Fate of selected pharmaceuticals and personal care products after secondary wastewater treatment processes in Taiwan

Angela Yu-Chen Lin, Cheng-Fan Lin, Yu-Ting Tsai, Hank Hui-Hsiang Lin, Jie Chen, Xiao-Huan Wang and Tsung-Hsien Yu

ABSTRACT

Pharmaceuticals and personal care products (PPCPs) constitute a class of chemicals of emerging concern due to the potential risks they pose to organisms and the environment, even at low concentrations (ng/L). Recent studies have found that PPCPs are not efficiently removed in secondary wastewater treatment plants (WWTPs). This study has: (1) simultaneously investigated the occurrence of sixty-one PPCPs using solid phase extraction and high-performance liquid chromatography-tandem mass spectrometry, (2) evaluated removal efficiencies of target PPCPs in six WWTPs that discharge effluents into major Taiwanese rivers, and lastly (3) examined matrix interference during analysis of target PPCPs in water samples. The twenty target PPCPs were chosen for their high detection frequencies, high influent concentrations, and stability during wastewater treatment processes. Caffeine and acetaminophen were detected at the highest concentrations (as high as 24,467 and 33,400 ng/L) and were effectively removed (both $>96\%$); other PPCPs were detected in the high ng/L range but were not effectively removed. Matrix interference (by ion suppression or enhancement) during the analysis resulted in underestimation of the removal efficiencies of erythromycin-H_2O, cefazolin, clarithromycin, ibuprofen, diclofenac, clofibric acid and gemfibrozil.

Key words | matrix interference, pharmaceuticals, wastewater treatment

Angela Yu-Chen Lin (corresponding author)
Cheng-Fan Lin
Yu-Ting Tsai
Hank Hui-Hsiang Lin
Jie Chen
Xiao-Huan Wang
Tsung-Hsien Yu
Graduate Institute of Environmental Engineering,
National Taiwan University,
71 Chou-Shan Road,
Taipei 106,
Taiwan, Chinese Taiwan
E-mail: *yuchenlin@ntu.edu.tw*

INTRODUCTION

Pharmaceuticals and personal care products (PPCPs) comprise a group of chemicals that have recently emerged as worthy of attention and increasing concern. Taiwanese consumers use great quantities of pharmaceuticals but also throw away 3.6 tons of pharmaceutical products annually, discarding unused drugs in toilets and rubbish bins. This results in the transmission of large quantities of drugs into surface waters through household drainage systems (The Union of Pharmacists Association, ROC 2008). The safety of water that has been treated for these pharmaceuticals is hotly debated. According to Dean (2007) and Lyons (2008), these contaminants have been found in water and therefore have the potential to enter the environment and harm local ecosystems and human residents.

Important removal pathways of organic compounds during wastewater treatment include biotransformation and adsorption onto sludge particles. In addition, physico-chemical properties of organic contaminants, such as solubility, hydrophobicity and biodegradability, are likely to have variable effects on the efficiency of wastewater treatment plants (WWTPs). PPCPs can survive conventional wastewater treatment processes and have been found to persist in treated water, albeit only in trace amounts (ng/L-μg/L) (Hirsch *et al.* 1999; Loraine & Pettigrove 2006;

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Farre *et al.* 2007; Zhang *et al.* 2008). In fact, WWTPs have been identified as a chief source of the PPCPs pouring into the environment, since PPCPs constantly enter WWTPs as either the parent compound or a range of secondary metabolites (Daughton & Ternes 2000). Kuster *et al.* (2008) found PPCP concentrations in effluents of less than 100 ng/L, with the exception of diclofenac, which was detected at 1200 ng/L. Sulfonamide and macrolide antibiotics were the most frequently detected compounds in terminal WWTP effluents in Canada, Switzerland, China and the UK (Miao *et al.* 2004; Xu *et al.* 2007; Barbara *et al.* 2009), and their elimination rates were very low, with almost none removed during wastewater treatment processes (Carballa *et al.* 2004; Matamoros *et al.* 2007; Lin 2007). Effluent concentrations of erythromycin-H_2O and clarithromycin were as high as 199 ng/L and 328 ng/L, respectively, and persisted through the winter, primarily because of their lower biological activity and higher influent concentrations (Mcardell *et al.* 2003). Hydrolysis of the conjugates may explain the increased erythromycin-H_2O concentrations in effluents (Barbara *et al.* 2009).

Studies have also demonstrated that secondary WWTPs that use advanced technologies such as membrane filtration, ozonation and activated carbons are effective at removing PPCPs (Huang *et al.* 2001; Roberts & Thomas 2006; Matamoros *et al.* 2007; Beltran *et al.* 2008). The most efficient advanced technology for PPCP elimination thus far appears to be reverse osmosis, followed by the use of O_3/UV, granular activated carbon and conventional disinfection with chlorine (Lin 2007). Elimination was minimal when pretreatment and sedimentation processes were used on acidic compounds with low k_{ow} values (Carballa *et al.* 2004). As these studies illustrate, it is essential to understand pharmaceutical concentrations in treated effluents and in their corresponding receiving rivers, as well as their removal rates following wastewater treatment, in order to improve our current understanding of their fate in the environment. Nevertheless, most WWTPs in Taiwan and around the world still use conventional treatment processes to remove PPCPs, and it is therefore important to monitor their occurrence and removal following WWTP treatment processes.

The current work contributes to our understanding of the occurrence of PPCPs, their negligible removal rates using conventional treatment processes and the probable health risks associated with releasing undertreated effluents into the rivers of Taiwan. Sixty-one PPCPs (including antibiotics, β-agonists, psychostimulants, vasodilators, psychiatric drugs, non-steroidal anti-inflammatory drugs (NSAIDs), an anti-ulcer agent and lipid regulators) were simultaneously analyzed, and twenty target PPCPs were chosen for their high detection frequencies, influent concentrations and stability during wastewater treatment processes (sulfamethoxazole, sulfamethazine, tetracycline, chlortetracycline, erythromycin-H_2O, clarithromycin, ampicillin, cloxacillin, cephalexin, cephradine, cefazolin, caffeine, acetaminophen, ibuprofen, naproxen, fenoprofen, ketoprofen, diclofenac, clofibric acid and gemfibrozil).

METHODS

Sample collection

Continuous sampling was not an option at the target sites because of technical difficulties. As a result, wastewater samples were collected as triplicate grab samples in one-liter pre-cleaned amber-glass bottles washed with methanol (MeOH) and deionized (DI) water according to the hydraulic retention time preferred by WWTPs. (The data derived using these methods have been consistent throughout our previous studies.) Eight mL of 0.125 M EDTA-2Na were added to amber-glass bottles to avoid adsorption of the compounds onto the glass. After collection, samples were stored in ice-packed containers to prevent bacterial growth during transit to the laboratory. All samples were vacuum-filtered through 0.45-μm and 0.22-μm membrane filters (cellulose acetate) and adjusted to pH 4 by the addition of sulfuric acid (2N) to avoid degradation of target analytes. Samples were then stored at 4°C before solid phase extraction (SPE) using Oasis HLB cartridges (500 mg, 6 mL, Waters, Milford, MA, USA). All samples were collected in August, 2008, and analysis was completed within two weeks of sample collection.

Site description and wastewater treatment process

Wastewater samples were collected from each of six Taiwanese WWTPs: four in Taipei (Duhua, Lotus Hill,

Huacheng and Neihu WWTPs), one in Taichung (Futian WWTP) and one in Tainan (Anping WWTP). Table 1 lists the characteristics of the six WWTPs investigated. These WWTPs were selected because their effluents are discharged into the major Taiwanese rivers, including the Danshue River, Keelung River, Xindian River, Green River and Anping Harbor. These rivers are the sources for drinking-water treatment processing plants, and their waters are distributed to large civilian populations.

Analytical methods

All target compounds were extracted using SPE, analyzed by high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) using Agilent's 1200 series HPLC system (Agilent Technologies, Palo Alto, CA, USA), and monitored using an API 4000 MS/MS system (Applied Biosystems, Taiwan) with data processing software (Analyst 1.4.2). The SPE extraction and instrumental methods were previously detailed in Lin *et al.* (2008) and Lin & Tsai (2009). In brief, Oasis HLB cartridges were preconditioned with 6 mL each of MeOH and DI water. Four hundred mL aliquots of the water samples were spiked with $^{13}C_6$-sulfamethazine (as a surrogate) and loaded into the cartridges. The analytes were eluted with 4 mL each of MeOH and MeOH-diethylether (50:50, v/v). The eluates were collected, evaporated to dryness with a flow of nitrogen gas, reconstituted to 0.4 mL with 25% aqueous MeOH and finally filtered through a 0.45-μm PVDF membrane filter before HPLC–MS/MS. All analyses were done in triplicate. Two multiple reaction monitoring (MRM) transitions were monitored for each compound. Compounds were identified using the LC retention time ±30% of the retention time of a standard. Method detection

Table 1 | Characteristics of the six wastewater treatment plants (WWTPs)

WWTPs	Population served ($\times 10^3$)	Primary treatment process	Secondary treatment process	Disinfection method	Hydraulic retention time (h)	Daily flow (m^3/d)	Discharge location
		• Aerated grit chamber	• Deep tank feed aeration tank	Chlorination	10	450000 to 500000	Danshue River
Dihua	2000	• Fine bar screen • Primary clarifier	• Secondary clarifier • Anaerobic sludge decomposition				
		• Fine bar screen	• Activated sludge aeration tank	Ultraviolet	20	800 to 1000	Keelung River
Lotus Hill	6.9	• Equalization basin • Primary clarifier	• Secondary clarifier • Sand filtration				
Huacheng	2.1	• Coarse bar screen • Equalization basin • Fine bar screen	• Trickling filter • Aeration tank • Sedimentation tank • Adsorption filter	Chlorination	36	540	Xindian River
Neihu	700	• Coarse bar screen • Fine bar screen • Vortex grit chamber • Primary clarifier	• Biological reactor • Secondary clarifier	Chlorination	12	150000	Keelung River
Futian	230	• Fine bar screen • Primary clarifier	• Aeration tank • Secondary clarifier	Chlorination	14	87500	Green River
Anping	570	• Fine bar screen • Vortex grit chamber • Primary clarifier	• Aeration tank • Secondary clarifier	Chlorination	15	132000	Anping Harbor

limits were determined using a 10:1 signal-to-noise ratio or better. The standard calibration curves were constructed by spiking waters with pharmaceutical standard solutions in the 0.5–2500 ng/L range, after which the same SPE procedures were followed, and linearity of the calibration curves was estimated by fitting a linear mode, least-squares regression analysis ($y = a + bx$).

Investigation of matrix interference

One major limitation of electrospray ionization mass spectrometry (ESI-MS) is the co-elution of matrix components due to the high susceptibility of the ionization source. This matrix effect results in either ion suppression or enhancement of the analyte signal. Therefore, signal suppression by the matrix presents a major challenge for quantitative LC-MS-MS analysis of organic compounds in wastewaters. It would be best to use as many labeled internal standards as possible to reduce the matrix effect. However, labeled internal standards are extremely expensive and were beyond our means. In this study, part of our goal was to determine which compounds were not affected (and could therefore be analyzed using current analytical methods) and to identify those that would need further investigation to establish more accurate concentrations. We therefore studied ion suppression and enhancement separately, to account for possible matrix interferences. Water samples from the Neihu WWTP were chosen for studying matrix interference because many effluents from this WWTP displayed higher pharmaceutical concentrations than influents did. We compared the magnitude of the ion suppression/enhancement calibration curves in spiked (1, 10, 100, 500, 1000 and 2,500 ng/L) influents, effluents and DI water (in 25% MeOH) samples.

RESULTS AND DISCUSSION

Occurrence of the target compounds

Effluent samples were collected in accordance with the hydraulic retention time tracking down the same water parcel. Figure 1 lists the 20 pharmaceuticals that were

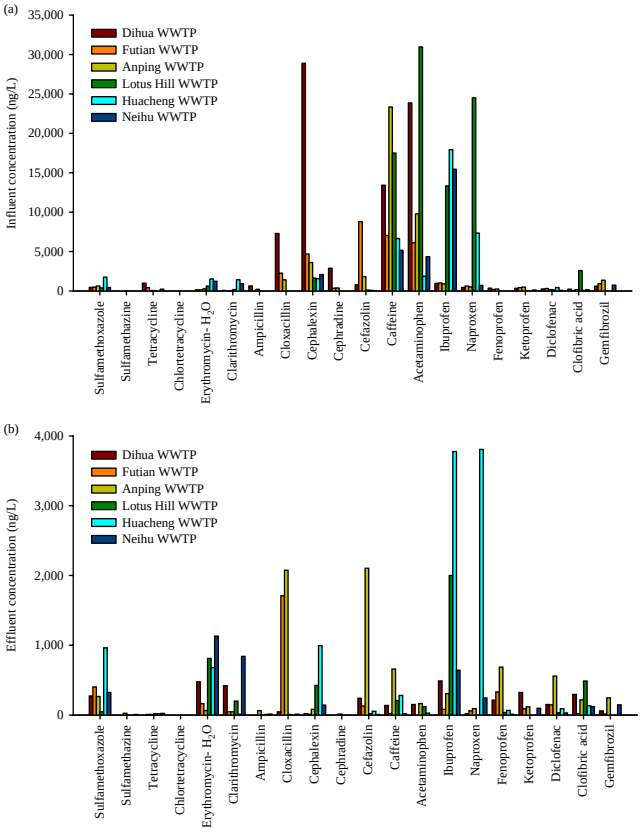

Figure 1 | Pharmaceuticals and personal care products detected in the influents (a) and effluents (b) of six wastewater treatment plants (WWTPs).

detected and their mean concentrations in the influents and effluents of the six WWTPs. Data were consistent for triplicate samples, and the standard deviation was less than 12% (error bars not shown). Since caffeine is a psychoactive stimulant drug that is often administered with other medications to increase their effectiveness, we grouped it with PPCPs for our study. Our results demonstrate that residuals from several PPCPs persisted through the WWTP treatment processes. Out of the twenty PPCPs studied, cephalexin, caffeine, acetaminophen, ibuprofen and naproxen had the highest influent concentrations, ranging from 1,536–28,889 ng/L, 5,173–23,345 ng/L, 1800–30967 ng/L, 711–17933 ng/L and 458–24,500 ng/L, respectively. Previous studies found similar aqueous concentrations. Cephalexin was found to be in the range of 670–2,900 ng/L in sewage treatment plant influents in Hong Kong (Gulkowska *et al.* 2008). High concentrations of caffeine (24,488–48,658 ng/L)

were observed in WWTP influents in Ohio (Spongberg & Witter 2008). In a study of the distribution of pharmaceuticals in WWTPs in Spain, concentrations of acetaminophen and ibuprofen were reported to be in the range of 7,100–11,400 ng/L and 14,600–31,300 ng/L respectively (Radjenovic *et al.* 2009). Concentrations of all five of these compounds were found in effluents at much lower levels, with maximum removal >95% for caffeine and acetaminophen. Among the twenty compounds studied here, concentrations of ibuprofen and naproxen were found to be high in effluents, ranging from 81–3,777 and 20–3,807 ng/L, respectively. Sulfamethoxazole, tetracycline, erythromycin-H_2O, clarithromycin and cefazolin were consistently detected but were present in relatively lower concentrations. Clarithromycin and erythromycin-H_2O persisted through the treatment process and were present at high concentrations in effluents, ranging from 45–419 and 62–712 ng/L. Chlortetracycline, cloxacillin, cephradine, sulfamethazine, ampicillin and gemfibrozil were only detected in samples from the Dihua, Futian and Anping WWTPs; the latter three were also detected in samples from the Neihu WWTP. The effluent concentrations of most PPCPs were below 1,000 ng/L, with the exception of ibuprofen, naproxen, cloxacillin and cefazolin, whose maximum detected concentrations ranged from 2,076–3,807 ng/L.

It is important to note that due to the high concentrations of pharmaceuticals in WWTP waters, method detection limits (MDLs) were determined using the water matrix upstream of each WWTP. Although the upstream matrix is similar to the influent sample, it is not exactly the same; therefore, our study could have reported a falsely low MDL. Nevertheless, because of the high loads of pharmaceutical concentrations in the influents and effluents, this would not significantly affect our results and conclusions.

Removal of target PPCPs during treatment processes

The primary methods for removal of organic species in any WWTP are biodegradation/biotransformation, adsorption onto sludge particles and volatilization. Since most pharmaceuticals have low values for Henry's coefficient, loss of PPCPs by volatilization is negligible (Khan & Ongerth 2004). Thus, it is clear that hydrophobicity and biodegradability dictate the removal efficiency of PPCPs in WWTPs. In this study, most of the target PPCPs were not removed during the primary treatment process in any of the six WWTPs. Carballa *et al.* (2004) also found no significant PPCP elimination resulting from pre-treatment and sedimentation processes for acidic compounds with low k_{ow} values. We observed similar phenomena in samples that had undergone primary treatment processes, but removal efficiencies were much improved after secondary treatment processes had been performed. Table 2 presents the influent concentrations and removal efficiencies for each PPCP in each of the six WWTPs. Caffeine and acetaminophen were removed to the greatest degree by the six monitored WWTPs. Where detected, tetracycline, ampicillin, cephalexin and cephradine were also mostly removed (except for the Huacheng WWTP, in which removal of tetracycline and cephalexin were 66 and 36%, respectively). On the other hand, sulfamethoxazole was 88% removed in the Lotus Hill WWTP but inadequately removed (20–59%) by all other plants during the disinfection process. Poor removal rates were also observed for sulfamethoxazole by Spongberg and Witter (2008) in their evaluation of pharmaceuticals in wastewaters. It has also been observed that sulfamethoxazole is sometimes not found in influents but is reported in effluents. This is attributed to the presence of sulfamethoxazole as a conjugated metabolite in influents, which is cleaved during the treatment process to release the individual moiety, resulting in detectable concentrations in the effluent (Lacey *et al.* 2008). For NSAIDs (ibuprofen and naproxen) in general, significant amounts were still present in the treated effluent. Ibuprofen is readily biodegradable (Quintana *et al.* 2005), with excellent removal efficiencies in WWTPs (Clara *et al.* 2005; Nakada *et al.* 2006); in our case, we found moderate removal (50–79%) in four WWTPs, with high removal (85–92%) in Lotus Hill and Futian WWTPs, respectively. For naproxen, >90% removal was seen in four WWTPs, while 48 and 66% removal rates were observed in the Huacheng and Neihu WWTPs, respectively. Naproxen showed degradation rates of 46% in batch culture studies (Quintana *et al.* 2005) with less than 50% removal in WWTPs (Nakada *et al.* 2006). Effluent concentrations of erythromycin-H_2O, clarithromycin and fenoprofen increased progressively after each treatment process (from influent, primary treatment,

secondary treatment, to disinfection) in many WWTPs, resulting in a no-removal (NR) rating, as shown in Table 2. Macrolide antibiotics survived WWTP processing and sometimes displayed higher effluent concentrations (Huang *et al.* 2001; Westerhoff *et al.* 2005; Kim *et al.* 2007; Xu *et al.* 2007). The increase in effluent compared to influent concentrations may be due to the presence of conjugated forms of these compounds in influents that may have segregated during the treatment process, resulting in high concentrations in effluents. However, no explanation has yet been proposed for the increased concentrations of fenoprofen in effluents.

Of the six WWTPs, the Huacheng WWTP reported peculiar results compared to the other five. Their removal rates of clarithromycin and diclofenac were 99 and 80%, respectively, in contrast to the low or no removal reported in the other five WWTPs. For the degradation of diclofenac, divergent results have been reported. Neither biotransformation nor biodegradation were found in batch culture experiments (Quintana *et al.* 2005; Joss *et al.* 2006); in contrast, Urase & Kikuta (2005) reported biodegradation in an activated sludge process. In addition, there is no consensus on the biodegradation of diclofenac in WWTPs, with removals ranging from 0–69% (Lindqvist *et al.* 2005; Radjenovic *et al.* 2007). The difference in the composition and age of the sludge and the complexity of wastewaters may explain the conflicting results obtained for diclofenac. For clarithromycin, poor removal rates have been reported (Gobel *et al.* 2007; MacLeod & Wong 2010), with the exception of membrane bioreactors with a high sludge age, in which 90% removal was observed (Gobel *et al.* 2007). Thus, the high removal rates of clarithromycin seen in

Table 2 | Occurrence and removal of target pharmaceuticals and personal care products in six wastewater treatment plans

			Removal efficiency (%) for each WWTP					
Compound	**MDL (ng/L)**	**Influent concentration (ng/L)**	**Dihua**	**Futian**	**Anping**	**Lotus Hill**	**Huacheng**	**Neihu**
Sulfamethoxazole	1.0	405–1760	42	20	59	88	45	26
Sulfamethazine	0.5	ND–22	72	91	NR	–	–	NR
Tetracycline	2.0	46–1007	> 99	98	83	70	66	90
Chlortetracycline	5.0	ND–22	76	87	6	–	–	–
Erythromycin- H_2O	1.0	141–1537	NR	NR	77	NR	56	NR
Clarithromycin	1.0	27–1433	NR	NR	10	NR	99	NR
Ampicillin	10	ND–650	> 99	> 99	71	–	NR	NR
Cloxacillin	2.5	ND–7297	99	24	NR	NR	–	NR
Cephalexin	2.5	1536–28889	> 99	> 99	98	74	36	93
Cephradine	1.0	ND–2889	> 99	> 99	96	–	–	–
Cefazolin	25	83–8793	70	99	NR	87	36	69
Caffeine	2.0	5173–23345	99	> 99	97	99	96	> 99
Acetaminophen	2.0	1800–30967	99	> 99	98	> 99	99	> 99
Ibuprofen	25	711–17933	50	92	66	85	79	56
Naproxen	10	458–24500	96	91	83	> 99	48	66
Fenoprofen	5.0	ND–357	40	NR	NR	NR	NR	28
Ketoprofen	10	ND–503	4	80	77	–	–	26
Diclofenac	2.5	3–437	42	55	NR	77	80	NR
Clofibric acid	1.0	36–2593	NR	68	NR	81	NR	NR
Gemfibrozil	1.0	ND–1378	91	98	82	–	–	NR

Note: MDL: method detection limit, ND: not detected, NR: not removed, "-" not detected in either influent or effluent; thus removal efficiency is not reported).

Huacheng WWTP can be attributed to their use of aged sludge along with high pharmaceutical concentrations, which make it available for degradation by microflora.

Matrix interference

Analysis of pharmaceuticals may be influenced by electrospray ionization (ESI) processes and by ion suppression via several different mechanisms (Choi *et al.* 2001; Gros *et al.* 2006; Gomez *et al.* 2006). Contaminants can mask the analyte peak, thereby raising the chromatogram's baseline and causing the chromatographic curve to be underestimated. In addition, the contaminant may reduce ionization efficiency by occupying the limited number of charged sites available on ES droplets (Gomez *et al.* 2006).

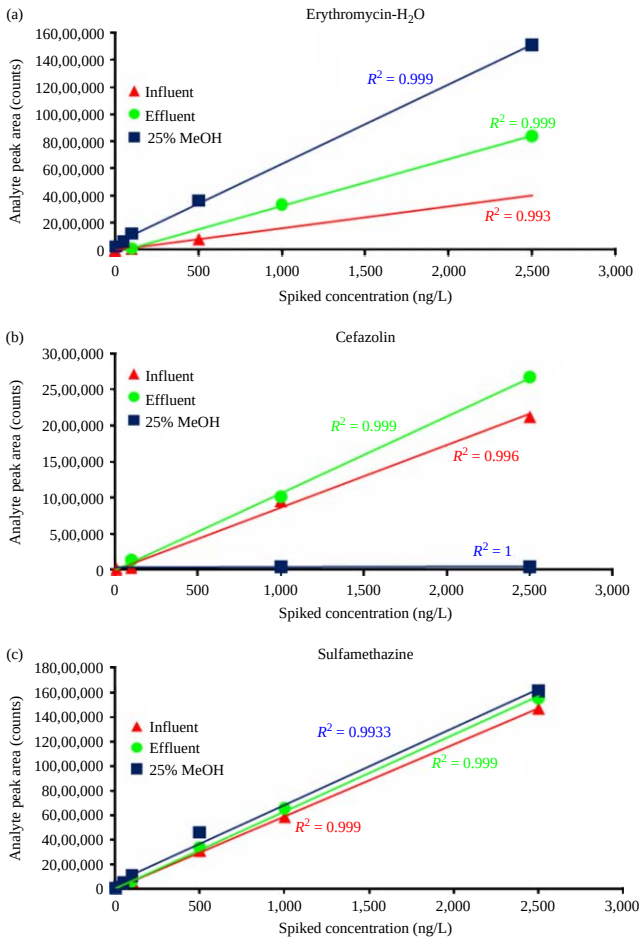

Figure 2 | Matrix interference study for (a) erythromycin-H_2O (b) cefazolin (c) sulfamethazine.

Our matrix interference study was performed using Neihu WWTP water and showed that both ion suppression and enhancement were present during the analysis and affected the calculated removal efficiencies; results for erythromycin-H_2O, cefazolin, and sulfamethazine are shown in Figure 2. Three curves were constructed to compare the matrix interference. One curve represents the spiked analyte in solvent (25% MeOH), while the other two depict the spiked influent and effluent samples. (Background influent and effluent concentrations were subtracted for ease of comparison.) Deviation from the solvent line implies ion suppression (Figure 2(a)) or enhancement (Figure 2(b)) due to matrix interference. Furthermore, no matrix interference was observed when the 25% MeOH solvent line was parallel with the spiked influent and effluent lines (Figure 2(c)).

Figure 2(a, b) show that the slopes of the spiked effluent lines were higher than slopes of the spiked influent lines, resulting in increased detected effluent concentrations (relative to the influents) and lowering the apparent removal efficiency. Analysis of erythromycin-H_2O, for example, demonstrated that influent water samples were much more suppressed than effluent water samples were, possibly due to the complexity of wastewaters before treatment. These phenomena could result in falsely higher effluent concentrations and underestimation of the true removal efficiencies during the treatment processes. This likely contributed to the nearly or completely nonexistent removal efficiencies reported for erythromycin-H_2O and cefazolin. Moreover, similar findings (as shown in Figure 2(a)) were observed during our analysis of clarithromycin, ibuprofen, diclofenac, clofibric acid and gemfibrozil (data not shown), with greater suppression in influent vs. effluent water samples, resulting in an underestimation of removal efficiencies in this study. Further details describing the process of quantifying signal suppression/enhancement are presented in the supplementary information section.

CONCLUSION

Elimination of PPCPs in WWTPs is an extremely intricate process that must take advantage of various removal mechanisms. The major factor that influences removal of PPCPs during wastewater treatment processes is the extent

to which PPCPs interact with solid particles, which facilitates their removal by physico-chemical or biological processes. Accordingly, PPCPs with low adsorption coefficients are likely to remain in the aqueous phase, allowing them to pass unhindered through WWTPs and into receiving waters (Roberts & Thomas 2006).

In this study, caffeine and NSAIDs were detected at the highest concentrations (up to 24,467 and 33,400 ng/L) and were removed effectively (>96%) by most WWTPs; other PPCPs were also detected in the high ng/L range but were not effectively removed via secondary wastewater treatment processes. Matrix interference resulted in significant suppression of influent samples and consequent underestimation of removal efficiencies for erythromycin-H_2O, clarithromycin, ibuprofen, diclofenac, clofibric acid and gemfibrozil. Hence, more extensive research is needed to determine and quantify the organic factors present in complex wastewaters. A prerequisite for monitoring PPCPs is a reliable, interference-free, multi-residue method that permits ng/L measurement. With such a method, matrix effects, influence of background organic materials, sorption of target compounds onto organic matter, etc. could be investigated at greater depth. This work provides insights into the performance of WWTPs and clarifies the fate of pharmaceuticals after treatment processes. Additionally, we have shown that effluents from treatment plants continue to increase the PPCP load in aquatic systems. The still-high levels present in treated water could induce specific ecological or biological alterations or harm in local flora/fauna/humans. Therefore treatment plants should be upgraded to eliminate these pharmaceuticals to the greatest possible extent before their effluents are released into the environment.

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