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Integration of solid phase extraction with HILIC-MS/MS for analysis of free amino acids in source water

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ABSTRACT

Amino acids (AAs) are prevalent in source water, particularly during spring run-off. Monitoring of amino acids in source water is desirable for water treatment plants (WTP) to indicate changes in source water quality. The objective of this study was to establish analytical procedures for reliable monitoring of amino acids in source water. Therefore, we examined two different methods, large volume inject (LVI) and solid phase extraction (SPE), for sample preparation prior to HILIC-MS/MS. The LVI-HILIC-MS/MS method can provide fast and sensitive detection for clean samples, but suffers from matrix effects, resulting in irreproducible separation and shortening column lifetime. We have demonstrated that SPE was necessary prior to HILIC-MS/MS to achieve reproducible and reliable quantification of AAs in source water. A natural heterocyclic amine 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCCA) was also included in the method to indicate changes in other natural nitrogenous compounds in source water. The SPE-HILIC-MS/MS method was able to achieve limits of detection from 2.6-3400 ng/L for the amino acids and MTCCA with RSDs (n=3) of 1.1%-4.8%. As well, retention times (RT) of the analytes were reproducible with variation less than 0.01 min (n=3) through the entire project. We further applied the SPE-HILIC-MS/MS method to determine AAs in authentic source water samples collected from two drinking water treatment plants (WTPs) during the 2021 spring run-off season. The results support that the SPE-HILIC-MS/MS method does not require derivatization and can provide reliable, accurate, and robust analysis of AAs and MTCCA in source water, supporting future monitoring of source water quality.

Introduction

Dissolved organic carbon (DOC) and dissolved organic nitrogen (DON) are commonly used to indicate the contents of natural organic matter (NOM) present in source water. Water treatment plants (WTPs) optimize disinfection parameters based on both DOC and DON to help control the forma-

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tion of disinfection byproducts (DBPs) in finished water. Current treatment technologies cannot completely remove NOM, particularly, the fraction that contains low molecular weight and highly soluble organic compounds (Dotson and Westerhoff, 2009; Lee and Westerhoff, 2006; Lee et al., 2006b). The composition of DON and DOC in source water can vary significantly due to seasonal climate changes like spring run-off, run-off from agricultural and urban sources, wastewater impact, and algal blooms (Lusk et al., 2020; Westerhoff and Mash, 2002; Lepisto et al., 2021; Mattsson et al., 2015; Sharp et al., 2006). These increases in DOC and DON require timely adjustment of disinfection processes to minimize DBP formation while maintaining complete inactivation of microbial pathogens. However, predicting the start of spring run-off is difficult. Therefore, identifying chemical markers to indicate the on-set of spring run-off is desirable. This can assist WTPs to promptly optimize treatment processes to minimize the DBPs produced.

Amino acids are ubiquitous in the environment, especially surrounding farming areas. Therefore, spring run-off water should contain higher levels of amino acids. Total amino acids (AAs), including peptides and proteins, constitutes up to 75% of DON in surface water (Westerhoff and Mash, 2002). Free AAs make up approximately 5%-10% of the total AAs (Dotson and Westerhoff, 2009; Peake et al., 1972). Several studies have reported an average concentration of free AAs between 500 - 30000 ng/L in water (Brosillon et al., 2009; Dotson and Westerhoff, 2009; How et al., 2014; Lee et al., 2006a). Because of the small molecular size and high water solubility, AAs are difficult to remove during the water treatment process (Dotson and Westerhoff, 2009). This is a significant issue for WTPs because chlorination and chloramination of AAs in source water can form odorous and/or nitrogenous DBPs (Chen and Westerhoff, 2010; Fox et al., 1997; Scully et al., 1988; Conyers and Scully, 1997; Freuze et al., 2004; Brosillon et al., 2009; Cai et al., 2019; Dong et al., 2021; Freuze et al., 2005; How et al., 2018; How et al., 2017). Therefore, it is useful to monitor amino acids in source waters for controlling odorous N-DBPs.

Liquid chromatography tandem mass spectrometry (LC-MS/MS) is commonly used to analyze AAs in water. Current LC-MS/MS analysis of AAs typically requires multiple sample preparation steps including derivatization and solid phase extraction (SPE) (Armstrong et al., 2007; How et al., 2014). Derivatization improves the separation and ionization efficiency, while SPE enriches analytes in samples. For example, How et al., used SPE-RPLC-MS/MS for 14 compounds in water to achieve limits of detection of 200-3800 ng/L (How et al., 2014). Routine monitoring of AAs in water requires a simple and rapid method. Therefore, it is desirable to simplify sample preparation, such as eliminating preconcentration and extraction procedures (Blackstock et al., 2017; Wu et al., 2014). Large volume injection (LVI) methods have been used to eliminate the preconcentration for analysis of other types of environmental contaminants in water (Backe and Field, 2012; Backe et al., 2014; Backe et al., 2011; Wu et al., 2014). Therefore, we examined LVI for analysis of AAs in source water in this study.

Reverse phase liquid chromatography (RPLC) separation does not adequately separate AAs because of their hydrophilic nature with varying isoelectric points and range from neutral, acidic to basic groups. For improving RPLC separation, AAs are often derivatized with large carbon-based functional groups to enhance interaction with the nonpolar stationary phase of RPLC (Dietzen et al., 2008; Krumpochova et al., 2015; Tian et al., 2017). Alternatively, hydrophilic interaction liquid chromatography (HILIC) can be used to separate hydrophilic compounds. HILIC has been applied for separation of amino acids in biological, food, and plant samples (Chirita et al., 2010; Guo et al., 2007; Ikegami et al., 2008; Schlichtherle-Cerny et al., 2003; Tang et al., 2016; Tolstikov and Fiehn, 2002). Krumpochova et al. compared 3 methods for determination of 17 amino acids in cellular matrices. Two methods required derivatization of amino acids prior to GC-MS/MS and RPLC-MS/MS analysis, which provided limits of detection (LODs) of 100 nmol/L and 50 nmol/L, respectively. The third method, HILIC-MS/MS, did not derivatize amino acids or use any other sample preparation prior to the analysis and achieved LODs of 1-300 nmol/L. However, the study observed that HILIC provided better separation of all amino acids compared to the GC-MS and RPLC-MS methods, it suffered significantly higher matrix effects (Krumpochova et al., 2015). In this study, we aimed to eliminate the derivatization step and reduce matrix effects while achieving reproducible HILIC separation and reliable quantification of AAs in source water using a HILIC-MS/MS method. Additionally, we took advantage of HILIC separations that use a high percentage of organic solvent (~65%-95%, typically acetonitrile or methanol) in its mobile phase to enhance electrospray ionization (ESI) efficiency and sensitivity of MS detection (Backe et al., 2014).

In this study, we developed and evaluated both LVI-HILIC-MS/MS and SPE-HILIC-MS/MS methods for analysis of AAs and heterocyclic amine 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCCA) in source water without derivatization. The analytical merits of both methods were assessed and compared. We demonstrated that the SPE-HILIC-MS/MS method was more reliable, accurate, and robust for routine monitoring, compared to the LIV-HILIC-MS/MS method. Finally, we applied the SPE-HILIC-MS/MS method to monitor amino acid concentrations in authentic source water samples collected from 2 WTPs during the 2021 spring run-off season.

1. Materials and methods

1.1. *Chemicals and materials*

Formic acid (FA), ammonium formate (AF), and polyvinylidene difluoride (PVDF) syringe filters (0.22 μm and 0.45 μm), nylon disk filters (0.45 μm), and 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCCA) were purchased from Sigma-Aldrich (St. Louis, MO). Optima water, acetonitrile (ACN), methanol (MeOH), aqueous ammonium hydroxide (30% wt), and amino acid standards were from Fisher Scientific (Fair Lawn, NJ). Oasis MAX cartridges (6 cc, 150 mg) were purchased from Waters (Milford, MA).

1.2. *LVI-HILIC-MS/MS method*

An Agilent 1290 series HPLC system was used for HILIC analysis. The LVI-HILIC-MS/MS method consisted of an InfinityLab

Table 1 – Analytical figures of merit for the SPE-HILIC-MS/MS analysis of AAs and MTCCA.

Analyte	LOD (ng/L)	LOQ (ng/L)	Linear Range (ng/L)	R^2	Δ signal (RSD, %, n=3)	Δ RT (min, n=3)
PHE	57	190	200-500000	0.9996	3.1	0.00
IEU	58	190	200-500000	0.9984	4.8	0.01
TRY	120	400	500-500000	0.9993	3.9	0.00
ISO	62	210	500-500000	0.9994	2.4	0.01
MET	2200	7500	10000-1000000	0.9986	3.6	0.01
VAL	170	590	500-500000	0.9839	2.5	0.02
PRO	23	75	100-500000	0.9999	2.3	0.01
TYR	97	320	500-500000	0.9998	3.0	0.01
CYS	2300	7600	10000-500000	0.9999	1.3	0.01
ALA	3400	1100	2000-1000000	0.9987	1.1	0.00
THR	190	630	1000-500000	0.9972	2.3	0.01
GLY	1900	6200	10000-1000000	0.9994	4.1	0.00
GLU	72	240	1000-1000000	0.9998	2.5	0.01
SER	170	570	2000-500000	0.9995	3.3	0.00
ASP	280	920	2000-1000000	0.9992	2.7	0.01
GLUA	88	300	1000-1000000	0.9996	4.7	0.01
ASPA	230	780	5000-1000000	0.9990	1.2	0.01
HIS	42	140	1000-500000	0.9987	4.0	0.01
ARG	330	1100	10000-1000000	0.9990	1.4	0.01
LYS	160	550	10000-1000000	0.9986	2.3	0.01
MTCCA	2.6	8.6	10-100000	0.9997	1.6	0.00

Poroshell 120 HILIC column (1.9 µm × 100 mm × 2.1 mm ID) (Agilent, Santa Clara, CA). The specific method parameters for the SPE-HILIC-MS/MS method including mobile phase, gradient, autosampler conditions, and column temperature can be found in Appendix A Table S1. A Sciex 5500 triple quad was used for HILIC analysis. Mass spectrometry parameters were optimized with standards first using direct injection, and then coupled with the HPLC. Appendix A Table S2 presents the optimized MS ionization parameters for the LVI-HILIC method, and Appendix A Table S3 shows the optimized multiple reaction monitoring (MRM) transitions and parameters for the LVI-HILIC-MS/MS method. In this study, a standard mixture of 20 amino acids was used for method development. The limits of detection (LODs S/N = 3) of the LVI-HILIC-MS/MS methods are shown in Appendix A Table S4. Cysteine was difficult to detect during optimization and had low sensitivity. Cysteine showed better sensitivity when the ion source temperature and voltage was lowered. However, this resulted in a loss of sensitivity of many other amino acids. For this preliminary method, we focused on achieving better sensitivity for the majority of amino acids.

1.3. *SPE-HILIC-MS/MS method*

An Agilent 1290 series HPLC system was used for HILIC analysis in conjunction with a triple quadrupole mass spectrometer (Sciex 5500) for targeted analysis. The HILIC method consisted of an InfinityLab Poroshell 120 HILIC-Z column (2.7 μm × 100 mm × 2.1 mm ID) (Agilent, Santa Clara, CA). The specific method parameters for the SPE-HILIC-MS/MS method including mobile phase, gradient, autosampler conditions, and column temperature can be found in Appendix A Table S5. A Sciex 5500 triple quad was used for HILIC analysis. As the LVI method stated, MS parameters were optimized with standards first using direct injection, and then coupled with the HPLC. Appendix A Table S6 presents the optimized MS ionization parameters for the SPE-HILIC method, and Appendix A Table 7 shows the optimized MRM transitions and parameters for the SPE-HILIC-MS/MS method. In this study, a standard mixture of 20 amino acids was used for method development. The LODs ($S/N = 3$) of the SPE-HILIC-MS/MS method is shown in Table 1. The MS method parameters were re-optimized for the SPE-HILIC-MS/MS method. This was done so that all 20 AAs were detectable. As stated in Section 2.2, cysteine showed better sensitivity when the ion source temperature and voltage was lowered. Thus, the SPE-HILIC-MS/MS method was optimized with a lower ionization voltage and ion source temperature. A schematic of the general steps for the SPE-HILIC-MS/MS method are included in Appendix A Fig. S1.

1.4. *Sample collection*

To demonstrate the applicability of the developed method, we determined the amino acids present in authentic source water samples collected during spring run-off period. The samples were source water collected from North Saskatchewan River and were collected at two drinking water treatment plants (WTPs), WTP1 and WTP2. Source water samples were collected on March 1; March 4; March 8; March 15; March 17; March 18; March 19. All samples were collected in 4L amber glass bottles. Bottles were rinsed three times with sample before they were fully filled without headspace remaining. All of the water samples were filtered through 1.5 µm glass microfiber filters followed by 0.45 µm nylon membrane disk filters to remove particles, and then stored at 4°C before further analysis.

1.5. *Sample preparation for SPE-HILIC-MS/MS*

Water samples were prepared by SPE. Aliquots of 500 mL of water sample were first prepared with addition of 2 mL of aqueous ammonium hydroxide solution (30% wt). Oasis MAX

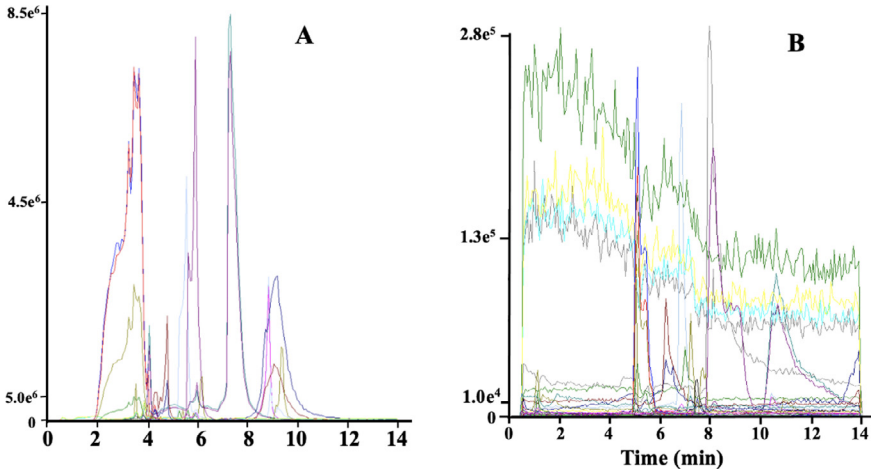

Fig. 1 – Total ion chromatograms for all analytes and their two MRM transitions using the LVI-HILIC-MS/MS method. (A) Standard solution mix run at 1000 ng/L. (B) Authentic water sample with 1000 ng/L standard addition.

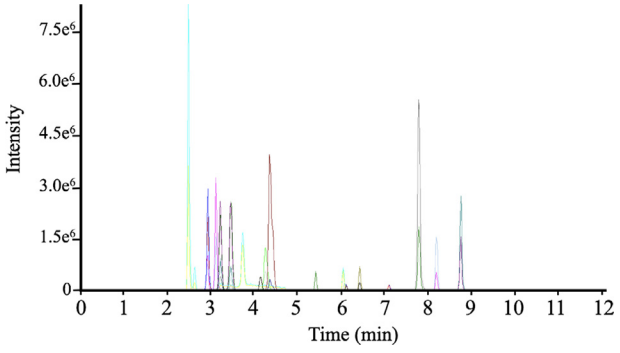

Fig. 2 – Total ion chromatograms of all analytes and their two MRM transitions using the SPE-HILIC-MS/MS method. Standards were run at 200000 ng/L.

cartridges (6 cc, 150 mg, Waters, Milford, MA) were first preconditioned with methanol (2 mL), followed by aqueous ammonium hydroxide solution (4 mL, 0.5% wt). Water samples were then loaded and passed through the MAX cartridge at approximately 1-2 mL/min. Following loading, SPE cartridges were washed with aqueous ammonium hydroxide solution (2 mL, 0.5% wt) and then eluted with methanol (10 mL, containing 0.2% Formic acid). The eluate was concentrated to 0.1 mL under a gentle stream of nitrogen. The extracted samples were reconstituted with 0.4 mL acetonitrile to a final volume of 0.5 mL and filtered using 0.25 µm PVDF syringe filters before HILIC-MS/MS analysis.

2. Results and discussion

2.1. *LVI-HILIC-MS/MS method*

First, we developed a simple and fast method without the requirement of preconcentration and derivatization. This method used direct LVIs of 100 µL water samples with HILIC-MS/MS analysis. Because of its ability to retain small and polar molecules, HILIC was able to provide good separation of amino acids (EIC of all compounds can be found in Appendix A Fig. S2). After subsequent optimization of the ESI parameters, the limits of detection (LOD at a minimum S/N=3) of the LVI-HILIC-MS/MS method were estimated in the range of 0.17–750 ng/L for all amino acids (Appendix A Table S4), except for cysteine which was undetectable. As discussed in Section 2.2, cysteine was not detected in the LVI method. Detection of cysteine required a lower ionization voltage and temperature, which resulted in significantly lower sensitivity for all other amino acids. Thus, the LVI method was optimized for the majority of amino acids, except cysteine, for fast and sensitive analysis.

While the LVI method provided simple and fast analysis of authentic water samples, it suffered from retention time shift. Additionally, changes in peak shape over time occured after multiple injections of authentic water samples due to matrix effects. Fig. 1 shows the TIC of the LVI-HILIC-MS/MS method of a 1000 ng/L standard (Fig. 1A) and of an authentic water sample with 1000 ng/L standard addition (Fig. 1B). The change in peak shape, increased background, and shift in retention time is clearly visible between the standards and the authentic water samples in Fig. 1. This is likely due to LVI resulting in increased matrix effects on both the HILIC separation and ESI ionization. Additionally, LVI significantly reduced column lifetime. Column cleaning did not improve the separation. These difficulties led us to develop a SPE method combined with HILIC-MS/MS for analysis of AAs in source water.

2.2. *SPE-HILIC-MS/MS method*

To overcome the difficulties encountered in the LVI-HILIC-MS/MS method, LVI was replaced with SPE. Although SPE is more time consuming compared to LVI, SPE can enrich the analytes and remove matrix to provide improved HILIC separation and ESI-MS detection. With the introduction of SPE to HILIC, the MS parameters were re-optimized so that all 20 amino acids, particularly cysteine, were detectable. As stated in Section 3.1, cysteine was better detected at lower ionization voltages and temperatures, though this lowered the sensitivity of other amino acids. However, with the addition of

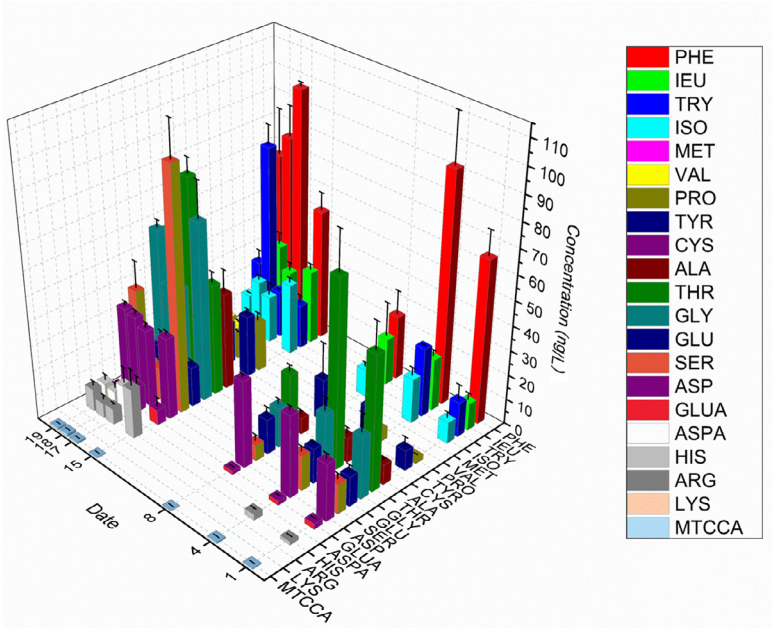

Fig. 3 – Amino acids and MTCCA detected using the SPE-HILIC-MS/MS in authentic water samples collected at WTP1 during spring 2021 run-off.

SPE to enrich and clean-up samples, the method was able to detect amino acids in authentic source water samples. After integrating SPE with the HILIC-MS/MS method, we obtained efficient separation (good peak shapes), and reproducible retention times. Fig. 2 shows the total ion chromatogram of the SPE-HILIC-MS/MS for all compounds at 200000 ng/L (EIC of all compounds can be found in Appendix A Fig. S3). The compound MTCCA was also included in analysis because it was recently identified as a natural heterocyclic nitrogenous compound and found to be a precursor for multiple nitrosamines (Qiu et al., 2021). Therefore, it was included in the method as an additional target.

Table 1 summarizes the analytical merits of the SPE-HILIC-MS/MS method. It was able to achieve limits of detection (LODs) in the range of 2.6-3400 ng/L and LOQ in the range of 8.6-7600 ng/L. The relative standard deviations (RSD%) for all compounds were in the range of 1.1%-4.8% (n=3). Table 2 presents the recovery and reproducibility of the SPE in the range of 63%-77% at 100000 ng/L (n=3) with RSDs in the range of 2%-35% (n=3) for the 20 AAs and MTCCA. The SPE-HILIC-MS/MS method provided reproducible and reliable quantification of all 20 AAs and MTCCA. Next, we demonstrated its application for monitoring amino acids and MTCCA in authentic source water collected during spring run-off.

Table 2 – Recovery and RSD of the SPE-HILIC-MS/MS method (n=3, 100 ng/L each).

Analyte	% Recovery	% RSD
PHE	73	6
IEU	68	5.5
TRY	72	5.9
ISO	66	5
MET	75	5.8
VAL	63	8.9
PRO	77	6.1
TYR	65	6.4
CYS	74	7.5
ALA	64	5.1
THR	66	6
GLY	74	5.9
GLU	73	4.7
SER	67	2.8
ASP	72	2
GLUA	69	3.4
ASPA	72	6.3
HIS	64	2.2
ARG	63	33
LYS	63	35
MTCCA	84	4.9

2.3. *Amino acids and MTCCA in authentic source water samples collected during spring run-off*

Source water samples were collected at two WTPs during the 2021 spring run-off period from March 1st to March 19th. Fig. 3 shows the levels of amino acids detected using the SPE-HILIC-MS/MS method in each sample with the corresponding collection date at WTP1. Fig. 4 shows those collected at WTP2. A total of 16 amino acids, as well as MTCCA, were detected at WTP1. The concentrations ranged from 0.01-70 ng/L over the course of sampling, specific values for each compound at WTP1 can be found in Appendix A Table S8. Similarly, a total of 16 amino acids, as well as MTCCA, were detected in the samples collected at WTP2. The concentrations ranged from 0.02-98 ng/L over the course of sampling, specific values for each compound at WTP2 can be found in Appendix A table S9. Overall, phenylalanine (PHE), threonine (THR), and glycine (GLY)

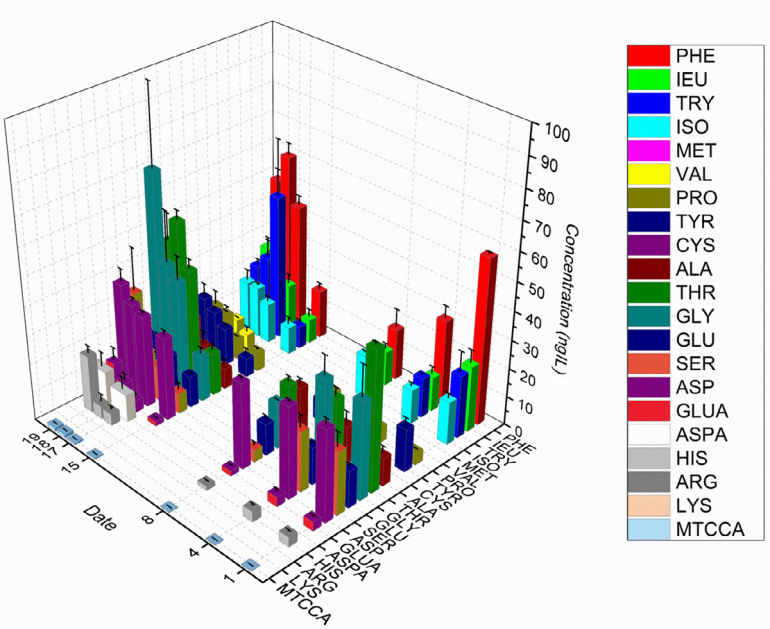

Fig. 4 – AAs and MTCCA detected using the SPE-HILIC-MS/MS in authentic water samples collected at WTP2 during spring 2021 run-off.

had the highest concentrations in the water samples from both WTPs. In general, the highest concentrations of AAs were found in the March 19 samples. Similar to the AA results, the concentration of MTCCA was highest in the March 19 samples. Generally, the concentration of MTCCA was lower than most of the AAs detected in all samples. These results demonstrate the application of the SPE-HILIC-MS/MS method for monitoring highly soluble compounds in source water. This pilot study served as testing and preparation for future monitoring.

3. Conclusion

This study demonstrated that the SPE-HILIC-MS/MS method can reliably and reproducibly quantify amino acids and MTCCA in water. The results highlight the integration of HILICs capability to separate small and polar compounds with SPE providing sample clean-up and reducing matrix effects. The analysis of spring run-off samples confirmed the capability of the SPE-HILIC-MS/MS method to provide reproducible, sensitive, and reliable determination of amino acids and MTCCA in authentic samples. Integrating SPE with HILIC provided multiple advantages compared to the LVI method. These include longer column lifetime, which is important as HILIC columns are expensive; reproducible retention time (RT), whereas LVI-HILIC suffered retention time shift; no requirement for derivatization to achieve sensitive analysis. The extended HILIC column lifetime, reproducible separation, sensitive and reliable quantification validate the SPE-HILIC-MS/MS method as a suitable choice for future monitoring of amino acids and other water soluble compounds, such as MTCCA, in authentic water samples. This pilot study establishes the procedures and method for future large monitoring project.

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Appendix A Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jes.2022.04.025.

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