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Pharmaceutical Compounds in Malaysian Urban Domestic Wastewater

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ABSTRACT

The emerging contaminants (ECs) is detected at trace concentration in the discharge of sewage treatment plant (STP) to the water bodies indicate incomplete removal during the treatment process. The presence of the ECs in the water has a potential impact on the ecological and human health associated with long-term ingestion of the mixture ECs compounds, and this includes the development of resistance in pathogenic bacteria, aquatic toxicity, genotoxicity, and endocrine disruption. In this study, we investigate the presence of ECs and review the occurrence of mainly of four pharmaceutical active compounds belonging to the group of non-steroidal anti-inflammatory drugs (NSAIDs) in influent and effluent of the STP. The target analytes (ibuprofen (IBU), diclofenac (DIC), ketoprofen (KET), and naproxen (NAP)) are extracted from the wastewater using the solid-phase extraction (SPE) followed by the identification and quantification using gas chromatography-mass spectrometry (GC-MS). The GC-MS detection was improved by the derivatisation technique using N-Methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA) and an internal standard of Ibuprofen-D3 used as the internal standard. The targeted analytes were detected in both influent and effluent wastewater in the range 5.04±5.9 to 37.4±28.4 µg/L with removal efficiency between 11 - 86% using the current activated sludge treatment process in the STP. This concentration of compounds shows inadequate current treatment techniques to eliminate the emerging contaminants in the wastewater.

Keywords: Emerging contaminants; sewage treatment plant; pharmaceutical active compounds; non-steroidal anti-inflammatory drugs

INTRODUCTION

Water management on reused and recycled water is one of the points of the green and sustainable city these days. To meet the purpose, many countries are reusing many sources of wastewater source to be recycled and this including irrigation of wastewater effluent, mainly used for crop irrigation, agriculture, and landscaping area. The main issue of using this water is indirectly exposed to chemically effect on the emerging contaminants, and most of these substances are pharmaceuticals, surfactants, biocides, personal care products, plasticizers, and flame retardants (Rogowska et al. 2020; Tran et al. 2019; Wluka et al. 2017). Some of these contaminants are persistent in the wastewater treatment plant such as pharmaceuticals, and personal care, which are partially removed during the treatment process (Jelic et al. 2012; Subedi & Kannan 2015).

The emerging contaminants such as pharmaceuticals are found in domestic wastewater mainly contributed from human excreta as direct oral consumption and original from the compound as is direct disposal unused medicine to the toilet (Heberer 2002). The increasing number of ECs in wastewater and treated potable water in recent years leads to an increase in environmental concern (Stuart et al. 2012; Grossberger et al. 2014). Their presence has been detected in drinking water (Cabrita et al. 2010) and a variety of crops such as tomato plants (Gorovits et al. 2020), radish (Al-Farsi et al. 2018), lettuce, and carrots (Carter et al. 2014). Due to not being completely removed in the wastewater treatment process, some of the pharmaceutical compounds are considered recalcitrant and did not break down in the environment for a long lifetime, thus will accumulate to plants, animals, and water sources which final will consume by a human through the food chain (Farzaneh et al. 2020).

Non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen, ketoprofen, naproxen, and diclofenac are widely used to relieve different symptoms such as fever, migraine, tooth pain, and muscle pain (Fokunang, 2018) are the most frequently detected with the most concentration in the water up the concentration of µg/L and consider as

emerging contaminant (Tyumina et al. 2020). As found by Li et al. (2013), the concentration of ibuprofen and naproxen in effluent wastewater in China was 0.146 and 0.062 µg/L, respectively. Meanwhile, Matongo et al. (2015) identified 58.71±1.82 µg/L of ibuprofen in the effluent of an STP in South Africa. Furthermore, the study performed by Larsson et al. (2014) found that the concentration of Ibuprofen, ketoprofen, naproxen, and diclofenac, in the effluent of wastewater treatment plant located in Sweden, was 0.52, 0.48, 0.78, and 0.36 µg/L, respectively, showing that their existence in the effluent of the wastewater treatment, and being directly discharged into the water bodies. Although they are at trace concentrations, their presence can affect aquatic life and human health such as the reproductive system and kidney (Chopra & Kumar 2020).

Nowadays, many analytical methods on the determination of pharmaceuticals in the aqueous sample have been developed by the researcher. For example, Semreen et al. (2019) in research detection of pharmaceuticals by solid-phase extraction (SPE) and liquid chromatography-tandem mass spectrometry (LC-MS/MS); Madikizela & Chimuka (2017) in research of detection naproxen, ibuprofen, and diclofenac in wastewater using SPE and high-performance liquid chromatography (HPLC); Roberts et al. (2015) in determination of pharmaceuticals and personal care products (PPCPs) in sewage using extraction method of SPE and detection using combination LC-MS/MS and GC-MS; meanwhile Togola & Budzinski (2007) in research of analytical detection the pharmaceuticals in a water sample by SPE and GC-MS. These studies have shown successfully an analytical method for the detection and determination concentration of targeted pharmaceuticals compounds using a different type of analytical method.

Thus, with the modification of the analysis from the literature, this work is to identify the targeted compound of therapeutic class NSAIDs which are ibuprofen (IBU), diclofenac (DIC), ketoprofen (KET), and naproxen (NAP) in the influent and effluent of local sewage treatment plant (STP), particularly in a tropical climate scenario and the advance treatment in removing the EC from wastewater using the analytical procedure includes a solid-phase extraction following by detection using gas chromatography-mass spectrometry (GC-MS).

METHODOLOGY

CHEMICAL AND REAGENTS

Pharmaceutical compounds used of Ibuprofen (IBU), Naproxen (NAP), Ketoprofen (KET), Diclofenac (DIC), and Isotope-labelled standard Ibuprofen-D3 (IBU-D3) were purchased from Sigma Aldrich, Germany with high purity >98%. Methanol (HPLC Grade), Ethyl Acetate (AR Grade), and hydrochloric acid 37% were purchased from Sigma-Aldrich, Germany. For the solid-phase extraction (SPE), the cartridges used Oasis® hydrophilic-lipophilic balanced (HLB, 6 cc, 200 mg) purchased from Waters (USA). MSTFA as the derivatization reagent was purchased from sigma Aldrich. Ultrapure water with a resistivity of 18.2MΩ cm was obtained from mili-Q system (Millipore).

Stock standard solutions were prepared at a concentration of 1 mg/mL by dissolving the appropriate amount of each compound in methanol. The stock solutions and mixtures were stored in the dark at 4°C.

SAMPLE COLLECTION AND PREPARATION

The wastewater sample was collected from both influent and effluent chambers of the sewage treatment plant (STP) design with a population equivalent (PE) of 150,000 and a daily flow of 33,750 m3/day. The nature of water treated in this STP is domestic and from commercial areas shown in Figure 1.

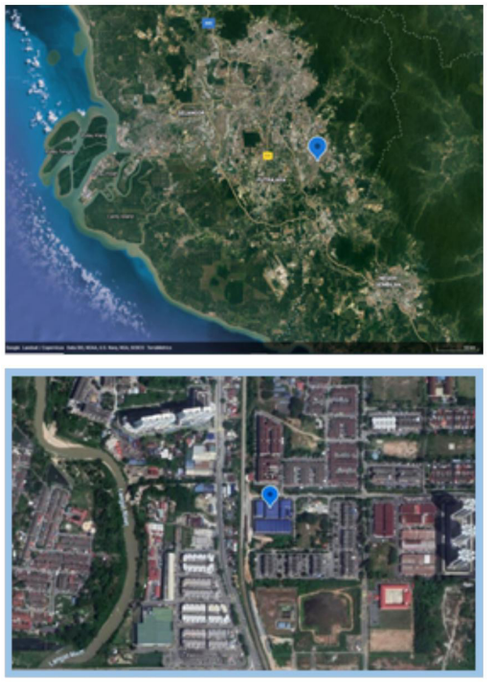


FIGURE 1. Sampling location

Wastewater samples were collected in 1 L dry amber glass bottles pre-rinsed with methanol and ultrapure water. Three replicate samples were collected for each location of sampling. In the first step of solid phase extraction, all collected samples were homogenised and filtered under vacuum through 0.7 µm glass fibre filter (GF/F) (Whatman, UK) to remove any particulate matter and kept 4°C in the dark prior to extraction maximum up to 1 week.

SOLID PHASE EXTRACTION

Solid phase extraction (SPE) is the most common method of extraction pharmaceuticals from water and wastewater as a replacement to liquid-liquid extraction (LLE). The cartridge selection is Oasis ® HLB (Hydrophilic-lipophilic balance) has no limited recovery for polar and non-polar compounds

(Kermia et al. 2016). As the selected targeted compound are high in polarity, thermal fragility, and weak volatility, the additional step of derivatization is needed to improve increase the volatility and stability of the compound in GC-MS detection. As the procedure was adapting to the (Nosek et al. 2014) with some modification.

The SPE procedure using Oasis® HLB cartridge (200 mg/6 cc) and the summary shown in Figure 2. The SPE cartridges were pre-conditioned using 3 mL ethyl acetate, 3 mL methanol, and 3 mL ultra-pure water at pH 3 (adjusted using 1 M HCl) at a flow rate of 3 mL/min. The filtered samples (200 mL influent and effluent adjusted pH to 3 using 1 M HCl) was then passed through the cartridge with a flow rate of 15 mL/min using a vacuum manifold system (Waters) connected to a vacuum pump as per set up shown in Figure 3.

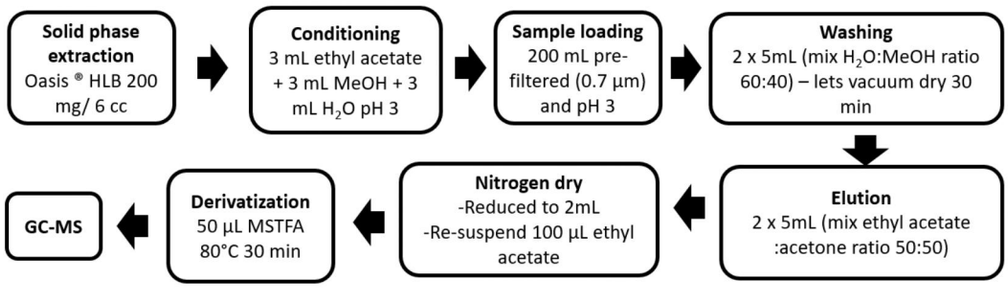


FIGURE 2. Flow chart of extraction by SPE

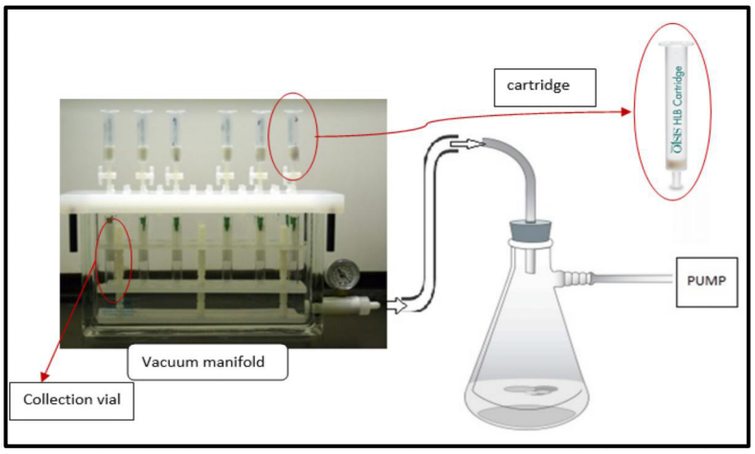


FIGURE 3. Apparatus set up for solid phase extraction (SPE) using vacuum manifold connected to pump (SPE manifold, Waters)

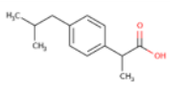
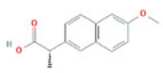
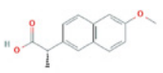
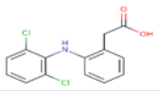
The cartridge then was rinsed with a solution (10 mL) of ultra-pure water: methanol (ratio 60:40) at a flow rate of 3 mL/min. and dried under vacuum for 30 min. Then, the elution was performed with 5 mL two times (total 10 mL) of ethyl acetate: acetone (ratio 50:50) and collected in 10 mL vials. The volumes of extraction were reduced under nitrogen gas to 2 mL and dissolved in 100 µL ethyl acetate. Finally, the derivatization reaction was performed by adding, 50 µL of MSTFA, with incubation at 80°C for 30 min.

GC-MS ANALYSIS

Currently, the most preferred choice of instrument in detection pharmaceutical in environmental water is liquid chromatography followed by tandem mass spectrometry (LC-MS/MS) because of avoiding the derivatization step. However, because of the limited availability and expensive of the LC-MS/MS instrument, and limitation on signal suppression phenomena during analysis (Gros et al. 2006). The GC-MS is chosen for the analysis due to widespread availability in environmental laboratories, less cost, and high sensitivity.

The target compounds were analysed by the method of GC-MS using an Agilent 6890N GC system connected to MSD 5975C detector (Agilent Technologies, USA). The carrier gas was ultrapure helium with purity >99.99% and set at the constant flow of mode, 1.3 mL/min. The chromatography separation was achieved in an HP-5 MS capillary column (30 m x 0.25 mm x 0.25 µm film thickness) (Agilent J&W, USA) connecting the inlet to the MS interface. The volume of extracted samples injected into the GC was 1µL and in split-less mode at 250°C using Agilent 7683B automatic liquid sampler injector. The GC oven temperature program was set initially at 70°C (2 min), and then increased to 280°C at the rate of 15°C/min and hold for 2 min. The MS was set for SIM mode for the selected mass on target compounds and identified with MS software NIST version 5.5 (Table 1).

TABLE 1. Chemical structure and molecular formula of targeted compounds

Targeted compounds	Chemical Structure	Molecular formula	CAS number	Molecular Weight (g/mol)
Ibuprofen (IBU)		$C_{13}H_{18}O_2$	15687-27-1	206.28
Naproxen (NAP)		$C_{14}H_{14}O_3$	22204-53-1	230.26
Ketoprofen (KET)		$C_{16}H_{14}O_3$	22071-15-4	254.28
Diclofenac (DIC)		$C_{14}H_{10}Cl_2NNaO_2$	15307-79-6	318.13

QUANTIFICATION

An external standard was used for monitoring the instrument and procedure for SPE and GCMS analysis. A four-point calibration curve with the concentration of standard from 500 µg/L to 5000 µg/L was prepared. A constant amount of surrogate Isotope-labelled standard Ibuprofen-D3 (IBU-D3) (100 µg/L) was added before the SPE to calibrate and compensate the experiment losses.

RESULT AND DISCUSSION

SELECTED PHARMACEUTICAL IN DOMESTIC WASTEWATER

The retention and characteristic ion of the target compounds are shown in Table 2 and all the compounds were separated in 12.799 min. The experiment shows satisfactory recovery between 73 to 102%. The recovery method was done by performed independently spike each compound to the wastewater at the concentration of 100 µg/L prior to the SPE method. The method detection limit (MDL) was determined to identify the minimum detection concentration of the compound and the limit is between 0.14 to 0.19 µg/L.

TABLE 2. Retention time, mass-to-charge (m/z) ratio, recovery, and method detection limit (MDL) of the analytical method

Compound	Retention time (min)	*m/z* ratio	Recovery (%)	MDL (µg/L)
IBU	8.155	161	102	0.16
NAP	11.57	185	97	0.14
KET	12.31	209	73	0.19
DIC	12.799	214	88	0.17
IBU-D3	8.155	164		

The concentration of the selected compound is shown in Table 3. The analysis has shown that all targeted compound is present in the influent and effluent chambers of the sewage treatment plant except for ibuprofen, where it was measured under the method detection limit (MDL). Besides ibuprofen, among them, naproxen is presence in influent with the highest concentration of 37.4±28.4 µg/L, meanwhile, the less concentration compound is ketoprofen 21.67±4.1 µg/L, followed by diclofenac 12.53±1.5 µg/L. By contrast, the concentration in the effluent, Naproxen has the lowest concentration in comparison to other compounds which are 5.01±5.9 µg/L, indicating 86.54% percent of removal. Lower removal efficiency can be seen on ketoprofen and diclofenac in effluent with 19.09±5.8 µg/L and 8.28±1.2 µg/L, respectively, giving removal efficiency of 11.89% of ketoprofen and 33.96% diclofenac. Results show that the studied STP could reduce the naproxen from the high initial concentration, however low removal efficiency for ketoprofen and diclofenac was observed. However, detected NSAIDs in the effluent wastewater showing that they were discharged into the open water bodies, along with the effluent of STP. The high concentration of naproxen, ketoprofen, and diclofenac in the effluent is considered pseudo-persistence because of their continuous use and release to the environmental consequence of the wide consumption of this medicine (Ebele et al. 2017).

TABLE 3. Concentration of targeted compounds ± standard error in influent and effluent (*n*=3)

Compounds	Influent (µg/L)	Effluent (µg/L)	removal efficiency (%)
IBU	<MDL	<MDL	<MDL
NAP	37.4±28.4	5.04±5.9	86.54
KET	21.67±4.1	19.09±5.8	11.89
DIC	12.53±1.5	8.28±1.2	33.96

<MDL: Method detection limit

A comparative study comparing similar targeted compound in previously reported in Algeria (Kermia et al. 2016), South Africa (Matongo et al. 2015), Poland (Nosek et al. 2014), Sweden (Larsson et al. 2014), and China (Li et al. 2013) to the current data (Malaysia) is tabulated as per Table 3. The comparison indicates that the concentrations of the targeted compound were present in influent and effluent of the wastewater treatment and usually vary from low ng/L up to high µg/L. The concentration of the compounds in the influent is higher than the concentration in the effluent, as we can see the range in influent was between 0.508 to 37.4 µg/L

and in the effluent between 0.04 to 19.09 µg/L. This showed that the compound is reducing during the treatment process but not fully degraded the compound in an average of about 48% from its concentration in the wastewater. Furthermore, the concentration of naproxen, diclofenac, and ketoprofen in the influent and effluent of the current study are detected higher than those reported in other countries. The higher concentration of NSAIDs in Malaysian wastewater was estimated due to higher consumption of the medicine in the citizen. As reported by (S Maria Awaluddin et al. 2017), about 14.2% among Malaysian adults in consumption of NSAIDs and about 4.2% of them is prevalence as daily NSAIDs user.

TABLE 4. Comparison with different studies locations (µg/L)

Location	IBU	NAP	DIC	KET	Reference
STP influent					
Algeria	1.608-8.613	1.220-9.585	0.991-2.319	<0.565	Kermia et al. 2016
South Africa	62.82±4.23	nd	nd	nd	Matongo et al. 2015
Poland	2.496±0.003	0.696±0.007	0.249±0.031	0.508±0.066	Nosek et al. 2014
Sweden	15.67-22.82	8.8-9.49	1.55-2.25	0.44-1.35	Larsson et al. 2014
China	18.6	19.4	nd	nd	Li et al. 2013
Malaysia	<MDL	37.4±28.4	12.53±1.5	21.67±4.1	This study
STP effluent					
Algeria	0.341-0.431	<334	1.616-2.711	<1.035	Kermia et al. 2016
South Africa	58.71±1.82	nd	nd	nd	Matongo et al. 2015
Poland	<0.042	0.313±0.015	0.545±0.001	0.485±0.029	Nosek et al. 2014
Sweden	0-0.52	0.22-0.78	0.04-0.36	0-0.48	Larsson et al. 2014
China	0.146	0.062	nd	nd	Li et al. 2013
Malaysia	<MDL	5.04±5.9	8.28±1.2	19.09±5.8	This study

<MDL: Method detection limit
nd: not determine

TREATMENT PROCESS IN REDUCING PHARMACEUTICALS IN WASTEWATER

Due to the detection concentration of NSAIDs (ibuprofen, diclofenac, ketoprofen, and naproxen) in the influent and effluent of the current studied STP, some modifications and additional processes are suggested to minimize and remove the compounds from the wastewater before final discharge to the environment. Currently, attention is much given to the advanced treatment using activated carbon adsorption, advanced oxidation processes (AOPs), and a combination of the treatment process.

The method of activated carbon including biological activated carbon (BAC), powdered activated carbon (PAC), and granular activated carbon (GAC) is usually used in experimental to removed pharmaceuticals from wastewater. For example, more than 80% to 90% of antibiotics has been eliminated in synthetic wastewater in work done by Sbardella et al. (2018) using a combination BAC and ultrafiltration system, and more than 95% of selected pharmaceutically active compounds (PhACs) has been removed using PAC and GAC from domestic wastewater treatment plant in the work done by Kårelid et al. (2017). Besides the advanced adsorption process, treatment by AOPs has been being studied in the removal of emerging contaminants from wastewater. In AOP, the treatment was based on the generation and reactivity of hydroxyl radical (OH.), which is offering great potential and promising results in the degradation of emerging contaminants (Loaiza-Ambuludi et al. 2013). Heterogeneous photocatalysis (HP) and electrochemical advanced oxidation processes (EAOP) are an example of the AOPs treatment. As an example, in the treatment of removal NSAIDs from domestic wastewater using electro-Fenton AOP performed by Villanueva-Rodríguez et al. (2019) they found that above 80% has been removed. In the work done by Helena et al. 2018 using a combination of AOP technology, the bio-electro-Fenton process, after 5 hours of treatment about 59-97% of targeted pharmaceuticals compound from wastewater has been eliminated.

CONCLUSION

The studied compounds of pharmaceuticals namely ibuprofen (IBU), diclofenac (DIC), ketoprofen (KET), and naproxen (NAP) are available in the influent and effluent wastewater. The presence of target compounds in the effluent of the studied sewage treatment plant (STP) showed that the plant is insufficient to remove the compounds from wastewater due to their persistence to the treatment process with a removal range between 11 to 86%. The continuous contribution due to the high consumption of medicine also contributes to the high concentration of the compound in the wastewater. The incomplete decomposition of NSAIDs

in the treatment process caused the compound available in the open water such as river which is known their presence in the environment has a negative ecotoxicological effect through their parent compound or via its metabolites. Advance treatment is needed to achieve efficient removal of the persistent compound of pharmaceuticals in wastewater treatment such as adsorption using activated carbon and advanced oxidation process (AOP). The factors such as operating cost, the effectiveness of treatment, and the final effluent byproduct and toxicity should consider in choosing the best treatment in removing emerging contaminants from wastewater.

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DECLARATION OF COMPETING INTEREST

None

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