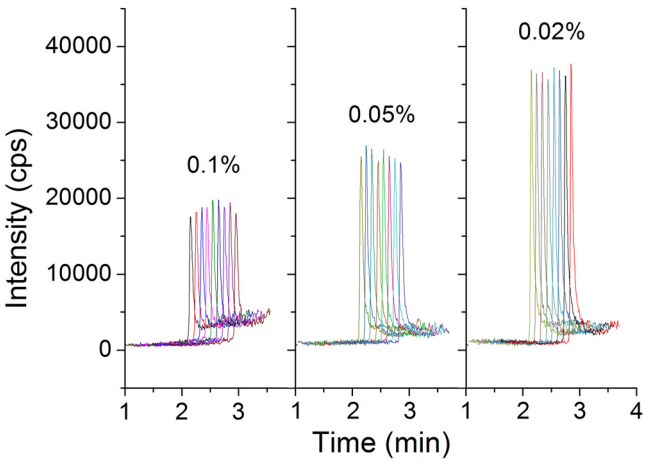

Fig. 4. The UHPLC-MRM chromatograms of new ion transition (*m/z* 441.0–395.0) for SUC (5 μg/L), showing peak intensities and the reproducibility when mobile phase contains 0.1, 0.05, and 0.02% of FA. Chromatography conditions were the same as in Fig. 3 except for the FA concentration.

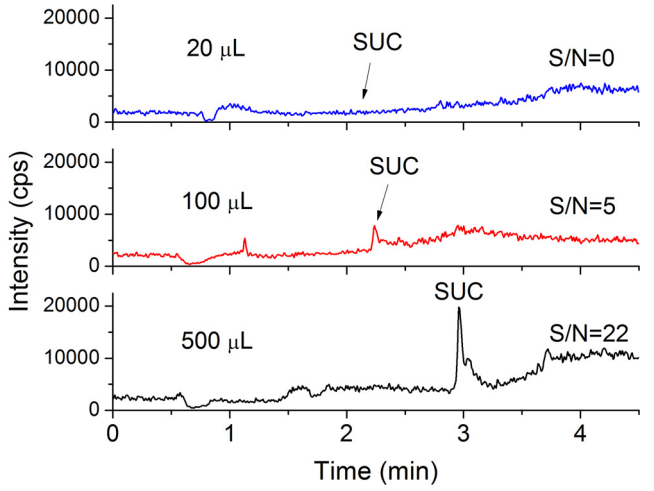

Fig. 5. UHPLC-MRM chromatograms of 0.1 μg/L of SUC obtained with injection volume of 20, 100, and 500 μL. Chromatography conditions were the same as in Fig. 3 except for the injection volume.

To further reduce the LOD, we incorporated the large volume injection (LVI) method that Field and coworkers elegantly demonstrated as a powerful tool to improve the sensitivity of LC-based methods [24,25]. To inject larger volume, we used a Rheodyne 6-port valve equipped with a larger injection loop instead of the autosampler of Agilent 1290. Fig. 5 shows the MRM chromatograms of SUC with the injection volumes of 20, 100, and 500 μL, corresponding to S/N of 0, 5, and 22, respectively. With the injection volume of 500 μL, the LODs for ACE and SUC (Fig. 6) are reduced to 0.2 and 5 ng/L, respectively. Accordingly, the total analysis time increased to 6 min, because the sample loading of 500 μL takes about 50 s. Taking the median ACE and SUC concentrations of 9 and 26 μg/L in wastewater [8], we can use this method to detect ACE and SUC in as much as 45,000 and 5200 times dilution, respectively. The results demonstrate that this large volume injection UHPLC-MS/MS method can directly determine ACE and SUC in water samples without SPE. Therefore, we used this method to investigate wastewater contamination in wells by analyzing SUC and ACE in 100 wells in Alberta.

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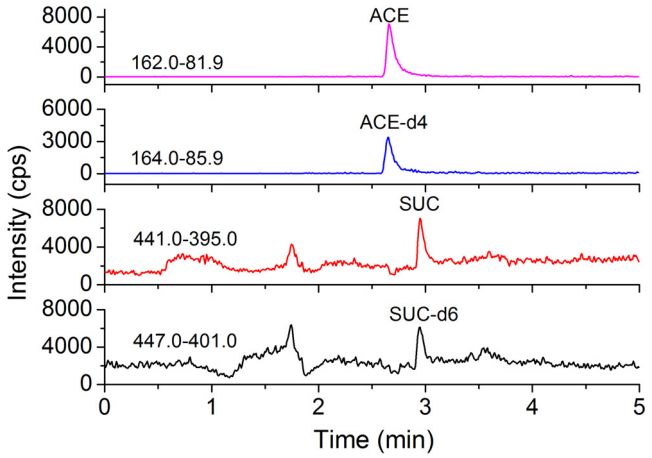

Fig. 6. UHPLC-MRM chromatograms of ACE (1 ng/L) and SUC (10 ng/L) with injection volume of 500 μL. Chromatography conditions were the same as in Fig. 3 except for the FA concentration of 0.02% in the mobile phase.

Table 2
The ACE and SUC in well water samples.

Sample name	ACE (ng/L)	SUC (ng/L)
4	124.3	65
7	635.0	162
9	1184	279
14	12.7	ND
15	166.5	106
16	3.9	ND
20	1.3	541
29	4.8	ND
30	3.5	ND
31	40.6	85
34	0.9	ND
36	1.2	ND
43	1534	161
52	842.7	244
58	63.7	ND
64	6.4	ND
71	118.8	ND
74	8.5	ND
81	8.2	ND
83	12.8	ND
84	5.0	ND
86	12.1	ND
88	111.5	ND
97	60.4	ND

ND: Not detected (<MDL).

3.3. Analysis of groundwater

Table 2 presents the concentrations of ACE and SUC in the 100 well water samples. ACE was detected in 24 samples with concentrations of less than 1–1.2 μg/L. SUC was detected in 8 well water samples with concentrations of 85–540 ng/L. Because both ACE and SUC are wastewater indicators, the presence of these two artificial sweeteners confirms that 24 out of 100 wells (24%) are impacted by wastewater. The main concern of the wastewater impact is the potential contamination of the well water by microbial pathogens, particularly viruses. On the basis of the precautionary principle of public health, these wells should be properly disinfected to ensure the safety of well water for drinking water.

4. Conclusion

We have developed and demonstrated a sensitive ACE and SUC analysis method for direct analysis of well water. The use of the FA adducts $[M+HCOO]^-$ as the precursor ion instead of the commonly used $[M-H]^-$ for SUC analysis in the negative MRM mode dramatically enhances the sensitivity of SUC. Combining the new ESI-MS method with the LVI approach, the UHPLC-MS/MS method significantly reduces LODs for SUC and ACE to 5 and 0.2 ng/L, respectively, without the need of preconcentration. We have successfully applied our method to investigate potential wastewater contamination in 100 domestic wells in Alberta. As many as 24% of the well water samples show wastewater contamination, highlighting the need for monitoring domestic well water. The method is simple, sensitive, and reliable for routine monitoring of wastewater contamination.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chroma.2014.07.035.

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