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Determination of pharmaceutical and personal care products in wastewater by capillary electrophoresis with UV detection

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ABSTRACT

Capillary electrophoresis (CE) offers a fast and cost-effective alternative analytical technique to LC-MS/MS for separation and quantitation of many PPCP compounds in wastewater. In this study, we have developed a method that can simultaneously analyze eight different PPCP compounds in untreated wastewater (ibuprofen, triclosan, carbamazepine, caffeine, acetaminophen, sulfamethoxazole, trimethoprim, and lincomycin), using capillary electrophoresis with UV detection (CE-UV). The method detection limit (MDL) ranged from 1.6 to 68.7 ppb through solid phase extraction. The standard limit of quantification (LOQ) ranged from 0.63 to 7.72 ppm. Factors affecting separation and quantification of PPCPs, such as pH, electrophoretic potential, buffer strength, buffer type, and additives, were investigated and optimized. Water samples from two different wastewater treatment plants were collected and analyzed. The results obtained were comparable with those of LC–MS/MS. The technique developed in this study provides a low cost, simple, fast, and relatively sensitive method for determination of various PPCPs in wastewater samples for PPCP screening.

1. Introduction

Pharmaceutical and personal care products (PPCPs) are used and disposed of every day. Over time various PPCP compounds are transported into different water sources, including wastewater [1–3]. Pharmaceuticals in natural and wastewater can also result in their occurrence in drinking water with unknown impacts on human health. Even though the risk to humans of pharmaceuticals in waters is not fully understood, due to their biologically active nature, it is important to know the concentrations of these compounds in natural and wastewaters. In recent years, a number of PPCP compounds have been detected in many natural water systems globally, including rivers, lakes, and reservoirs [4–15]. Therefore, the U.S. EPA has heightened government awareness of the possible health hazards associated with PPCPs [5,16]. The EPA has created a web site that lists the published literature relevant to PPCPs as potential environmental contaminants [17]. This web site also contains a specific listing of Drug Disposal and Environmental Stewardship Contamination topics, and now includes over 2000 publications.

Determining the level of PPCPs in wastewater, prior to treatment, is important for determining the effectiveness of the treatment. Many methods have been developed for identification and quantification of PPCPs in water samples by using liquid chromatography – tandem mass spectrometry (LC–MS/MS) [15,18–23]. However, separation and quantification of PPCP compounds using capillary electrophoresis (CE) in wastewater samples have not been extensively investigated based on our knowledge. Instrument availability, failure and disaster recovery plans may require development of alternative and higher separation techniques, especially for routine testing laboratories to ensure continuity of measurements. CE has been demonstrated to be a versatile separation technique with high resolution for many different compounds, short analysis time, and low waste generation [24,25]. CE truly offers a simple, fast and cost-effective alternative to LC–MS/MS for the analysis of PPCPs in wastewater. The advantages of CE over LC–MS/MS are the cost and flexible selectivity through buffer concentration, additives, and pH tuning, which is crucial for separation of many PPCP compounds in wastewater samples. Several CE methods have been developed to measure individual PPCP compounds in natural water [18], livestock feed [26], meat and groundwater [27], dietary products [28] and other matrices [29,30]. However, no CE methods have been developed for determining PPCP in wastewater. In this study, we developed a novel CE-UV method that can detect lower ppm levels (<10 ppm) of PPCPs for direct injection of standards and ppb levels (<70 ppb) of PPCPs in wastewater through sample preparation. The method is capable of analyzing eight specific PPCPs in Missouri wastewaters. The selection of these eight PPCP compounds was based on the occurrence of PPCPs in Missouri's surface water systems as delineated in our previous study.

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2. Material and methods

2.1. Chemicals

Acetaminophen, caffeine, trimethoprim, carbamazepine, ibuprofen, sulfamethoxazole, 1,4,7,10,13,16-hexaoxacyclooctadecane (18 Crown 6), boric acid (H_3BO_3), and tetrasodium ethylenediamine tetraacetate hydrate ($Na_4EDTA{\cdot}2H_2O$) were purchased from Sigma–Aldrich (St. Louis, MO). Sodium phosphate dibasic (Na_2HPO_4), phosphoric acid (85%), methanol (Optima grade) and sodium hydroxide were purchased from Fisher Scientific (Fair Lawn, NJ). Lincomycin was purchased from MP Biomedicals (Aurora, OH). Triclosan (Irgasan) was purchased from Fluka (Switzerland). Ultra pure water (18.2 MΩ) was prepared by a Millipore Advantage A10 Milli-Q system.

2.2. Running buffer solutions

A 50 mM borate buffer solution was prepared using ultra pure water and boric acid. The buffer was prepared by dissolving approximately 1.55 g of boric acid in 400 mL of ultra pure water. The solution was transferred to a 500 mL volumetric flask and diluted to volume with ultra pure water. The resulting mixture was filtered via vacuum filtration through a 0.22 μm nylon membrane filter (Osmonics, Inc., Minnetonka, MN). The borate buffer was split into two aliquots and the pH of the aliquots was adjusted using 1 N sodium hydroxide to 8.52 and 9.51.

Phosphate buffer solutions (5, 10, 50, 100 mM) were prepared using ultra pure water and sodium phosphate dibasic. The buffer was prepared by dissolving the sodium phosphate dibasic in ultra pure water (to about 80% of the total volume). The solutions were transferred to a volumetric flask and diluted to volume with ultra pure water. The resulting solutions were filtered via vacuum filtration through a 0.22 μm nylon membrane filter (Osmonics, Inc., Minnetonka, MN) for the buffer selection experiment and 0.45 μm nylon membrane filters (Pall, Inc., Ann Arbor, MI) for all subsequent experiments. The pH of the phosphate buffers was adjusted using concentrated phosphoric acid (85%) and an Accumet® Excel XL15 pH meter from Fisher Scientific (Fair Lawn, NJ).

To enhance separation of the selected PPCP compounds, the crown ether 18 Crown 6 was added to the buffer solution [31–33].

2.3. Standard preparation

Most PPCP compounds have minimal solubility in pure water. Therefore, individual standards were initially prepared in Optima grade methanol. A mixture of the eight compounds was prepared by combining 1.0 mL of each individually prepared standard into one solution denoted as PS-1. The first calibration standard (CS-1) was prepared by diluting 100 μL of to the PS-1 solution into 1500 μL of running buffer. The concentrations of the individual compounds in CS-1 solution ranged from 8.1 to 131.8 ppm. The remaining calibration standards (CS-2 through CS-8) were created from CS-1. These standards were used in the determination of the instrumental detection limit (IDL), instrument quantification limit (IQL), method detection limit (MDL).

2.4. Wastewater sample collection and preparation

Wastewater samples were collected from two independent wastewater treatment facilities in Mid-Missouri within one week from each other. Each sample was collected in a 4-L amber glass bottle (rinsed thoroughly with ultra-pure water) to minimize contamination and to prevent photo degradation. The water sample collection procedures were as follows: using a large pre-cleaned wide mouth bottle or beaker to take the water at a representative area, and carefully fill the sample bottle from the container to completely full but take care not to flush out solid chemical in the bottle. No air bubbles should pass through the sample as the bottle is filled, or be trapped in the sample when the bottle is sealed. Seal the bottle and agitate by hand for 1 min. Place it in cooler with frozen ice pack. The wastewater samples were refrigerated (~4 °C) until analyzed. Step wise filtration using filter paper and 0.45 μm nylon membrane filters was performed on each sample to remove as much of the physical particulate prior to solid phase extraction (SPE) of the PPCPs. After filtration, the pH of the samples was adjusted to 2.0 ± 0.2 with concentrated hydrochloric acid [15,19].

Samples were separated into two groups with 1-L aliquots for each wastewater source. Five-hundred milligrams of $Na_4EDTA{\cdot}2H_2O$ were added to each of the samples as a stabilizing agent during the SPE process [15,19]. Solid phase extraction was performed by following EPA method 1694. Briefly, the SPE was accomplished using Waters Corp. Oasis HLB 20 cm^3 cartridges. The cartridges were pre-conditioned with 20 mL of methanol, 20 mL of ultra-pure water adjusted to pH 2.0, and 20 mL of unbuffered ultra-pure water [15,19]. The wastewater was passed through the SPE cartridges at a rate of one drop every 2-to-3 s. After the extraction was complete, 20 mL of ultra-pure water were passed through the SPE membrane to remove the EDTA stabilizer [15,19]. The retained PPCPs were eluted into 50 mL glass centrifuge tubes using 20 mL of methanol, followed by 20 mL of methanol and acetone (1:1, v/v) at a rate of about one drop every 2-to-3 s [15,19]. The eluent was evaporated to about 100 μL using a Turbovap LV operating at 50 ± 5 °C [15,19]. The samples were reconstituted by adding 600 μL of methanol to the eluent. The reconstituted solution was then transferred to a 1.5 mL CE vial. Finally, 100 μL of the reconstituted sample solution was diluted to 1600 μL with CE running buffer and then was injected for analysis.

2.5. Instrumentation

A CARY 50 Bio UV-Visible Spectrophotometer (Agilent Technologies) was used to measure the absorption properties of each compound to ensure that the best UV wavelength was selected to detect the analytes.

The CE instrumentation was a Beckman Coulter P/ACETM MDQ CE System with UV detection. The capillary used was from Polymicro Technologies (Phoenix, AZ) 50 μm i.d. × 55 cm (45 cm to the detecion window). The capillary was pretreated with sodium hydroxide (1.0 N) for 30 min, ultra-pure water rinse for 15 min, hydrochloric acid (1.0 N) for 10 min, and a final rinse using ultra-pure water for 15 min. Finally, the capillary was rinsed and conditioned with running buffer. Samples were injected using pressure injection (0.5 psi).

An algorithm was written using Microsoft Excel to remove the baseline noise. For the standard injections, the algorithm was applied to any other noise not associated with the standard peak to aid in peak area integration for quantification purposes. For the samples, the algorithm was applied only to clean up the baseline noise to assist in peak area determination.

3. Results and discussion

3.1. UV-absorbance evaluation

The CE-UV instrument is configured to run one of four different wavelengths, 200, 214, 254 and 280 nm. Therefore, UV absorbance scans were performed on the PPCP standards to determine the best

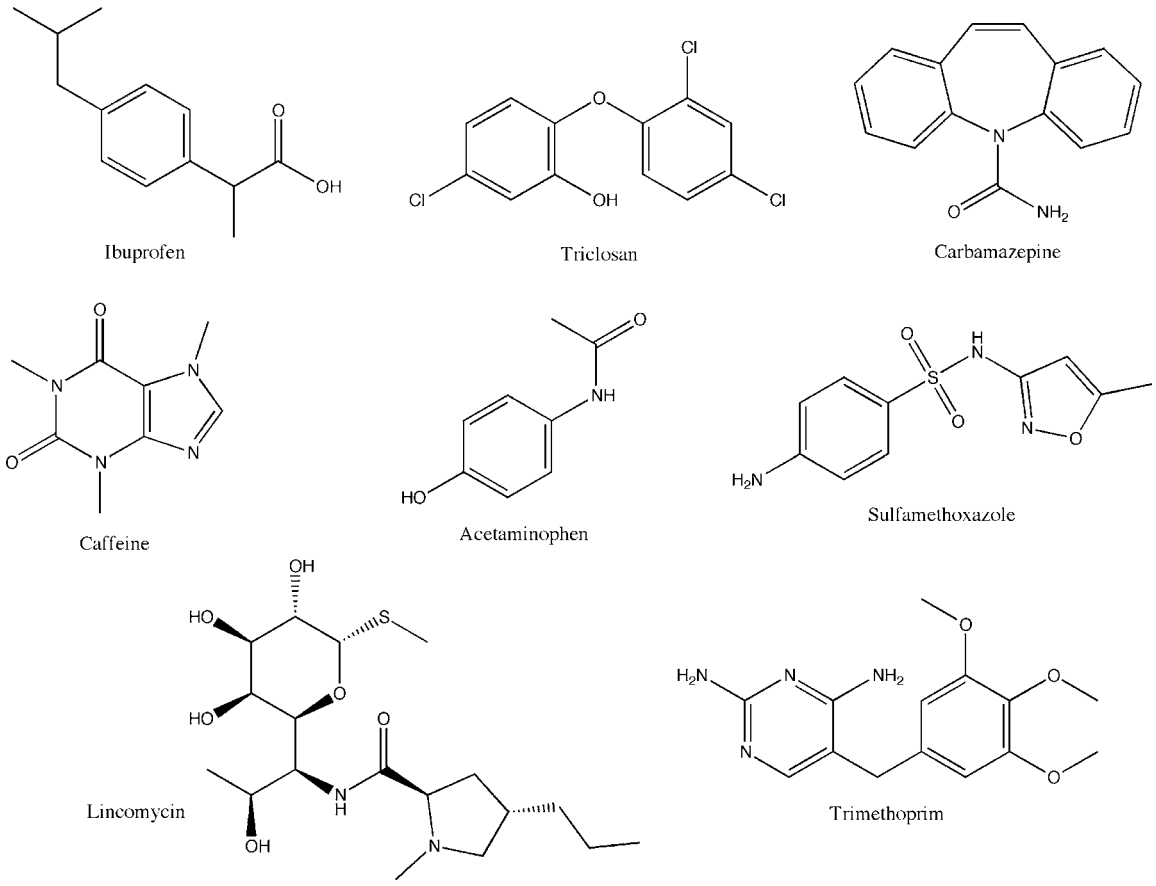

Fig. 1. Structures of PPCP compounds investigated.

wavelength for analysis. Based on the UV scans obtained, 214 nm was selected as the detection wavelength. The concentrations of the standards during this experiment were approximately 1 mg/mL in methanol (data not shown).

3.2. Buffer selection

Several methods have been published for quantifying individual PPCPs in unrelated matrices by CE [26,29,34]. The buffer selection varied from phosphate to borate, ammonium acetate, lactic acid, Tris, and sodium carbonate [26,30,34–36]. Several additives were also used to aid separation including SDS, methanol, acetonitrile, and cyclodextrine [29,30,36]. Initial investigations began with alkaline phosphate and borate buffer solutions. Based on the literature, useful pHs for phosphate buffers range from 1.14 to 3.14 and 6.20 to 8.20 and for borate buffers 8.14 to 10.14 [37]. Some of the compounds under investigation were not soluble in acid conditions. Therefore, acidic pHs were excluded. A study was performed to compare borate and phosphate buffers with pHs that encompassed the recommended alkaline range. Starting buffer strength of 50 mM was chosen and standards were injected individually for screening. Additionally, the electrophoretic potential was evaluated for each pH. The voltage ranged from 10 to 30 kV. Results demonstrated that phosphate buffer, pH 7.2, and 20 kV showed the most promise. One reason for phosphate buffer performing better than the borate buffer is that many of our compounds have hydroxyl functional groups, which can complex with boric-based buffers and affect separation of the compounds [38]. The structures of the PPCP compounds investigated are shown in Fig. 1.

3.3. Buffer strength

Preliminary experimental data showed that simple selection of buffer type and pH was insufficient to adequately separate all of the PPCP compounds. Since buffer strength can affect the electroosmotic flow (EOF) of the system and the separation [39], buffer strengths of 10, 50, and 100 mM were compared using electrophoretic potentials of 10, 20, and 30 kV. Results showed that buffer strength of 10 and 50 mM did not provide adequate separation. Our observations confirmed previous findings that the solute migration time was inversely proportional to the cationic charge density of the buffer [40]. At 100 mM, there was still room for improvement, but the current was approaching 150 μA and the potential loss of resolution due to Joule heating was becoming a concern [37,39]. Buffer strength of 100 mM and 20 kV was selected for this study.

3.4. Buffer pH study

It is well known that buffer pH has a significant effect on CE separations due its impact on the magnitude of EOF [37,39]. For the pH study, a standard mixture was used to perform all testing. This removed injection to injection variability that could mask potential co-elution of individual standards. The characterization of the pH was centered on pH 7.2. Buffer solutions with pHs of 6.4, 6.8, 7.2, 7.6, and 8.0 were prepared. The same buffer was used for both sample dilution and running buffer. At each pH, electrophoretic potentials (EP) of 5, 10, 15, and 20 kV were investigated to evaluate the interaction between pH and EP. Fig. 2 shows the effect of pH on the separation of PPCPs at 15 kV, the EP that showed the most promise.

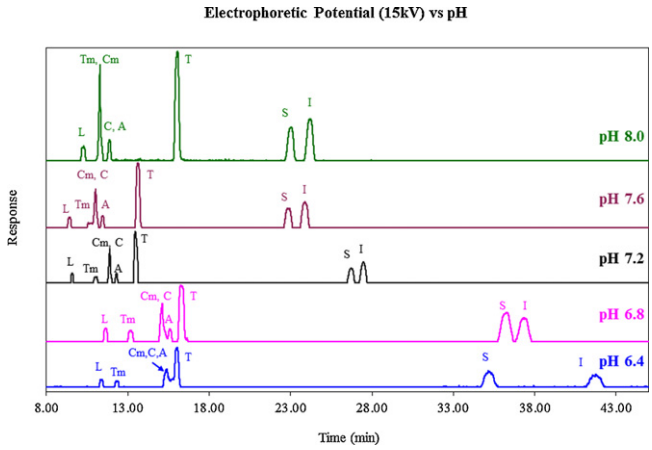

Fig. 2. Effect of pH on separation OF PPCP standards by CE-UV at 214 nm. Capillary, 50 μm (i.d.) × 55 cm (45 cm to the detection window); applied voltage, 15 kV; temperature, 25 °C; sample injection, 0.5 psi for 10 s; running buffer, 100 mM Na_2HPO_4. Peak identifications: (L) lincomycin, (Tm) trimethoprim, (Cm) carbamazepine, (C) Caffeine, (A) acetaminophen, (T) triclosan, (S) sulfamethoxazole and (I) ibuprofen.

At pH 7.2 (middle trace), the separation of the compounds and the overall runtime provided an optimum solution. However, it was observed that two of the compounds investigated, acetaminophen and caffeine, could not be resolved.

3.5. Additives

Additives in the buffer matrix can selectively affect the electrophoretic mobility of ions [37,41]. The approach in the buffer pH study to separate the eight selected compounds has worked well except for the separation of caffeine and acetaminophen. In order to separate these two compounds, 18 Crown 6 was added to the running buffer as an additive to improve the separation. Initial investigations included 5, 10, 20, 50, and 100 mM of 18 Crown 6 diluted in the running buffer (100 mM phosphate, pH 7.20), while keeping the sample dilution buffer unchanged. Fig. 3 shows the PPCP separation at 15 kV, the most promising EP for this investigation. The concentrations of 18 Crown 6 *versus* electrophoretic potentials of 20, 25, and 30 kV were also investigated (data not shown).

It can be clearly seen from Fig. 3 that separation of all of the compounds used was achieved after 100 mM of 18 Crown 6 were added to the running buffer. However, the last two compounds

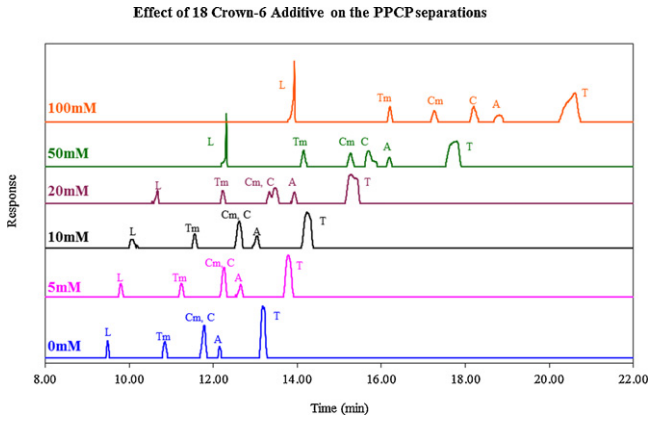

Fig. 3. Separation of PPCP standards at different 18 Crown 6 concentrations. Other electrophoretic conditions were the same as those in Fig. 2. Peak identifications: (L) lincomycin, (Tm) trimethoprim, (Cm) carbamazepine, (C) Caffeine, (A) acetaminophen and (T) triclosan. Sulfamethoxazole and ibuprofen not shown due to scale.

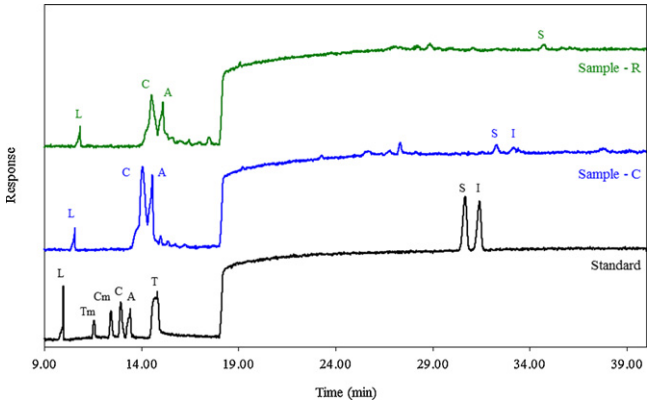

Fig. 4. Representative electropherogram of both wastewater samples (R and C) and a standard injection. Capillary, 50 μm (i.d.) × 55 cm (45 cm to the detection window); applied voltage 15 kV for 18 m/30 kV for 22 m; temperature, 25 °C; sample injection, 0.5 psi for 10 s; running buffer, 100 mM Na_2HPO_4, pH 7.2, 80 mM 18 Crown 6. The PPCP compounds detected in the wastewater samples were: (L) lincomycin, (Tm) trimethoprim, (Cm) carbamazepine, (C) caffeine, (A) acetaminophen, (T) triclosan, (S) sulfamethoxazole, and (I) ibuprofen.

(sulfamethoxazole and ibuprofen) eluted well beyond 60 min. Therefore, using data previously collected, it was determined that a lower voltage (15 kV) could be used to elute the first six compounds then stepped up to a higher voltage (30 kV) to speed up the elution of the last two. Additionally, concentrations of 60 and 80 mM 18 Crown 6 were compared with the initial concentration study (data not shown). The final separation parameters chosen were: applied voltage 15 kV for 18 min and then 30 kV for 22 min; temperature, 25 °C; sample injection, 0.5 psi for 10 s; running buffer, 100 mM of Na_2HPO_4, pH 7.2, 80 mM of 18 Crown 6.

3.6. Method validation

Validation of the optimized method included linearity range, IDL, IQL, MDL, and selectivity [42]. The same extraction technique was used as our previous study, therefore recovery was not investigated during validation [15].

Linearity, IDL, IQL, and MDL were determined through serial dilutions of the standard mixture. Instrument detection limits were based on the 3σ criterion. Here, peak heights less than three times the standard deviation were considered noise. Instrument quantification limits were similarly determined using 10σ of the baseline [43]. For standards that have the same IDL and IQL, the peaks that were detected had intensities greater than 10σ, but the next dilution injected fell below 3σ of the baseline. MDL was determined by taking the standard peak area from the IDL and back calculating the detection limit based on the sample concentration factor. The results are summarized in Table 1. Selectivity was performed through elution matching and standard additions of standards to the standard mixture and wastewater samples to assure proper identification of the peaks in the water matrix.

3.7. Wastewater analysis

Two different wastewater samples were collected from two different Missouri wastewater treatment facilities (denoted R and C) within one week from each other. The samples were concentrated and diluted with running buffer. Each sample was prepared twice and run in triplicate by the optimized CE method previously described. Fig. 4 shows the electropherograms of the two samples *versus* the standard.

It can be seen in Fig. 4 that five compounds, lincomycin, acetaminophen, caffeine, sulfamethoxazole and ibuprofen can be

Table 1
Instrument linear range, instrument detection limit (IDL), instrument quantitation limit (IQL), and method detection limit (MDL) for the selected PPCP compounds. The experimental conditions are the same as those in Fig. 4.

Standard	Instrument linear range (ppm)	IQL (ppm) 10s	IDL (ppm) 3s	MDL (ppb)
Lincomycin	3.86–123.5	7.72	3.86	1.6
Trimethoprim	0.95–3.79	0.95	0.95	7.9
Carbamazepine	0.69–5.54	1.38	1.38	17.2
Caffeine	0.63–10.1	0.63	0.63	7.7
Acetaminophen	0.71–11.4	1.42	0.71	4.6
Triclosan	2.39–38.3	2.39	1.20	68.7
Sulfamethoxazole	1.66–26.5	1.66	0.83	55.4
Ibuprofen	2.00–32.0	2.00	1.00	36.3

Table 2
PPCP concentrations from two wastewater samples collected from wastewater treatment facilities. All concentrations listed in ppb. The experimental conditions are the same as those in Fig. 4.

Compound	CE-UV			LC-MS/MS		
	Facility 'R' Average (ppb)		Facility 'R' SD (ppb)	Facility 'R' Average (ppb)		Facility 'R' SD (ppb)
Lincomycin	3.5	±	0.6	5.2	±	2.0
Caffeine	381.0	±	17.8	325.3	±	26.4
Acetaminophen	932.9	±	38.3	907.3	±	86.0
Sulfamethoxazole	106.1	±	12.0	107.6	±	4.8
	Facility 'C' Average (ppb)		Facility 'C' SD (ppb)	Facility 'C' Average (ppb)		Facility 'C' SD (ppb)
Lincomycin	20.0	±	0.9	19.8	±	3.2
Caffeine	757.0	±	36.3	706.6	±	81.9
Acetaminophen	2083.2	±	544.9	1736.5	±	206.5
Sulfamethoxazole	87.0	±	9.1	116.1	±	5.5
Ibuprofen	228.5	±	46.9	189.4	±	12.3

detected in sample 'C'. Only four compounds were detected in sample 'R' (ibuprofen not detected). Peaks were identified using both elution time matching and standard addition. The remaining three compounds, triclosan, trimethoprim and carbamazepine were not detected in the wastewater samples collected. To confirm our findings, the samples were independently analyzed using LC–MS/MS, as outlined by Wang et al. [15]. Table 2 summarizes the results of all analyses.

The data in Table 2 shows that CE with UV detection is capable of measuring trace amount of PPCPs in Missouri wastewater samples. The result variations observed between CE-UV and LC-MS/MS can be attributed to several factors, including the wastewater matrix and sample preparations. Overall, most of the CE data were comparable with those of LC–MS/MS. In Fig. 4 the water matrix has clearly caused some interference with the caffeine and acetaminophen peaks. This interference can be overcome through further optimization for the specific wastewater matrix. The sample matrices have also caused subtle shifts in the elution time. In Fig. 4, this shift can be observed from the standard injection to sample 'C' and to sample 'R' (order of analysis). This is contributed to differences in the matrix as well as a change in the double layer over time. This is minimized using a NaOH (0.1 N) rinse between injections. However, when samples are complex, injection-to-injection variability can be difficult to control. Therefore, standard addition is required for peak identification. Additionally, large dilutions are necessary for LC–MS/MS analysis to ensure samples are not too concentrated to overload the MS detector. The propagation of error through these large dilutions also contribute to the discrepancy between the two techniques [42].

4. Conclusions

It is well documented in this study that PPCPs can find their way to wastewater streams. These PPCPs pose potential health hazards to living species, including humans. To aid waste treatment facilities, a fast, simple, low-cost, and sensitive CE-UV method was developed and validated to separate and quantify select PPCP compounds in Missouri wastewater. The data obtained by CE-UV was validated using a previously published LC–MS/MS method. Although more data is required to determine its applicability, the method offers an alternative to LC/MS and LC–MS/MS for PPCP determination in wastewater in the event of unavailability, failure or disaster recovery.

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