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Transport and Attenuation of an Artificial Sweetener and Six Pharmaceutical Compounds in a Sequenced Wetland-Steel Slag Wastewater Treatment System

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Abstract: The occurrence of pharmaceutically active compounds (PhACs), nutrients, and an artificial sweetener acesulfame in wastewater, and subsequent removal in an engineered system comprising aerobic wetland, anaerobic wetland, and steel slag cells, were investigated. The PhACs evaluated in this study covered a range of octanol–water partition coefficients (log K_{ow} = 0.07–2.45) and acid dissociation constants (pK_a = 1.7–13.9) and included carbamazepine, caffeine, sulfamethoxazole, ibuprofen, and naproxen. The mean flow rate in the system was 0.89 m^3 day^{-1} (0.02 to 4.27 m^3 day^{-1}), representing a hydraulic retention time of 5 days. The removal efficiencies of PO_4-P, NH_3-N, and $cBOD_5$ in the treatment system were >99, 82, and 98%. The removal efficiencies for the PhACs and acesulfame were classified into four groups, including those that were (a) efficiently removed (caffeine by >75%); (b) moderately removed (ibuprofen by 50–75%); (c) poorly removed (sulfamethoxazole and naproxen by 25–50%); and (d) recalcitrant (carbamazepine and acesulfame by <25%). Variability in concentrations and treatment efficiencies was observed in different sampling events, which may be due to variations in input concentrations or changes in the flow rate. The addition of a steel slag cell increased the overall removal efficiency of the studied compounds, except for carbamazepine.

Keywords: pharmaceutical compounds; acesulfame; steel slag; wetland; wastewater treatment system

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1. Introduction

Pharmaceutically active compounds (PhACs) have been identified as potential surface water and groundwater contaminants over the last two decades. PhACs can be introduced to surface water and groundwater through sewage-treatment plant effluent, surface runoff from agricultural applications of manure and sewage sludge, waste-disposal sites, septic systems, and pharmaceutical production plants [1–4]. The individual concentrations of these contaminants are usually very low (ng L^{-1} to µg L^{-1}) in surface water and groundwater [5–12]. PhACs exhibit ecotoxicological effects on living organisms, as they are reproductive and developmental toxicants and endocrine disruptors [13]. Moreover, the combined ecotoxicological effect of multiple PhACs is more detrimental, compared to their individual components, and has the potential to develop a significant environmental concern [14]. Immense attention has been paid to these compounds due to their wide distribution in aquatic ecosystems and their unknown individual or collective impact on living organisms. Efforts are underway to explore effective remediation options for preventing the release of PhACs to groundwater and surface water flow systems.

PhACs caffeine, ibuprofen, and naproxen are typically removed in conventional wastewater treatment plants with high efficiencies (>99, 90, and 66%), but carbamazepine

(−25 to 96%), sulfamethoxazole (−25%), and acesulfame are often highly persistent [15–21]. There was no significant effect of the hydraulic retention time on the removal efficiency of neutral drugs including carbamazepine in sewage treatment plants, and negative removal was even observed with an increased retention time [17]. The interpretation of concentration data for influent and effluent samples requires caution for many compounds because of the potential for changes in influent concentrations within the hydraulic retention over a particular sampling event [17]. Although changes in the influent concentration may occur for any component, these changes may be particularly significant for PhACs because of the very low concentrations of these compounds.

Acesulfame is identified as a potential tracer of anthropogenic contamination due to its widespread distribution and persistence in the environment. Acesulfame is detected in a wide variety of water samples including untreated and treated wastewater (12–46 μg L^{-1}; [22,23]), surface waters [22], groundwater [22–25], septic system plumes [26], and tap water (up to 2.6 μg L^{-1}; [22]). Toth et al. [27] observed that concentrations of artificial sweeteners, including acesulfame, declined following the removal of natural organic matter and hydroxyl radical scavengers in water using radical-based advanced oxidation and reduction methods.

A significant positive influence of higher temperatures (summer conditions) on the removal of certain pharmaceuticals, including caffeine, carbamazepine, diclofenac, ibuprofen, ketoprofen, naproxen, salicylic acid, and methyl dihydrojasmonate, was observed, as higher temperatures usually favor biodegradation, volatilization, and photodegradation [28–33]. Nivala et al. [33] observed that the removal of emerging organic contaminants was most efficient in the summer (~20 °C) and least efficient in the winter (~6 °C) in six treatment wetlands. Hijosa-Valsero et al. [34] observed a higher removal of carbamazepine [winter (W): 24–36%; summer (S): 48%] and ibuprofen (W: 51–54%; S: 48%) in a floating-macrophyte surface-flow constructed wetland (CW). In addition, a greater removal of caffeine (W: 58–65%; S: 99%) was observed in a horizontal subsurface flow CW, and a greater removal of naproxen (W: 66%; S: 83%) was observed in a planted horizontal subsurface flow CW during summer compared to winter. Conkle et al. (2008) reported high removals of carbamazepine (51%), sulfamethoxazole, caffeine, ibuprofen, and naproxen (>99%) from wastewater in a combination of a series of aerated lagoons, constructed wetlands, a UV disinfection unit, and a natural forested wetland [35].

Although gravel is the most commonly used substrate in CWs designed for pharmaceutical removal [33,36–39], some other materials are reported to be used as a substrate in CWs, including sandy soil or sandy clay loam soil [40,41], a combination of soil, stone, and gravel layers [42], a combination of roots, lava rock, and gravel layers [43], and a combination of red soil, volcanic rock or zeolite, and gravel layers [44]. Substrate materials rich in organic matter, including soil, compost, and agricultural waste, can sorb non-polar organic contaminants through hydrophobic processes, while clay-type substrate materials can sorb polar or ionic contaminants through electrostatic interactions or ion-exchange reactions [45].

The substrates selected for use in CWs provide support for the growth of plants and microorganisms, and they improve the contaminant removal efficiencies through sorption and other reactions. The physico-chemical properties of the substrates including the pH, porosity, surface area, availability of nutrients, and organic matter content can influence the development of microbial communities [46]. Although some studies showed limited to no significant influence of pH (pH between 6.48 and 8.34) on the sorption of PhACs [29], there are examples where pH influences the removals of certain PhACs (e.g., the inverse relationship between substrate pH and sorption by sands and soils; [29,47–50]). Specifically, Kurwadkar et al. [47] reported that the sorption of the anionic form of sulfonamides to soils tends to decrease at pH > 7.5.

Steel slag has been used in previous laboratory and field investigations to treat phosphorus-rich water [51–57]. This material has not yet been evaluated for treating wastewater containing PhACs and artificial sweeteners. Zero-valent iron (ZVI) is a strong

reductant; it is environmentally friendly, cost-effective, and easy to obtain. Zero-valent iron has been widely used to treat different types of contaminants, including conventional inorganic contaminants such as heavy metals [58], organic contaminants such as tetrachloroethylene [59], and emerging contaminants, including perchlorate, pharmaceuticals, artificial sweeteners, and perfluoroalkyl substances [60–64].

In this study, the removal of selected PhACs (including carbamazepine, caffeine, sulfamethoxazole, ibuprofen, and naproxen) and acesulfame was evaluated in a demonstration-scale treatment system. Wastewater was sampled at different stages along the treatment system over six sampling events to evaluate the treatment effectiveness under a range of operational conditions.

2. Materials and Methods

2.1. Chemicals

Carbamazepine, naproxen, sulfamethoxazole, ibuprofen, and caffeine were obtained from Sigma Aldrich Canada Ltd. (Oakville, ON, Canada). Isotope-labeled internal standards (IS) were used to quantify each analyte. The type of IS and the properties of each analyte and IS are provided in Table S1. Both native and isotope labeled acesulfame-d4 were obtained from Toronto Research Chemicals Inc. (Toronto, ON, Canada). Sulfamethoxazole d_4 was obtained from Toronto Research Chemicals (Toronto, ON, Canada), and all other ISs were obtained from CDN Isotopes (Pointe-Claire, QC, Canada). The purity of all native samples and ISs was $\geq$99%. Ultrapure water was generated using a 0.45 µm Millipore Q-Gard1 unit (Milli-Q, Billerica, MA, USA). High-performance liquid chromatography (HPLC) grade methanol (99.9%), ammonium acetate, formic acid, acetic acid, and acetonitrile were obtained from Caledon Laboratories Ltd. (Georgetown, ON, Canada).

2.2. Field Methods

2.2.1. System Configuration

The demonstration system is a multi-stage Constructed Wetland (CW)-Phosphate treatment system, which was installed in the fall of 2009 at the Center for Alternative Wastewater Treatment, Fleming College, Lindsay, Ontario. Basic oxygen furnace slag (BOFS) was collected from the US Steel Stelco Hilton Works facility (Hamilton, ON, Canada). Zero valent iron (ZVI) was obtained from the Connelly-GPM (Chicago, IL, USA). The treatment system consisted of four stages (cells two to five); a detailed description of each cell is summarized in Table 1. The physical and chemical characteristics of BOFS and ZVI are provided in the supplementary information (Tables S4 and S5). The effluent from cell one passed through cells two to five in sequence prior to being released into the sewer system for the City of Kawartha Lakes (Figure 1). The flow was continuously monitored with an automatic flow meter, with interruptions when the meter was clogged. The flow volume was calculated based on the periods when the flow was automatically monitored. During other times, the flow rates were assumed to be consistent with the periods when monitoring data were available.

Table 1. Description of the treatment cells, including the cell volume, media volume, porosity, and hydraulic retention time.

Cell ID	Cell Type	Cell Description	Cell Volume (m^3)	Media Volume (m^3)	Porosity (θ)	Hydraulic Retention Time (HRT) (Day)
Cell one	Pre-treatment septic tank effluent chamber	The influent of the treatment system, wastewater, was received from this pre-treatment septic tank and periodically pumped to cell two	1	-	-	-
Cell two	Subsurface flow constructed wetland (HSSF CW Cell)	Filled with granitic gravel and vegetated with cattails (*Typha* spp.)	24	19.4	0.35	7.64

Table 1. *Cont.*

Cell ID	Cell Type	Cell Description	Cell Volume (m^3)	Media Volume (m^3)	Porosity (θ)	Hydraulic Retention Time (HRT) (Day)
Cell three	Subsurface flow aerated constructed wetland (Aerated VSSF CW Cell)	Filled with granitic gravel and vegetated with cattails (*Typha* spp.)	24.2	19.3	0.35	7.61
Cell four	Downward vertical flow cell (BOFS Cell)	Filled with BOFS and ZVI to remove phosphate. BOFS media were covered by a granitic gravel layer and then a plastic trap and a sand layer to avoid atmospheric oxygen ingress. A sacrificial BOFS chamber was placed before cell four to prevent the formation of a $CaCO_3$ scale around the cell four inlet	27.4	13.3	0.4	5.97
Cell five	pH-adjustment unit	Equipped with a CO_2 sparger and an adjusted pH between 6.5 and 8.5 before releasing into the City of Kawartha Lakes sewer system	2	-	-	-

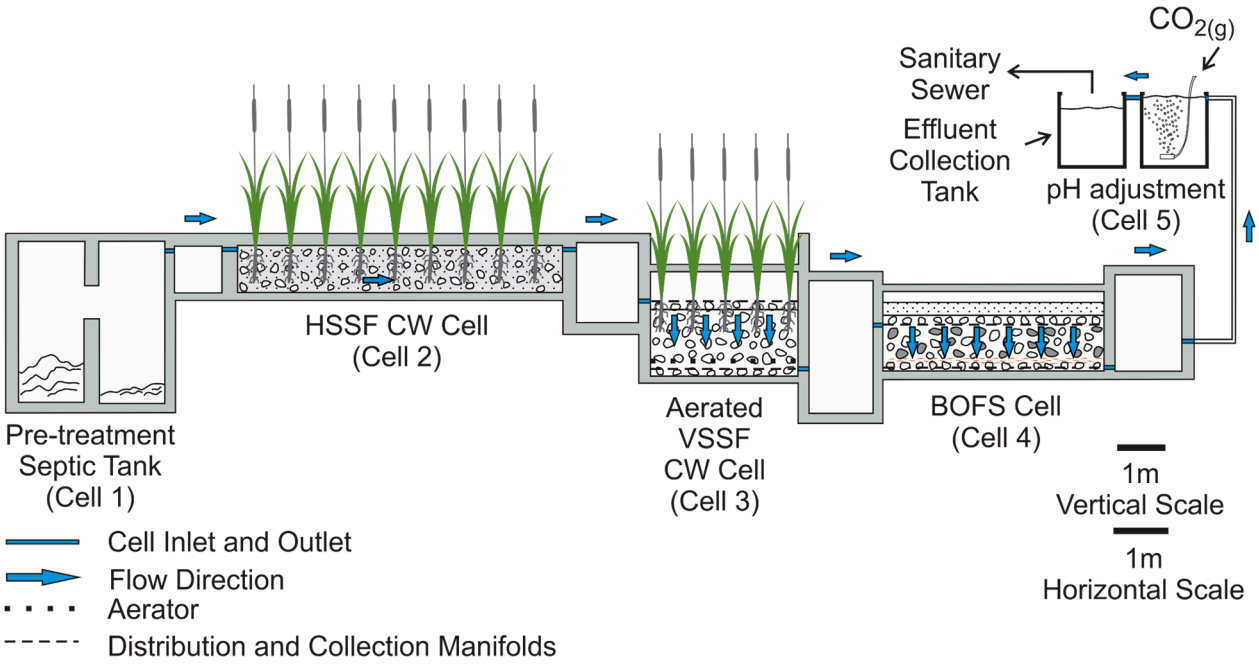

Figure 1. Schematic diagram of the CW-BOFS demonstration-scale treatment system. Wastewater was continuously flushed through the system by a combination of gravity feed and pumping. A detailed description of the cells is provided in Table 1.

2.2.2. Sampling Procedure

Water samples were collected throughout the treatment system for the analysis of PhACs, acesulfame, and other water quality parameters. All samples were filtered with 0.45 µm cellulose acetate filters prior to preservation. Samples for PhACs and acesulfame analyses were collected using a sampling pump with dedicated tubing (Masterflex precision pump tubing with 4.8 mm ID) and passed through 0.45 µm filter membranes into 500 mL amber glass bottles, followed by acidification with 18 N H_2SO_4 to pH < 2 for sample preservation. The samples for PhACs and acesulfame were collected from each cell effluent except cell five (pH adjustment cell) because this unit was not regulated systematically during the sampling events. Sample analyses were performed within three days of collection. Duplicates of each sample were collected in the field and archived in a freezer. Field blanks

for PhACs consisted of ultrapure water collected using the same collection and preservation methods as other samples in the field to evaluate whether contamination occurred during the filtering process or transport. The trip blanks for PhACs were unfiltered ultrapure water (brought to the field) collected directly from a plastic container in the field without using a pump and preserved following the same method as the other samples. All samples were maintained at 4 °C until analysis.

The values of pH, Eh, and alkalinity were measured on site immediately after the samples were collected following the same procedure as described in Hussain et al. [57]. Samples, field, and trip blanks were collected for the analysis of cations, anions, PO_4-P, and NH_4-N following the same collection and preservation methods as described in Hussain et al. [57]. The samples were collected during the winter and pre-spring period. The average minimum and maximum air temperatures were −4.0 and 17.6 °C, and the influent sample temperatures were between 4.3 and 14.2 °C. The samples were stored at 4 °C up to one month before analysis.

2.3. Analytical Methods

The samples were analyzed to determine the dissolved concentrations of major cations, trace metals, and Cl, NO_2-N, NO_3-N, SO_4, PO_4-P, and NH_3-N using the methods described in Hussain et al. [57]. Unique isotopically labelled PhACs were added to each sample prior to analysis for use as internal standards (ISs) to track the potential loss of analytes during the solid phase extraction (SPE) processes and to account for matrix effects during the analysis [65]. The concentrations of the PhACs, including carbamazepine, caffeine, sulfamethoxazole, ibuprofen, and naproxen, were determined using HPLC (Agilent 1100, Agilent Technologies, Hong Kong, China) coupled with electrospray tandem mass spectrometry (4000 Q TRAP, Applied Biosystems, Waltham, MA, USA) after SPE. The analytical procedure was modified from procedures described by Vanderford et al. [66] and Stafiej et al. [67]. Details of the analytical procedure used in this study are provided in Liu et al. [20].

2.4. Quality Control and Quality Assurance

In addition to the use of internal standards, additional continuous calibration blanks (CCB) and continuous calibration verification (CCV) samples were analyzed on a regular basis to ensure that cross-contamination between injections was minimal and to assess the recovery of the analytes. The CCB samples were methanol/H_2O (50/50, v/v). The CCV samples consisted of methanol/H_2O (50/50, v/v) spiked with unlabelled analytes and a stock mixture of ISs. A CCV sample was analyzed directly after each CCB to ensure ongoing acceptable calibration performance during the analysis of each batch of samples. This calibration pair (CCB and CCV) was analyzed after initial calibration, after every ten samples, and at the end of the analysis. The CCV values were within ±15% of the expected values (Table S2).

Aqueous blanks were prepared with ultrapure water spiked with a mixture of ISs. Quality control (QC) samples were prepared from ultrapure water spiked with analytes of different concentrations and the mixture of ISs. One aqueous blank and one QC sample were processed through the SPE procedures with each set of 10 unknown samples. The aqueous blank samples were used to check for any cross-contamination and the recovery of the ISs. The QC samples were used to check whether there was any loss of ISs or analytes during storage, SPE, and analysis. A linear calibration curve (0.1–40 μg L^{-1}, $R^2 > 0.9999$) with nine calibration standards was used to quantify the concentrations of target compounds. The limits of detection (LODs), limits of quantification (LOQs), and IS recoveries for target contaminants, including acesulfame (ACE), caffeine (CAF), carbamazepine (CBZ), sulfamethoxazole (SMX), ibuprofen (IBU), gemfibrozil (GEM), and naproxen (NAP), are reported in Table S2.

2.5. Statistical Analysis

A statistical calculation (*t*-test) was conducted to evaluate the removal of target PhACs through the treatment system. The *p*-values from the *t*-tests (two-sample assuming unequal variance) for the pooled sample sets (concentrations of each chemical in six sampling events) (SigmaPlot 11.0) are summarized in Table S3.

3. Results and Discussion

The flow rate was dependent on the availability of septic tank effluent, which was proportional to the on-campus student population during different times of the year. The observed flow rate was highly variable (σ = 625) during the study period. The mean flow rate was calculated to be 0.89 m^3 day^{-1} during the study period. The hydraulic retention time (HRT) is one of the major factors for the removal efficiency of PhACs [35]. The mean HRTs in cells two, three, and four were 7.6, 7.6, and 6.0 days.

3.1. Characteristics of Wastewater

The chemical composition of the effluent of the treatment cells reflected the pH conditions in each of the cells (Figure 2). The pH in cells one, two, and three was slightly alkaline (8.2 $\pm$ 0.8 in Cell 1, 8.7 $\pm$ 1.0 in Cell 2, and 7.8 $\pm$ 0.4 in Cell 3). In cell four, the pH increased substantially up to 10.9 $\pm$ 1.5, and a corresponding elevated total alkalinity was observed at the onset of the experiment (maximum 1620 mg L^{-1} as $CaCO_3$; Figure 2). The total alkalinity in cell four effluent decreased with time as the cell was flushed with the near neutral effluent from cell three, likely due to the leaching of free lime (CaO) and portlandite [$Ca(OH)_2$] from the BOFS during the study. The high pH effluent from cell four was neutralized in cell five (indoor pH adjustment tanks; Figure S1). The highest mean Eh was observed in cell three effluent, and the lowest mean Eh was observed in cell one effluent (Figure 2). The low mean dissolved oxygen (DO) concentrations were observed in the effluents of cell one (1.61 mg L^{-1}) and cell two (2.26 mg L^{-1}), indicating relatively anoxic conditions in these cells. High average DO concentrations, up to 8.93 mg L^{-1}, were observed in cell three effluent. However, the DO concentrations decreased significantly (mean concentration, 4.70 mg L^{-1}) in the cell four effluent. The mean concentrations of NH_3-N were 50, 53, 21, and 19 mg L^{-1} in the effluent collected from cells one, two, three, and four, indicating a decrease along the flow path (Figure 2). In contrast, the mean concentrations of NO_3-N were 9, 2, 49, and 43 mg L^{-1}, showing an increase along the flow path. The calculated ratios of NH_3-N/NO_3-N increased from 5.6 to 1100 and then decreased to 0.44, showing the influence of oxidation reactions. The presence of the fresh ZVI layer added to cell four may have initially led to the reduction of NO_3-N to NH_3-N. The reduction of NO_3-N to NH_3-N by ZVI is reported in previous studies [68]. Thus, the changes in Eh values were directly proportional to the changes in DO and NO_3-N concentrations and inversely proportional to the changes in the NH_3-N concentration along the flow path.

Consistent concentrations of SO_4 ranging from 43 to 50 mg L^{-1} were observed in cells one to four, while the mean values of redox potential (Eh) in cells one, two, three, and four were 21.3, 64.5, 329, and 94.8 mV, respectively. These Eh values fall within the sulfide oxidation range (−220 to 280 mV) defined by Stumm and Morgan [69], except for cell three. In cell two, a gravel-based horizontal subsurface flow CW, the presence of plant-derived organic carbon and biomass created reducing conditions, as indicated by a mean Eh value of 65 mV, near the range of Fe(III) reduction (−550 to 50 mV; [69]). Similar reducing conditions have been observed in previous studies [70,71].

During aeration, the behaviors of dissolved Fe and Mn vary. In cell three, aeration promoted oxidizing conditions (Eh of 329 mV), leading to the precipitation of Fe(III) oxides and a decrease in dissolved Fe(II) concentrations. However, the concentrations of dissolved Mn increased, indicating that the residence time was likely insufficient to promote the formation of insoluble Mn oxides under the conditions in cell three. A similar increase in the Mn concentration is observed by Morgan et al. [72].

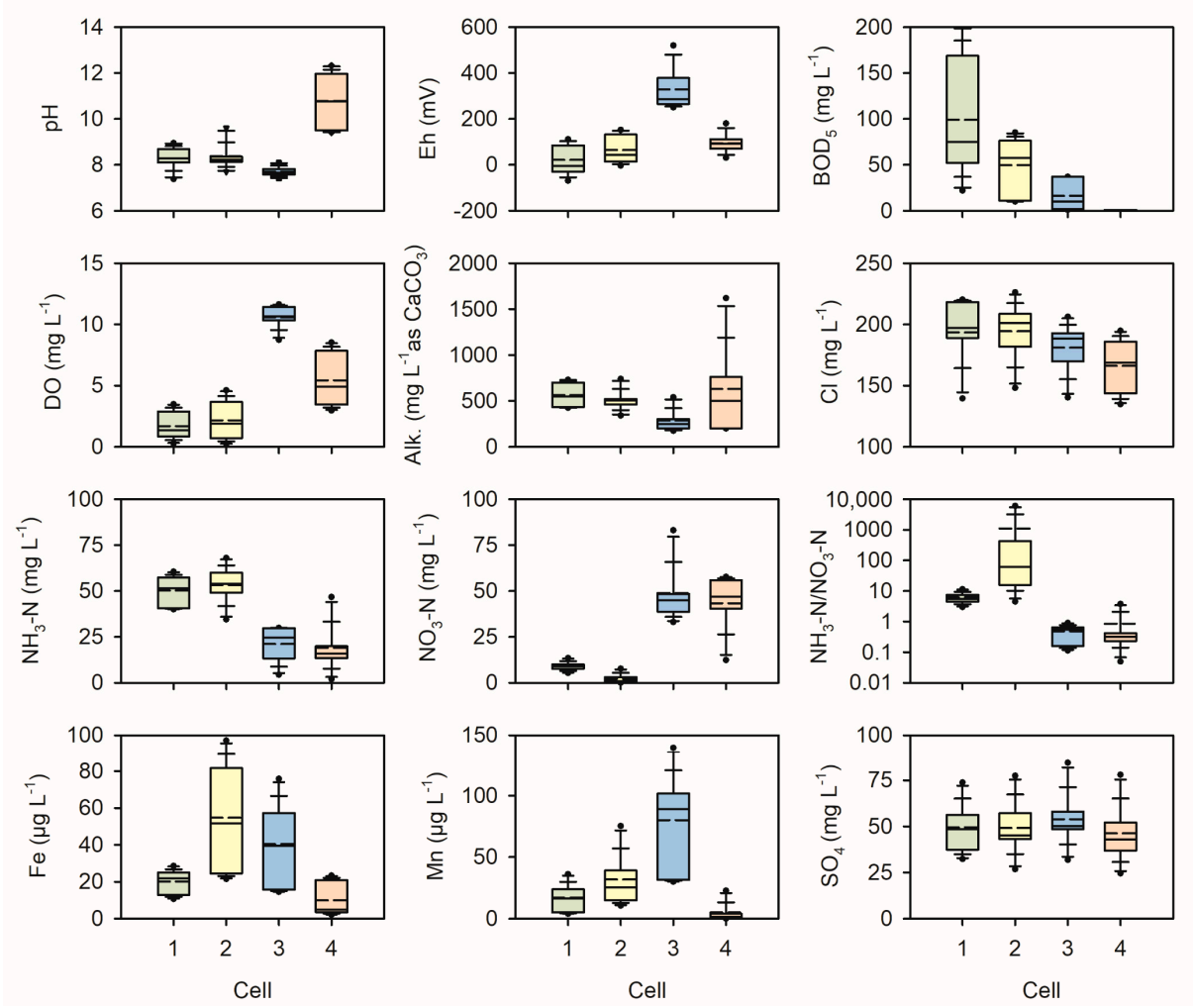

Figure 2. Box plots of pH, Eh, $cBOD_5$, DO, alkalinity, Cl, NH_3-N, NO_3-N, NH_3-N/NO_3-N, Fe, Mn, and SO_4 versus distance (Cells 1–4) along the treatment flow path. Horizontal solid lines and broken lines on the boxes represent median and mean concentrations.

The decrease in the Fe and Mn concentrations in cell four, with BOFS and ZVI, may be due to various processes. A thin layer of Fe(III) oxyhydroxides on the ZVI particles provides a high surface area for the adsorption of Fe and Mn ions, while chemical reactions between ZVI and slag components form solid phases that incorporate the metals, effectively removing them.

3.2. Carbonaceous Biochemical Oxygen Demand ($cBOD_5$)

High concentrations of $cBOD_5$ were observed in cell one effluent (mean, 99.12 mg L^{-1}). The mean $cBOD_5$ concentrations in cells two, three, and four were 49.5, 16.1, and 0.83 mg L^{-1}. The $cBOD_5$ removal efficiencies in cells two, three, and four were 50, 34, and 15%. Thus, the overall $cBOD_5$ removal efficiency in the treatment system was >99%. The removal of $cBOD_5$ in cell two can be explained by the influence of plants, which introduces atmospheric O_2 in the system through the roots. The residual amount of $cBOD_5$ in the wastewater after treatment in cell three was removed in cell four, which suggests that highly alkaline conditions in cell four can lead to the degradation of the remaining labile organic compounds. Both the $cBOD_5$ and NH_3-N removal efficiencies in cell three were considerably higher (33.7% and 63.9%; Figure 2) than those in other cells. The high oxidation-reduction potential measurements in cell three effluent resulted from aeration. The $cBOD_5$ removal efficiency in cell three indicates that aerobic degradation was the dominant mechanism leading to the removal of organic matter. These results are consistent with previous studies [73,74]. A sharp increase in NO_3-N and a

decrease in NH_3-N in cell three suggest that higher NO_3-N concentrations were derived from the oxidation of NH_3-N (Figure 2).

3.3. Pharmaceutical Compounds (PhACs)

A decrease in concentrations was observed for the majority of the PhACs in the effluent from each cell along the treatment system (Figure 3). However, carbamazepine, which showed little to negative removal (an increase in concentration), was a notable exception. Influent PhACs concentrations (in cell one) fluctuated, likely in response to changes in the student population at the college. The mean influent concentrations of target PhACs were 47 μg L^{-1} for ibuprofen, 8.8 μg L^{-1} for naproxen, 23 μg L^{-1} for caffeine, 3.6 μg L^{-1} for carbamazepine, and 0.06 μg L^{-1} for sulfamethoxazole (Figure 3). The presence of relatively high concentrations of PhACs, including ibuprofen, naproxen, and carbamazepine, in the cell two effluent compared to the cell one effluent (system influent) in some of the sampling events suggests carryover from earlier loading events and the variation in input concentrations. The carryover of contaminants from earlier loadings occurred in cell two but not in other cells, likely due to the variations in input concentrations in cell one associated with fluctuations in the student population.

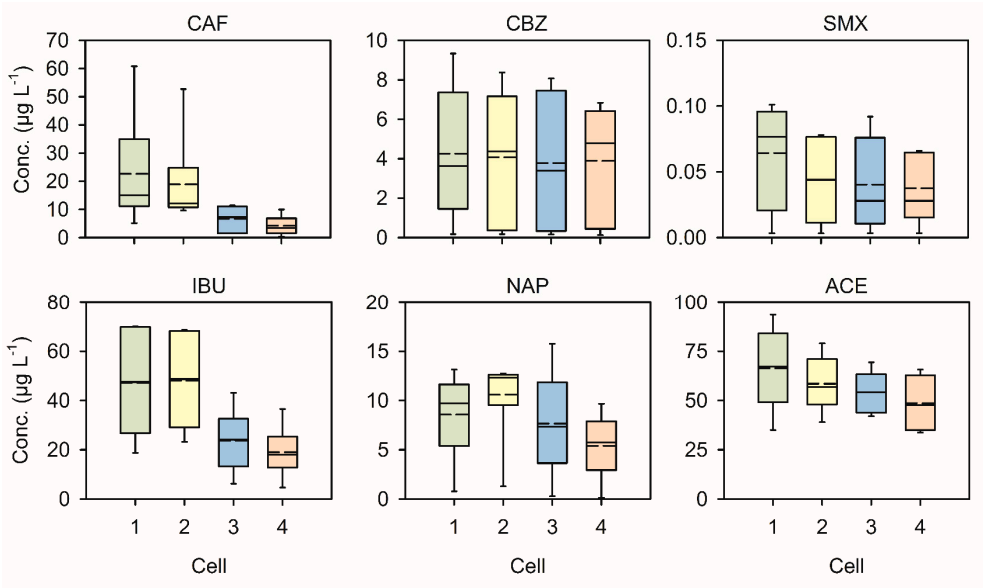

Figure 3. Box plots of selected pharmaceutical compounds, caffeine (CAF), carbamazepine (CBZ), sulfamethoxazole (SMX), ibuprofen (IBU), naproxen (NAP), and an artificial sweetener, acesulfame (ACE), along the treatment flow path. Horizontal solid lines and broken lines on the boxes represent median and mean concentrations.

The results of the statistical analysis show that the concentrations of ibuprofen between cells one and three, cells one and four, cells two and three, and cells two and four and the concentrations of naproxen between cells two and four were significantly different (p <0.05). In contrast, the concentrations of ibuprofen and naproxen with other cell combinations and the concentrations of caffeine, carbamazepine, sulfamethoxazole, and acesulfame with all cell combinations were not significantly different (p >0.05) between cells. These relatively greater p-values (>0.05) were likely due to the high variability in PhAC concentrations in each treatment cell. The pronounced decreases in concentrations of caffeine, ibuprofen, and naproxen along the flow path from cells two to three (not statistically significant for caffeine and naproxen) were likely due to enhanced biodegradation associated with the significant increase in DO concentrations [75]. Similar removals of caffeine, naproxen, and ibuprofen were also reported in CW systems [75,76]. However, the increase in DO between cells two and three did not enhance the biodegradation of carbamazepine and acesulfame due to their recalcitrance. For select sampling dates (e.g., 9 February 2010: caffeine, carbamazepine,

ibuprofen, and acesulfame; 6 April 2010: caffeine, ibuprofen, and acesulfame; 13 April 2010: ibuprofen, naproxen, and acesulfame; 10 December 2010: ibuprofen and naproxen; and 28 January 2011: ibuprofen and acesulfame), obvious decreases in concentrations were observed, suggesting removals on these dates.

3.3.1. Analgesic Anti-Inflammatory Drugs

Ibuprofen is a non-steroidal anti-inflammatory drug and is considered to be biodegradable [19]. There were no significant changes in the concentrations observed in the cell two effluent, and the mean concentration increased slightly from the system influent of 47.0 μg L^{-1} to 48.0 μg L^{-1}. A sharp decrease to a mean concentration of 23.7 μg L^{-1} was observed in the cell three effluent. An additional decrease to a mean value of 19.0 μg L^{-1} was observed in the cell four effluent. The removal efficiency for ibuprofen in cell three (52%) was consistent with or higher than that in other studies [34,77]. Matamoros and Bayona [78] observed a similar to slightly greater removal of ibuprofen under more oxidizing conditions in a shallow bed subsurface flow constructed wetland (50–80% removal efficiency between May and July). In this study, all samples were collected in winter and early spring. The removal efficiencies for ibuprofen observed in this study (range: 38–75%, mean: 60%) were much higher than the removal efficiencies observed by Matamoros et al. [77] (range: 2–34%) and Hijosa-Valsero et al. [34] (range: 27–74%) in winter months. However, greater removal of ibuprofen (~82%) in winter is reported by Dordio et al. [19]. The aeration process increased the amount of oxygen in cell three, which probably favored the aerobic biodegradation of ibuprofen. A positive linear correlation between the redox potential and the removal efficiency for ibuprofen was observed in this study, which is consistent with observations by Hijosa-Valsero et al. [34].

Naproxen is also a non-steroidal anti-inflammatory drug, and its concentration profile was similar to that of ibuprofen. Concentrations of naproxen increased in the cell two effluent relative to the system influent, with a mean value of 11.0 μg L^{-1}, and then gradually decreased in the effluents of cells three and four, with mean concentrations of 7.82 and 5.44 μg L^{-1}. In this treatment system, naproxen had a much lower removal efficiency (39%) than ibuprofen (60%). This removal rate is consistent with the values reported by Hijosa-Valsero et al. [34] (range: 27–66% in CWs) and Matamoros et al. [77](range: 10–36% in CW).

3.3.2. Caffeine

A decreasing trend in caffeine concentrations was observed along the flow path. The mean concentrations in the effluents of cells two, three, and four were 18.9, 6.60, and 4.14 μg L^{-1}. The sharp drop in concentrations in cell three effluent compared to those in the cell two effluent was similar to the changes observed for ibuprofen. The total removal efficiency for caffeine was 82%, which was the highest removal observed for the PhACs. The removal efficiencies for caffeine were higher than those reported for the winter months in a previous study by Hijosa-Valsero et al. [34], with a range between 58% and 65% in a CW. Hijosa-Valsero et al. [34] showed that the caffeine removal efficiency in summer (average temperature 19.9 °C) was approximately three times greater than the rates observed in winter (average temperature 7 °C). Matamoros et al. [77] also reported a similar removal efficiency of caffeine in a CW (consisting of two horizontal surface flow cells, filled with gravel, water depth: 0.5 m, planted with *Phragmites australis*, HRT: 4–6 days) in summer (75 ± 3%); however, they reported a very low efficiency in winter (2 ± 9%).

3.3.3. Anti-Epileptic Drug

The mean concentrations of carbamazepine, an anticonvulsant and antidepressant drug, in the effluent from cells two, three, and four were 4.07, 3.77, and 3.89 μg L^{-1}. An increase in carbamazepine concentrations was observed in cell two effluent compared to those in the cell two influent. A small decrease in concentrations was observed in cell three effluent with respect to those in the cell two effluent. In cells one and two,

carbamazepine concentrations showed a trend that was similar to those observed for caffeine, ibuprofen, and naproxen. Carbamazepine did not show a similar decreasing trend in the cell four effluent. Although the mean removal efficiency of carbamazepine was about 8% in cell three with respect to cell two effluent, the overall mean removal efficiency for this compound in the treatment system was negative 9% (Figure 4). This was the most recalcitrant pharmaceutical compound analyzed in this study. The recalcitrant nature of carbamazepine is widely reported [35,37,74,79]. In contrast, Dordio et al. [19] reported removals of about 96% and 88% of the influent carbamazepine in a microcosm constructed wetland system during the summer and winter months, respectively. The reasons for these large differences are unclear.

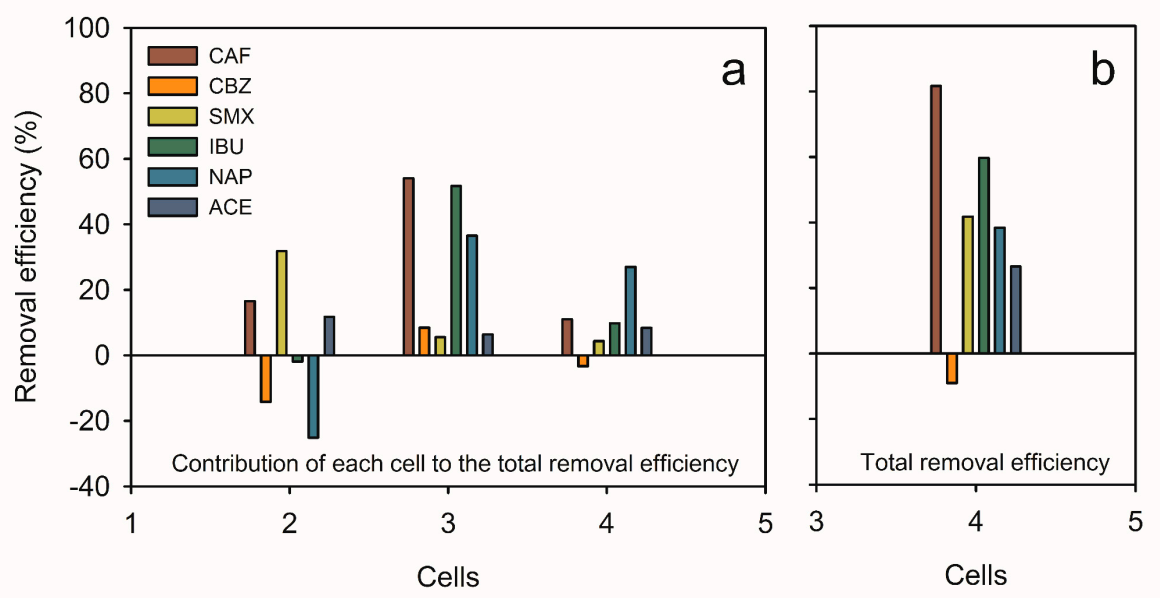

Figure 4. Selected pharmaceutical compounds, caffeine (CAF), carbamazepine (CBZ), sulfamethoxazole (SMX), ibuprofen (IBU), naproxen (NAP), and an artificial sweetener, acesulfame (ACE), along the treatment flow path. (**a**) Contribution of each cell to the total removal efficiency; (**b**) total removal efficiency.

3.3.4. Sulfonamide

A decrease in concentration of 32% for sulfamethoxazole, an antibiotic sulfonamide, was observed in the cell two effluent (0.003–0.08 μg L^{-1}). This decrease in concentration in the aerated cell may be due to oxidation reactions. Neither cell three (6% removal) nor cell four (4% removal) provided a significant removal of sulfamethoxazole. Sulfamethoxazole has been reported to be relatively recalcitrant, closely resembling carbamazepine [80,81]. The removal efficiencies for sulfamethoxazole were 24% in a conventional sewage treatment plant [7]. Even higher removals have been observed in other studies (as high as 78%), especially in systems with a long HRT (e.g., 30 days; [35]).

The removal efficiencies of sulfamethoxazole in cells three and four were similar to the extent of removal (38%) reported in a laboratory experiment at a low biomass concentration [82]. However, Al-Ahmad et al. [83] reported no biodegradation of sulfamethoxazole in a closed bottle test and noted that only a small group of bacteria present in the inoculum are affected by sulfamethoxazole. High biomass conditions usually favor the biodegradation of sulfamethoxazole [84]. Thus, the >30% removal efficiency for sulfamethoxazole in cell two (32%) is attributed to the higher biomass in this cell because it was well vegetated and was operational long before the other cells were reconstructed.

3.3.5. Summary of PhAc Removal Efficiency

Among the treatment cells, the removals of caffeine, carbamazepine, and naproxen were greater in cell three compared to those in other cells, likely due to the oxidizing

conditions in this cell, which favored their aerobic degradation. Based on the removal efficiency observed during this study, the selected PhACs can be classified into four different groups: (a) efficiently removed, with >75% removal (e.g., caffeine); (b) moderately removed, with 50–75% removal (e.g., ibuprofen); (c) poorly removed, with 25–50% removal (e.g., sulfamethoxazole and naproxen); and (d) very poorly removed or recalcitrant, with <25% removal (carbamazepine).

3.4. Artificial Sweetener

The mean concentration of acesulfame, an artificial sweetener, in cell one (influent) was 66 μg L^{-1}. The concentrations of acesulfame gradually decreased along the flow path; the mean concentrations of acesulfame were 58.5, 54.2, and 48.7 μg L^{-1} in cells two, three, and four, with removal efficiencies of 12.0, 6.4, and 8.4%. Thus, the treatment system removed ~27% acesulfame from the wastewater. According to Toth et al. [27], the presence of hydroxyl radicals and low natural organic matter favors acesulfame removal. However, with very low $cBOD_5$ concentrations, the expected removal of acesulfame in cell four was not observed. The mechanism of acesulfame removal in cell two was not clear. Tran et al. [21] also reported the persistence of acesulfame (with removal between −5.5% and 23%) in a biological wastewater treatment system.

3.5. Removal Mechanisms

3.5.1. Sorption

Although acesulfame and the target PhACs have similar molecular weights, the octanol–water partitioning coefficients (K_{ow}) and hydrophobicity of these compounds are different. The compounds analyzed in this study covered a range of K_{ow} values and acid dissociation constants (pK_a). Acesulfame, ibuprofen, naproxen, and sulfamethoxazole are expected to dissociate predominantly into their anionic forms in the treatment system, as the pH values of each treatment cell effluent including the septic tank effluent (system influent) were greater than the pK_a values of these compounds (Table S1, Figure S2). The pH values in cells one, two, and three were less than the pK_a value of caffeine, whereas the pH in cell four was greater than the pK_a value of caffeine (Figure S2). These conditions indicate that caffeine was predominantly in its neutral form in cells one to three and its anionic form in cell four. The pH values of each cell effluent were substantially less than the pK_a value of carbamazepine; as a result, carbamazepine was predominantly in its neutral form in all of the cells (Figure S2).

The adsorption of negatively charged compounds onto the CW materials (including calcium carbonate and calcium phosphate) is generally not expected under high pH conditions. However, due to the presence of metal oxides with a high pH zero-point of charge (pH_{zpc}), including 33 wt.% CaO (pH_{zpc} = 8.1; [85]), 24 wt.% Fe_2O_3 (pH_{zpc} = 6.9; [86]), 8–9 wt.% MgO (pH_{zpc} = 12.4; [86]), and 4–6 wt.% Al_2O_3 (pH_{zpc} = 9.1; [86]) in BOFS media, the adsorption of the negatively charged compounds, including acesulfame, ibuprofen, naproxen, and sulfamethoxazole, to positively charged BOFS in cell four may be possible. Moreover, upon continuous flushing with wastewater, labile CaO and $Ca(OH)_2$ would be removed from the outer layer of the BOFS, leading to a decrease in alkalinity. The adsorption and/or precipitation of other inorganic compounds may coat the outer layer of the BOFS grains and restrict the CaO and $Ca(OH)_2$ from dissolving and creating alkaline conditions. The FTIR spectra indicated evidence of calcite ($CaCO_3$, pH_{zpc} = 9.5; [86]) and hydroxyapatite ($Ca_5OH(PO_4)_3$, pH_{zpc} = 7.6; [87]) precipitation on the BOFS surface, which may also favor the adsorption of negatively charged compounds (acesulfame, ibuprofen, naproxen, and sulfamethoxazole). Based on the decreasing trend of pH, it can be predicted that, over time, with continuous flushing, the pH of cell four is expected to decrease, potentially leading to an improved removal of negatively charged contaminants. However, the adsorption of neutral PhACs, including carbamazepine and caffeine, is unlikely to adsorb onto positively charged BOFS reactive media. Other CW substrate materials (such

as plant-derived organic carbon and biomass in cells two and three) can remove the target PhACs through hydrophobic sorption processes [88].

3.5.2. Hydrophobic Interactions

Compounds can be classified on the basis of log K_{ow} values as hydrophilic (log K_{ow} < 1; [89,90]), intermediate or transphilic (1 < log K_{ow} < 3; [90]), and hydrophobic (log K_{ow} > 3; [90]). Amiard-Triquet et al. [91] further classified the hydrophobic compounds as moderately hydrophobic (3 < log K_{ow} < 7) and very hydrophobic (log K_{ow} > 7). Due to the acid-base transformation of the soluble organic compounds, pH-dependent K_{ow} values (log D_{ow} values) can be calculated and are usually distinctly different than the intrinsic hydrophobicity when partial or complete dissociation takes place [92]. The log D_{ow} expresses the relationship between K_{ow}, pH, and pK_a and can be calculated using the following equation [93].

$$\log D_{ow} = \frac{K_{ow}}{1 + 10^{\mathrm{pH} - pK_a}} \quad (1)$$

The log D_{ow} values vary substantially from the log K_{ow} for acidic drugs that dissociate under the pH conditions at the site. This difference has important implications for the predicted fate and transport of PhACs. Caffeine, sulfamethoxazole, and naproxen are hydrophilic under the conditions in the treatment cells (with pH values between 7.38 and 12.32) based on the log D_{ow} values (<1) (Figure S3). Carbamazepine is moderately hydrophobic and did not show any significant change (log D_{ow} from 2.45 to 2.44) under the pH range observed in the treatment system. Ibuprofen showed very low to low hydrophobicity (log D_{ow} > 1) below pH 7.82 (Figure S3). However, carbamazepine (the most hydrophobic among the target contaminants) was transported through the system, despite its moderate hydrophobicity, indicating limited hydrophobic interaction between target contaminants and the reactive media of the treatment cells.

3.5.3. Aeration

Aeration, which creates oxidizing conditions, is an important factor affecting the attenuation of several PhACs. The removal of caffeine, acetaminophen, and naproxen often exceeds 99% from the influent concentrations [35]. Aeration also facilitates volatilization, a function of Henry's coefficient (K_H), and the air flow contacting the wastewater, which is one of the removal mechanisms of pharmaceutical compounds in sewage treatment plants [94]. The compounds studied are not expected to be volatile, nor was the aeration aggressive. Therefore, the attenuation of these compounds, particularly in cell three, is attributed to the presence of oxidizing conditions which enhanced the aerobic biodegradation (microbial activity) of target contaminants. The enhancement in the biodegradation of caffeine, ibuprofen, naproxen, acesulfame, and sulfamethoxazole with aeration has been reported previously [95,96] and likely occurred in cell three in this study.

3.5.4. Biodegradation

Biodegradation is the main mechanism for removing emerging contaminants such as acesulfame and PhACs in CW systems [97,98]. The biodegradability of contaminants under aerobic conditions varies. Caffeine and ibuprofen are highly biodegradable, naproxen is moderately to highly biodegradable, sulfamethoxazole is moderately biodegradable, and carbamazepine and acesulfame have low biodegradability [76,96,99]. The primary pathway for the removal of caffeine in constructed wetlands is identified as aerobic biodegradation [100]. Biodegradation played important roles for the removal of naproxen in wetland mesocosms, while there is no notable influence of biodegradation on the removal of carbamazepine [101]. In cell three, with the high removal efficiency of $cBOD_5$ and high levels of DO, aerobic biodegradation is likely to be one of the most important removal mechanisms for caffeine, ibuprofen, naproxen, sulfamethoxazole, and acesulfame. These results compare favorably with those of previous studies.

3.5.5. Photodegradation

The experiment was conducted under subsurface conditions, and the PhACs and acesulfame are not likely photodegraded. However, the effluent of cell two which spreads over the surface of cell three, was exposed to light, and may promote partial photodegradation before percolating downward. Caffeine and sulfamethoxazole photodegrade when exposed to sunlight, while carbamazepine is the compound most resistant to photodegradation [102]. Direct photodegradation is a removal mechanism for naproxen; however, it is not a removal mechanism for ibuprofen and carbamazepine [103]. Photodegradation of acesulfame in the environment is also reported [104].

3.5.6. Reduction through ZVI

CW treatment systems designed for the removal of pharmaceutical compounds commonly use gravel and/or sand as a substrate [34,37,74,78]. ZVI has been used as a reactive medium for the removal of metals from groundwater [105,106], for the removal of antibiotics from aqueous solution [107], and for the degradation of pharmaceutical diazepam [108]. In cell four, a reactive zone containing ZVI was placed at the bottom of cell four, and the DO concentration in the effluent of cell four was much lower than that in the cell three effluent. Zero valent iron promotes the reduction in water through the reaction:

$$Fe^0 + 2H_2O => Fe^{2+} + H_2 + 2OH^- \quad (2)$$

ZVI is oxidized to Fe^{2+} in the presence of H_2O (predominant electron acceptor), leading to an increase in pH and a decrease in redox potential [109–111]. Although an increase in the pH does not favor the adsorption of the pharmaceutical compounds on the surfaces of the substrates, reducing conditions created due to the presence of ZVI may have contributed to the additional treatment in cell four, which has also been observed by Liu et al. [62]. Liu et al. [62] reported that >97% of the input carbamazepine, caffeine, sulfamethoxazole, ibuprofen, and naproxen (~10 μg L^{-1}) and 10–60% of the input acesulfame (~100 μg L^{-1}) were removed using a passive treatment system containing ZVI alone. Therefore, the removal of target contaminants, including caffeine, ibuprofen, and acesulfame, by ZVI likely occurred in cell four.

3.5.7. Plant-Mediated Phytodegradation

Phytodegradation is a passive technology that utilizes plants and associated rhizosphere microorganisms to eliminate contaminants in soil and water [112]. Phytodegradation significantly enhanced the removal of PhACs, including ibuprofen, gemfibrozil, naproxen, and carbamazepine, in planted CWs compared to unplanted CWs, but not for caffeine and sulfamethoxazole [95,113,114]. There are three main removal processes involved in phytodegradation, including direct uptake, translocation, and transformation [115]. PhACs can be translocated to other parts of plants such as stems and leaves once they are taken up by the roots. However, the hydrophobicity and charge of PhACs can affect the uptake and translocation processes. Hydrophobicity likely reduces the translocation of PhACs from the roots to the leaves. Carbamazepine with an intermediate hydrophobicity (log K_{ow} = 2.45) accumulates 46% more in the leaves of lettuce than in the roots. Higher-hydrophobicity compounds (e.g., diclofenac, log K_{ow} = 4.5) are maintained 89% more in the roots than in the leaves [116]. In addition, charge can also affect the uptake of compounds by plants. For instance, the repulsive forces between negatively charged compounds and negatively net charged membranes tend to hinder the uptake of negatively charged compounds, such as ibuprofen and naproxen [75]. The phytodegradation of the target contaminants in this study using *Typha* spp. has not been previously reported. However, Dordio et al. [117] reported the phytodegradation of a similarly small-molecule polar PhAC, clofibric acid, by *Typha* spp., indicating the possible phytodegradation of the target contaminants in cell four in this study.

3.5.8. Other Potential Removal Mechanisms

In addition to the abovementioned removal mechanisms, there is potential for the removal of PhACs through other degradation reactions. Hydrolytic degradation is one of the most common degradation pathways for organic contaminants in the environment. The hydrolysis of organic compounds involves the substitution of an atom or group of atoms by water or hydroxide ions. Hydrolytic reactions are not important degradation processes in the environment for caffeine, carbamazepine, and naproxen due to the lack of hydrolysable functional groups in these chemicals [118]. Ibuprofen is not expected to undergo hydrolysis, as carboxylic acid functional groups are generally resistant to hydrolysis [118]. Under field conditions, hydrolysis is also not a likely degradation process for sulfamethoxazole [102] or acesulfame [22]. While there is potential for additional removal mechanisms, this study did not focus on the delineation of those mechanisms.

4. Conclusions

The overall treatment efficiencies observed in the multi-cell system evaluated in this study were similar to those observed in large-scale wastewater treatment systems and comparable to those in mesocosm-scale constructed wetlands. The removal of PhACs was affected by the measured pH and Eh values; however, the extent of the impact was compound-specific. The highly alkaline condition of cell four (BOFS and ZVI) likely promoted the dissociation of some compounds, enhancing the mobility (i.e., sulfamethoxazole and ibuprofen). The incorporation of BOFS and ZVI may have provided additional removal through reduction processes. Biodegradation, phytodegradation, and photodegradation are additional factors that impact the attenuation of certain pharmaceuticals and acesulfame in the environment. Caffeine, ibuprofen, naproxen, and sulfamethoxazole, for instance, are susceptible to aerobic biodegradation. In this study, carbamazepine and acesulfame showed minimal biodegradation and photodegradation effects. Although the system was operated during the winter and early spring, the treatment performances observed for caffeine and ibuprofen were higher than those observed in similar wastewater treatment systems during winter periods.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/w15152835/s1, Figure S1: pH versus distance (Cells 1-5) along the treatment flow path; Figure S2: pK_a of each pharmaceutical of interest plotted on the pH scale with dotted lines and the pH range of the treatment cells (Cells 1-4) shown with vertical bars; Figure S3: Calculated values of log D_{ow} versus pH in the influent (Cell 1 effluent) and three other treatment cells (Cells 2, 3, and 4); Table S1: Chemical properties and structures of target pharmaceutically active compounds and artificial sweetener acesulfame; Table S2: Quality control samples and preparation blanks, continuing calibration verification, and continuing calibration blanks. Target contaminants included artificial sweetener acesulfame (ACE), carbamazepine (CBZ), caffeine (CAF), sulfamethoxazole (SMX), ibuprofen (IBU), and naproxen (NAP); Table S3: P-values obtained from t-Test, two-sample assuming unequal variances, for Cells 1-2, 2-3, 3-4, 1-3, 1-4, and 2-4 for the selected contaminants, including caffeine (CAF), carbamazepine (CBZ), sulfamethoxazole (SMX), ibuprofen (IBU), naproxen (NAP), and an artificial sweetener, acesulfame (ACE); Table S4: Physical and chemical properties of the BOFS materials used in the experiments; Table S5: Physical and chemical properties of the ZVI materials used in the experiments.

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