HOLLOW FIBER LIQUID PHASE MICROEXTRACTION OF PHARMACEUTICALS IN WATER AND *EICHHORNIA CRASSIPES*

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by

NOMCHENGE YAMKELANI MLUNGUZA

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Supervisor: Dr LAWRENCE M. MADIKIZELA

Co-supervisor: Prof LUKE CHIMUKA

Co-supervisor: Dr PRECIOUS N. MAHLAMBI

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Declaration

I declare that this dissertation is my own and unaided work. It is for the first time being submitted for the **Master of Applied Sciences in Chemistry**, Durban University of Technology, Durban, South Africa. It has not been submitted before for any degree or examination to any other institution.

Ms. Nomchenge Yamkelani Mlunguza

Department of Chemistry, Durban University of Technology, Durban. 4001

This thesis is submitted after examination and approval by the following supervisors;

Dr L.M. Madikizela (Supervisor)

Department of Chemistry, Durban University of Technology, Durban. 4001

Prof. L. Chimuka (co-supervisor)

School of Chemistry, University of the Witwatersrand, Johannesburg, 2016

Dr P.N. Mahlambi (co-supervisor)

School of Chemistry and Physics, University of Kwazulu-Natal, Pietermaritzburg, 3209

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Indeed, there is a living God out there (***NDIMBONA APHA KUM***).

Dedication

I dedicate this dissertation to my kids Tar Ayzo, Aya, Mno, Nhanha, Esi, Itha, Miyoza, Malema, Nika and Lino. My mother Queen Thirdish and her better-half King Morutsi, my siblings Sis K, Tar Shava and Tar Lambesa and the whole LA Familia.

Abstract

This work describes a simple and rapid method for the simultaneous isolation, enrichment, and quantitation of selected pharmaceuticals in aqueous environmental samples and E*ichhornia crassipes*. This was achieved by developing a hollow fiber liquid phase microextraction (HF-LPME) technique coupled with ultra-high-pressure liquid chromatography-high resolution mass spectrometry for the simultaneous extraction, pre-concentration and quantitation of four non-steroidal anti-inflammatory drugs (NSAIDs) and three antiretroviral drugs (ARVDs) from aqueous matrices and different segments of water hyacinth plant species. The target compounds for NSAIDs were naproxen (NAP), fenoprofen (FENO), diclofenac (DICLO) and ibuprofen (IBU) whereas the selected ARVDs included emtricitabine (FTC), tenofovir disoproxil (TD) and efavirenz (EFV). A multivariate approach by means of a half-fractional factorial design was used to optimize the HF-LPME technique focusing on six factors; donor phase (DP) pH, acceptor phase (AP) pH, extraction time, stirring rate, supported liquid membrane carrier composition (SLM carrier comp.) and salt content. Four of these factors (DP pH, AP pH, stirring rate and extraction time) were identified as vital for an enhanced enrichment of each of the selected NSAIDs and four of the previously mentioned vital factors including the SLM carrier composition were classified as significant for the selected ARVDs from aqueous samples into the hollow fiber. These essential factors were further paired according to their level of significance. The paired significant factors were then optimized using central composite designs (CCD) where empirical quadratic response models were used to visualize the response surface through contour plots, surface plots and optimization plots of the response outputs. The optimized factors for individual analytes belonging to each class were then altered to universal conditions for their simultaneous extraction from same sample solution. The acceptability of the universal conditions was

defined using desirability studies. A composite desirability value of 0.7144 was obtained when the optimum factors of the three ARVDs were applied for their simultaneous extraction while a simultaneous extraction of NSAIDs had a desirability value of 0.7735. This implied that the set conditions were ideal for a combined extraction of the target compounds from the donor phase into the acceptor phase across a supported liquid membrane impregnated with a carrier molecule. For the simultaneous extraction of ARVDs, the universal optimum HF-LPME conditions were found to be DP pH of 4, AP HCl conc. of 200 mM (pH = 0.4) with SLM carrier comp. set at 4.5 (%w/w) and stirring at 1000 rpm. Under optimum conditions, the enrichment factors (EF) for ARVDs from aqueous phase were 78 (FTC), 111 (TD) and 24 (EFV). These conditions yielded recoveries in the range of 96 to 111%. The sensitivity of the analytical method through limits of quantification (LOQ) for the selected ARVDs in wastewater samples were 0.033 µg L^{-1} (FTC), 0.10 µg L^{-1} (TD) and 0.53 µg L^{-1} (EFV). The LOQ values were computed for surface water samples using the same target ARVDs were 0.169 µg L^{-1} (FTC), 0.018 µg L^{-1} (TD) and 0.113 µg L^{-1} (EFV).

For NSAIDs, the overall conditions were DP pH of 10, AP pH of 3 at an extraction time of 60 min with stirring rate at 1000 rpm. The recoveries yielded under these optimum conditions for the target compounds ranged from 86 to 116%. The EF for the target NSAIDs from aqueous media were 49 (NAP), 126 (FENO), 93 (DICLO) and 156 (IBU). The LOQ values for each target NSAID in wastewater samples were 0.47 µg L^{-1} (NAP), 0.09 µg L^{-1} (FENO), 0.59 µg L^{-1} (DICLO) and 0.49 µg L^{-1} (IBU).

The specific universal conditions were then used in the analysis of ARVDs in wastewater and surface water whereas for NSAIDs analysis, only wastewater samples were analysed. The surface water samples were obtained from North of Johannesburg in Hartbeespoort dam and the wastewater samples were collected from various wastewater treatment plants located in Durban, KwaZulu-Natal.

The technique was also applied in the analysis of the target compounds in plant samples obtained from Hartbeespoort dam in North of Johannesburg, Umgeni river located in Springfield (Durban in KwaZulu-Natal) and Mbokodweni river located in south of Durban city, KwaZulu-Natal. The plant samples were first cut and separated into different segments (roots, stems and leaves) and the target analytes then extracted into 20 mL water using an optimized microwave assisted extraction technique (MAE). The HF-LPME technique initially optimized for water samples was then applied for pre-concentration of the target pharmaceuticals from the MAE water extract. Factors that were optimized for MAE technique were irradiation time and temperature for ARVDs whereas irradiation time and solvent volume were optimized for the extraction of NSAIDs. For extraction of both ARVDs and NSAIDs, the optimum irradiation time was 20 min while the irradiation temperature was set at 90˚C during the extraction of ARVDs and 100˚C for NSAIDs.

Generally, the studied ARVDs were all detected in most samples with concentrations for FTC (0.11 – 3.10), TD (0.10 – 0.25) and EFV (1.09 up to 37.3) µg L^{-1} recorded in wastewater samples. EFV had the highest concentration of 37.3 µg L^{-1} in the wastewater effluent. The concentration of ARVDs in the roots of the water hyacinth ranged from 7.4 to 29.6 µg kg^{-1}, 0.97 to 11.42 µg kg^{-1} in the stem and 0.98 to 9.98 µg kg^{-1} in the leaves of the aquatic plant. Roots of the water hyacinth plant had higher concentrations of the investigated ARVDs. Lastly, the NSAIDs were also detected in various wastewater samples with concentration for NAP (1.15 to 3.30) µg L^{-1}, FENO (<LOQ to 2.03) µg L^{-1}, DICLO (0.36 to 3.13) µg L^{-1} and IBU (<LOQ to 0.92) µg L^{-1}. In this case, NAP had the highest concentration in the wastewater effluent. In terms of the water hyacinth plant, the concentration range in the roots of the plant

was 2.76 to 4.74 µg kg^{-1}, whereas in the stem of the plant, the concentration range was 0.21 to 3.22 µg kg^{-1} and the leaves accumulated 0.11 to 3.35 µg kg^{-1} of the selected NSAIDs in study. This indicated that the roots of the water hyacinth in this case has the highest uptake of the target compounds.

Overall, hollow fiber liquid phase microextraction proved to be an ideal tool for isolating and pre-concentrating the selected antiretroviral drugs from aqueous and plant samples. A manuscript on the results of analysis of ARVDs has been accepted in the Journal of Hazardous Materials and is presented in this dissertation as manuscript 2 in Section 4.2. In the analysis of NSAIDs, a manuscript has been submitted to a peer reviewed journal that is recognized by the Department of Higher Education in South Africa and is presented in this study as Paper 3 in Section 4.2. Manuscript 1 given as Section 4.3 is an article already published in Journal of Environmental and Chemical Engineering. The article is a review of adsorbents and removal approaches of NSAIDs from contaminated water bodies.

List of publications

Nomchenge Yamkelani Mlunguza, Somandla Ncube, Precious Nokwethemba Mahlambi, Luke Chimuka, Lawrence Mzukisi Madikizela. Adsorbents and removal strategies of non-steroidal anti-inflammatory drugs from contaminated water bodies. *Journal of Environmental Chemical Engineering 7 (2019) 103142*.

Nomchenge Yamkelani Mlunguza, Somandla Ncube, Precious Nokwethemba Mahlambi, Luke Chimuka, Lawrence Mzukisi Madikizela. Determination of selected antiretroviral drugs in wastewater, surface water and aquatic plants using hollow fiber liquid phase microextraction and liquid chromatography-tandem mass spectrometry. *Journal of Hazardous Materials 382 (2019) 121067*.

Nomchenge Yamkelani Mlunguza, Somandla Ncube, Precious Nokwethemba Mahlambi, Luke Chimuka, Lawrence Mzukisi Madikizela. Optimization and application of hollow fiber liquid phase microextraction and microwave assisted extraction for the analysis of non-steroidal anti-inflammatory drugs in aqueous and plant samples. *Submitted in a peer review journal.*

Table of Contents

List of Tables

List of Figures

List of Annexures

Abbreviations

AP – Acceptor phase

MeCN – Acetonitrile

ARVDs – Antiretroviral drugs

DEHPA – di-2-(ethylhexyl)phosphoric acid

DHE – Dihexyl ether

DICLO - Diclofenac

DP – Donor phase

EFV - Efavirenz

FTC - Emtricitabine

EF – Enrichment factor

FENO - Fenoprofen

FA – Formic acid

HPLC – High performance liquid chromatography

HF – Hollow fiber

HCl – Hydrochloric acid

HF-LPME – Hollow fiber liquid phase microextraction

IBU - Ibuprofen

LC – Liquid chromatography

NAP - Naproxen

MAE – Microwave assisted extraction

MS – Mass spectrometry

PDA – Photodiode array

SLM – Supported liquid membrane

STR – Single tablet regimen

TD – Tenofovir disoproxil

UHPLC-HRMS – Ultra high pressure – high resolution mass spectrometry

WWTP – Wastewater treatment plant

1. CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Many South African citizens especially those residing in informal settlements and rural areas are without access to clean water. As stipulated in South African constitution, every individual needs access to clean and healthy water, as water is a basic human right (Glaweski and Devenish, 2001). Due to unceasing increase in the population growth, people diagnosed with various diseases also increases, hence, industries formulate more pharmaceuticals which therefore lead to amplified consumption rates. These pharmaceuticals make their way to the water systems through direct disposal of unused or expired drugs (Ruhoy and Daughton, 2007), defecation (Jelic et al., 2012) and disposal of empty pill containers which contain pharmaceutical residues (Musson and Townsend, 2009). Since water is a necessity for aquatic nature and in human lives, this has led to various attempts to try to remove these pharmaceuticals from water. It has been previously reported that wastewater treatment plants (WWTPs) are the core contributors of pharmaceuticals and their metabolites to the environment which is due to that they are partially removed during the treatment process and hence discharged with the effluent to the rivers. The main sources of pharmaceuticals in wastewater treatment plants include hospitals, households and effluent from pharmaceutical formulating industries (Cardoso et al., 2014; Daughton and Ternes, 1999) as shown in **Figure 1.1**. Sewage effluent from households is documented as a key source of various pharmaceuticals, inflowing into the aquatic environment (Gaw et al., 2014). The use of effluent and sludge from WWTP for crop irrigation as well as the manure are the other ways in which pharmaceuticals can be transferred from the treatment plants to the environment, where they can reach rivers via runoff and can end up in drinking water.

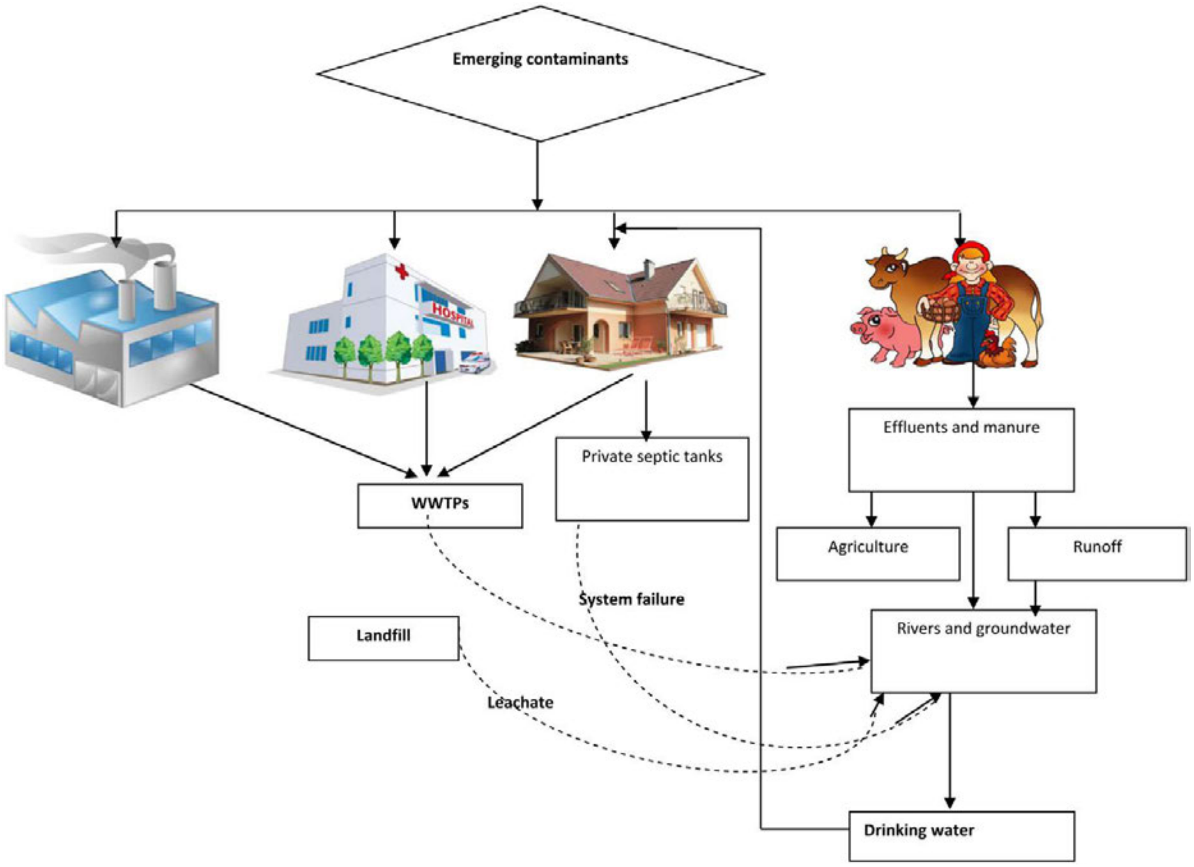


Figure 1.1: Sources of pharmaceuticals in wastewater treatment plants. Adapted from (Sophia and Lima, 2018) with permission from Elsevier.

Pharmaceuticals are regarded as recalcitrant in nature and are easily transported from wastewater to other water-based matrices (de Wilt, 2018). As a result, removal rates for pharmaceuticals in WWTPs array from less than 10 to almost 100% (Barfi et al., 2015; Madikizela and Chimuka, 2017; Patrolecco et al., 2013). The removal rates are largely dependent on type of treatment technology used and the physicochemical properties of the pharmaceuticals (Kummer, 2009).

To date, various classes of pharmaceuticals have been detected in environmental waters around the world. These classes include ARVDs (Abafe et al., 2018; K'oreje et al., 2016, 2012; Mosekiemang et al., 2019; Mtolo et al., 2019; Ngumba et al., 2016; Ramaswamy and Arul Gnana Dhas, 2014; Schoeman et al., 2015; Wood et al., 2015; Wooding et al., 2017), NSAIDs (Feng et al., 2013; Gilart et al., 2013; Gumbi et al., 2017; Madikizela et al., 2017; Radke et al., 2010; Shanmugam et al., 2014; Vergeynst et al., 2015; Wang and Wang, 2016), antibiotics (Balakrishna et al., 2017; Lapworth et al., 2012; Yang et al., 2017) and steroid hormones (Aris et al., 2014; Yang et al., 2017). Several review articles discussing various pharmaceuticals detected in the environment have been published (Feng et al., 2013; Leal et al., 2010; Madikizela et al., 2017; Modi et al., 2012; Rivera-Utrilla et al., 2013; Sophia and Lima, 2018). Pharmaceuticals that have been detected in South African water bodies are given in **Table 1.1**.

Table 1.1: Selected pharmaceuticals detected in South African water bodies.

Pharmaceutical class	Detected compounds	Method used	Target samples	City	Reference
NSAIDs	Naproxen, diclofenac, fenoprofen, ibuprofen and ketoprofen	SPE using Oasis HLB and MAX cartridges as well as MIPs	Wastewater, river water	Durban, Ladysmith	(Madikizela et al., 2017; Madikizela et al., 2014; Madikizela and Chimuka, 2017a, 2017b; Madikizela and Chimuka, 2016)
	Fenoprofen	SPE using MIP	Wastewater	Durban	(Mbhele et al., 2018)
	Naproxen, diclofenac, ibuprofen	SPE using Oasis HLB cartridges and sonication	Surface water and aquatic plants	Durban	(Sibeko et al., 2019)
		SPE using Oasis HLB cartridges, sonication		Durban	(Gumbi et al., 2017b, 2017a)
	Naproxen, ibuprofen	POCIS followed by SPE, HF-LPME	Wastewater	Johannesburg	(Amdany et al., 2014, 2015)
ARVDs*	Emtricitabine, efavirenz	SPE using Strata SDB-L cartridges	Wastewater	Cape Town	(Mosekiemang et al., 2019)

	Tenofovir	SPE using Oasis HLB cartridges	Surface water	Johannesburg	(Wood et al., 2015)
	Efavirenz	Direct sorption	Surface water	Johannesburg	(Wooding et al., 2017)
	Efavirenz	SPE using Oasis HLB cartridges	Wastewater	Durban	(Abafe et al., 2018)
	Efavirenz, tenofovir	SPE using Bond Elute Plexa cartridges	Surface water	Johannesburg	(Rimayi et al., 2018)
	Efavirenz	SPE using MIP	Wastewater	Durban	(Mtolo et al., 2019)
	Efavirenz	SPE using Bond Elute cartridges, sonication	Wastewater	Johannesburg	(Schoeman et al., 2015)
Antibiotics	Nalidixic acid, ciprofloxacin, ampicillin	Sonication, SPE using Oasis HLB cartridges	Wastewater and surface water	Durban	(Agunbiade and Moodley, 2016)
	Sulfamethoxazole, Ciprofloxacin, ampicillin, streptomycin, erythromycin, chloramphenicol, tylosin tartrate, tetracycline, nalidixic acid	SPE using Oasis HLB	Surface water	Durban	(Agunbiade and Moodley, 2014)

Sulfamethoxazole, sulfamethazine, trimethoprim	Sonication, SPE using Oasis HLB cartridges	Wastewater	Durban	(Matongo et al., 2015a, 2015b)

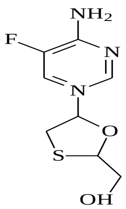
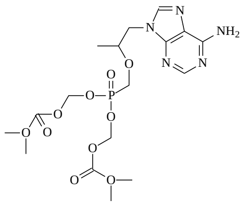
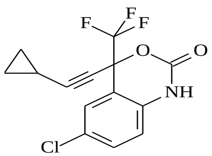
*ARVDs given in the Table are those selected for investigation in this study, POCIS – Polar Organic Chemical Integrative sampler

These include those that belong to the classes of NSAIDs, ARVDs and antibiotics. Among these pharmaceuticals, ARVDs are regarded as the least monitored in the world. This is due to that ARVDs were only introduced into the human population in 1987 with zidovudine administered as the first ARVD (Warnke et al., 2007). A concern with this is that as of 2018 there was over 20 million people consuming ARVDs with Ncube et al. (2018) predicting that in 2016 alone, there was 21.1 tons of Atripla consumed worldwide (Ncube et al., 2018). Studies have shown that these ARVDs are released into the environment as part of sewerage from domestic wastewater. The environmental fate of these drugs is still not well understood. There is a growing interest to monitor the occurrence of ARVDs in the aquatic environment. Thus far, some ARVDs have been detected in surface water from two African countries which are South Africa (Wood et al., 2015; Wooding et al., 2017) and Kenya (K'oreje et al., 2018, 2016, 2012; Ngumba et al., 2016). ARVDs have been detected in South Africa and has been observed in the provinces of Gauteng, Western Cape and KwaZulu-Natal. However, unlike other groups of pharmaceuticals, the interest to monitor ARVDs in South African water resources started recently (in the last five years).

Statistics South Africa has reported an increase in the number of its citizens infected with the human immune virus (HIV) in the year 2018 (*Mid-year population estimates*, 2018). The number has surpassed 7 million people in 2018 with over 3 million people on the antiretroviral program. This is of environmental concern because all the ARVDs used in these programs have the potential to enter the environment as surface run-off and through sewerage into WWTPs.

ARVDs have pKa values at the basic nitrogen ranging from -1.5 to 3.74 and 1.35 to 14.29 at their acidic oxygen with low water solubility at 25ºC (**Table 1.2**). However, their polar functionalities lead to the failure of WWTPs to completely remove them during the water purification process. This introduces ARVDs as part of WWTP effluents into the surface water (Halling-Sørensen et al., 1998). Direct disposal of ARVDs to the environment lead to the contamination of water resources. As a result, several ARVDs have been found present in in different WWTPs of Durban, KwaZulu-Natal (Abafe et al., 2018).

Table 1.2: Molecular structures and physicochemical properties of the selected antiretroviral drugs

Compound	Class	Structure	Molecular weight (g mol^{-1})	Water solubility (mg mL^{-1})	pKa		Human health side effects
					Strongest Acidic	Strongest Basic	
Emtricitabine	Nucleoside reverse transcriptase inhibitor		247.248	112	14.29	-3.1	Nephrogenic diabetes insipidus, Fanconi syndrome, nephrotoxicity and renal failure
Tenofovir disoproxil	Nucleoside reverse transcriptase inhibitor		519.443	13.1[a]	18.59	4.13	Nephrogenic diabetes insipidus, Fanconi syndrome, nephrotoxicity, renal failure and bone loss
Efavirenz	Non-nucleoside reverse transcriptase inhibitor		315.675	0.00855[b]	12.52	-1.5	Lipoatrophy, central nervous system adverse effects, hypertriglyceridemia, rash and hepatotoxicity

[a] as a disoproxil fumarate salt. [b] practically insoluble in water.

Various techniques have been reported for the analysis of both ARVDs and NSAIDs as shown in **Table 1.1**. It is noted that solid phase extraction (SPE) is the most common. Despite the high extraction efficiencies reported for this technique, there is still no method accepted universally. Generally, SPE using HLB cartridges is known to be non-selective (Dias and Poole, 2002) extracting both hydrophilic and lipophilic compounds. The end result is unfavourable detection limits. It is also noted that most studies have mentioned environmental water samples. Thus, in this study the idea was to investigate the applicability of HF-LPME as an extraction technique that can offer better selectivity and sensitivity in analysis of both ARVDs and NSAIDs in complex matrices. The technique was also applied for the extraction of both ARVDs and NSAIDs. The idea was also to investigate if aquatic plants have the potential to accumulate these pharmaceuticals from polluted water sources. The potential of this technique has been reported in the analysis of other polar analytes including muscimol in human urine (Ncube et al., 2016), phenolic compounds from water samples and soil extracts (Dolatto et al., 2016) as well as triazine herbicides in sea and transition water (Sime et al., 2019).

While studies have reported which pharmaceuticals are quantified in surface water bodies, possible strategies that can be used as remediation tools remain limited. We have published a review article in the Journal of Environmental and Chemical Engineering (Paper 1, Section 4.1) in which we identified strategies that can be used for the removal of organic pollutants such as NSAIDs whereby adsorbents have the potential of reducing contaminants in water bodies. With synthesis of adsorbents rather proving a main challenge, natural approaches such as phytoremediation also known as botanical bioremediation might be a solution. One of the major points mentioned in the review is that the initiative to apply plant species such as *Typha spp* and *Scirpus validus* in constructed wetlands for removal of NSAIDs from contaminated water has yielded promising results. However, this approach has been mostly investigated for single analytes, whereas, in most cases, NSAIDs are simultaneously detected in water bodies. The review further states that future studies should focus on the application of various plant species for the simultaneous uptake of NSAID group from water. Using a variety of plants enables for the understanding of the accumulation of the compounds as it differs significantly with each species based on their anatomical, morphological, physiological and genetic features (Lone et al., 2008). A review by Madikizela et al 2018 has given a better evaluation of the uptake of pharmaceuticals by plants from water and soil. Their graphical abstract which summarizes their findings **(Fig 1.2)** shows that plants that grow naturally in water bodies can be used as phytoremediators of pharmaceuticals. In this study, the potential of *Eichhornia crassipes* (known as the water hyacinth) to bioaccumulate the target compounds was investigated.

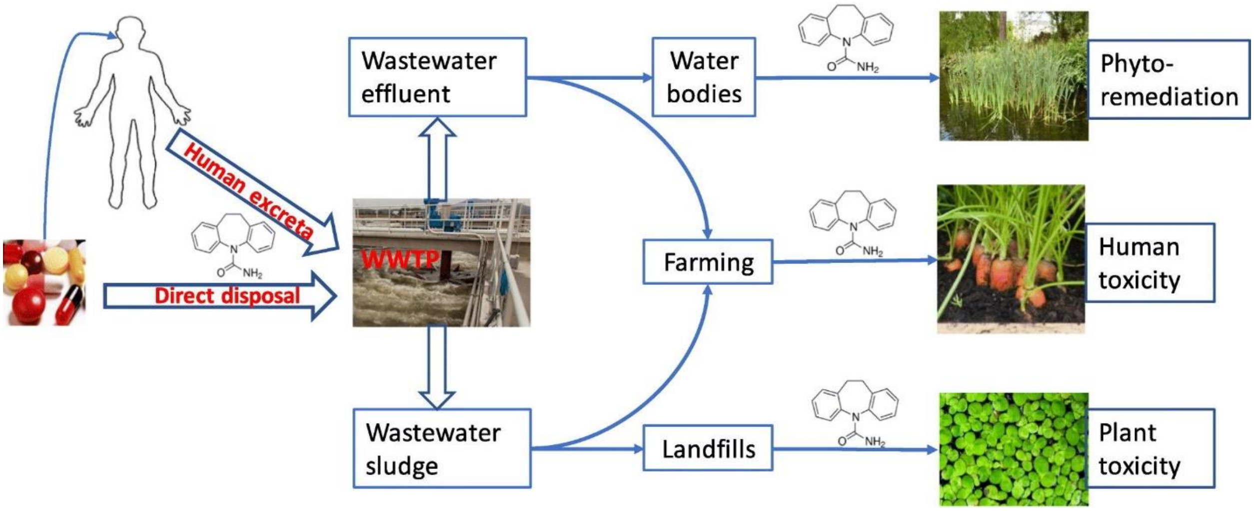


Figure 1.2: Disposal of pharmaceuticals into the environment and their transportation. Adapted from (Madikizela et al., 2018a) with permission from Elsevier.

1.2 TARGET PHARMACEUTICALS

1.2.1 Antiretroviral drugs

Highly active antiretroviral therapy has brought new hope for those individuals who are HIV infected and has been proven to be the best combination in combating the multiplication of HIV (Ncube et al., 2018). These antiviral drugs work by inhibiting the ability of the HIV virus to replicate. This study focused on the analysis of emtricitabine, tenofovir disoproxil and efavirenz in environmental samples. The three ARVDs form part of Atripla, a single-dose combination pill recommended by WHO to be given to anyone diagnosed with HIV. Usually, a person receiving HIV treatment takes two or more tablets every day, each drug attacks the virus differently, and the combination is key. A single tablet regimen (STR) has several advantages. The STR is easy to take and keep track as it is taken once daily at the same time which works well for patient taking the pill. The lower pill burden and great adherence is associated with better virological suppression, and STR can improve patient satisfaction. The patient can take the pill anywhere without worrying about incorrectly counting the pills before the intake which thus creates consistency in the intake of the pill (Hodder et al., 2010; Nachega et al., 2014). The relevant physicochemical properties of the three ARVDs are summarized in **Table 1.2**.

Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor (NRTI) with a chemical name of 5-fluoro-1-(2R, 5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-ylcytosine] corresponding to the molecular formula $C_8H_{10}FN_3O_3S$. FTC is an equivalent of cytidine which differs from other cytidine correspondents, since fluorine is in 5^{th} position (Venkatesan and Kannappan, 2014). FTC is freely soluble in water and methanol with its physicochemical properties outlined in **Table 1.2**.

Tenofovir disoproxil (TD) is a pro-drug of tenofovir which is used in combination with FTC and FTC/TD/EFV. TD is also an NRTI with a chemical name and molecular formula $C_{19}H_{30}N_5O_{10}P$. TD is an active ingredient against chronic hepatitis B virus amongst its ability to HIV. Chemically it is [[(2*R*)-1-(6-aminopurin-9-yl)propan-2-yl]oxymethyl-(propan-2-yloxycarbonyloxymethoxy)phosphoryl]oxymethyl propan-2-yl carbonate (Martindale, 2002).

Efavirenz belongs to a class known as the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Drugs in the NNRTI class block HIV from replicating within cells by binding near reverse transcriptase active site and inhibiting polymerase activity. It is chemically described as (*S*)-6-chloro-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one, with a chemical formula $C_{14}H_9ClF_3NO_2$ (Staff, 2008). EFV is practically insoluble in water as shown in **Table 1.2**.

1.2.2 Non-steroidal anti-inflammatory drugs

NSAIDs are the most extensively used drugs that can be purchased over the counter for remedial purposes. Hence they are responsible for approximately 5-10% of all medications prescribed yearly (Onder et al., 2004). These drugs are used to treat and ease pain as well as inflammation in different post-operative and arthritic situations. They are known for their three main therapeutic actions which can be described as either anti-inflammatory, antipyretic or analgesic (Kress et al., 2016; Modi et al., 2012; Smith, 2014). Naproxen, fenoprofen, diclofenac and ibuprofen are classified as weak organic acids (**Table 1.3**) with acid dissociation constants (p*K*a) extending from 4.15 to 4.91 (Lindqvist et al., 2005), with their octanol-water partition coefficients (*K*ow) ranging between 0.7 and 3.97 (Behera et al., 2011). The properties of these compounds include their polar nature and high water solubility at neutral pH which could possibly cause a strain in their removal efficiency in the sewage treatment processes (Dahane et al., 2013; Koutsouba et al., 2003; Larsson et al., 2009).

NSAIDs act by inhibiting a cyclooxygenase (COX) trail through hindering the making of the prostaglandins. Two of three existing Amongst the three existing COX enzymes two are associated to the biological activity of NSAIDs. COX-1 enzyme in this case plays a role in production of prostaglandins that act as the intestine protector and stomach lining. COX-2 enzyme is correlated to the production of prostaglandins that are linked with inflammation. COX-2 is consequently induced by endotoxins, cytokines and mitogens (Manrique-Moreno et al., 2016). Like any other pharmaceuticals, NSAIDs exhibits several side effects after long term exposure or incorrect usage. Common side effects of NSAIDs include stomach pain, heart burn, stomach ulcers, headaches and dizziness (Auriel et al., 2014). To some extent, tendency to bleed and liver or kidney problem (Hörl, 2010). Each NSAID has its own common side effects as documented in the following paragraphs.

Naproxen (NAP) is in the propionic acid class and is sold under the brand name Naprosyn among others. It is was patented in 1967 and was approved for medical use in the United States in 1976. NAP was approved for over the counter medication in 1994 and is widely used for the treatment of menstrual cramps, rheumatoid arthritis, pain and inflammation and fever (Brutzkus and Varacallo, 2018). Off label uses of NAP include first abortive medication for the treatment of acute migraines (Schafer, 1999), NAP is a non-selective COX-inhibitor (Manrique-Moreno et al., 2009).

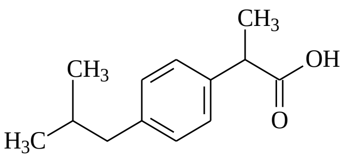
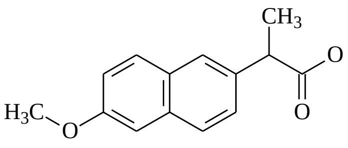
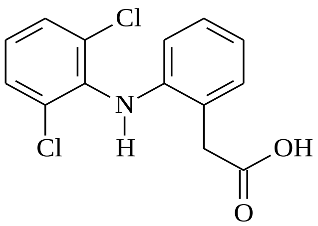
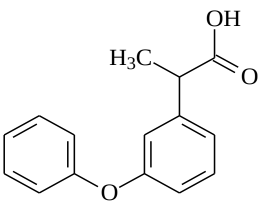
Fenoprofen (FENO)is a propionic acid nonsteroidal anti-inflammatory agent. Its effectiveness is similar to other NSAIDs, although it may be more nephrotoxic. Since fenoprofen displays significant antiplatelet activity, it may be of value in lessening the incidence of temporary ischemic attacks. The calcium salt is used clinically for the management of mild to moderate pain, and for relief of inflammatory disorders such as arthritis (Brogden et al., 1977).

Diclofenac (DICLO) is the most widely prescribed NSAID worldwide and was first formulated in 1973 with a number of new diclofenac-containing drugs. (Altman et al., 2015; McGettigan and Henry, 2013). DICLO, similar to other NSAIDs, is associated with an increased risk of serious dose-related gastro intestinal, speech impediment and renal side effects.

Ibuprofen (IBU) is chemically known as (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid. Ibuprofen was the first in propionic acid derivatives to be introduced in 1969 as a better substitute to Aspirin. Gastric uneasiness, vomiting and nausea, even though its strength is less than aspirin or indomethacin, they are still the most shared side effects. Ibuprofen is one of the mostly used and frequently prescribed NSAID. It is also a non-selective inhibitor of COX-1 and COX-2. Even though its anti-inflammatory properties may well be weaker than those of some other NSAIDs, it has a prominent antipyretic and analgesic role (Abraham et al., 2005; Manrique-Moreno et al., 2016).

The physicochemical properties of non-steroidal anti-inflammatory drugs are summarized in **Table 1.3**.

Table 1.3 Molecular structures and physicochemical properties of the selected non-steroidal anti-inflammatory drugs.

Compound	Structure	Water solubility @ 25 ºC (mg L^{-1})	pKa	xlogP3	log Kow
Ibuprofen		58	4.91	3.5	3.5
Naproxen		44	4.15	3.3	3.18
Diclofenac		10	4.15	4.4	4.51
Fenoprofen		81	4.5	3.3	-

1.3 HOLLOW FIBER LIQUID PHASE EXTRACTION

1.3.1 Principle of the hollow fiber liquid phase microextraction technique

The HF-LPME technique encompasses the transfer of analytes from a donor phase (DP) which is the aqueous sample, where they are in their neutral forms across a liquid membrane on the pores of a hollow fiber. An acceptor phase (AP) is placed inside the lumen of the fiber which therefore accepts the analytes through dissemination and ionisation processes (Chimuka et al., 2010). In this context, supported liquid membrane extraction (SLME) was employed in this study as this is the widely used type of a three-phase membrane-based extraction in analytical chemistry (Larsson et al., 2009; Lee et al., 2008; Mtibe et al., 2012). SLME involves the use of three different phases, which is the DP, AP, and the supported liquid membrane (SLM) which is an organic solvent. After the extraction process, the extract is either diluted or directly injected into an analytical instrument mostly chromatographic techniques which separate the extracted compounds, followed by their identification and quantification. Trapping the analytes in the acceptor solution is vital for the three-phase liquid membrane extraction process. It is also vital to optimize the acceptor conditions and then to obtain the desired selectivity and high enrichments for target compounds.

1.3.2 Advantages of the HF-LPME

Chemists around the globe are striving to perform greener, time-effective, inexpensive, sensitive, convenient and accurate analytical methods. In this regard, HF-LPME is viewed as one of the sample preparation techniques that are rapid as it could be done without any further sample clean-up or pre-concentration step (Nomngongo et al., 2014). Furthermore, this technique is recognised as a greener sample preparation method as it uses trace amounts of organic solvents (Bello-López et al., 2012; Payán et al., 2011). During the extraction process, the AP and the DP do not mix up thus minimal solvent volumes are required. In HF-LPME process, the enrichment factors are improved due to the ratio of the sample to acceptor-volume which is increased with the DP volume ranging from 50 µL to 1 L while the AP is usually less than 30 µL (Hadjmohammadi and Ghambari, 2012; Larsson et al., 2009; Ncube et al., 2016; Saleh et al., 2011). Since this is a pre-concentration step, this therefore affords enhancement in sensitivity of the analytical methods.

1.3.3 Supported liquid membrane extraction- a three-phase carrier mediated extraction

In SLM extractions, the barrier between AP and DP is the fixed organic solvent embedded in pores of the hollow fiber **(Figure 1.3)**. The organic solvents used must be immiscible in the acceptor and donor phases to prevent mixing of the two phases during the extraction process. The most commonly employed solvents are hydrocarbons with long chains such as *n*-undecane and less polar compounds comparable to dihexyl ether (DHE) (Al Azzam et al., 2010; Saaid et al., 2009). The analytes must exist in both non-ionic and ionic form on the DP and the AP, correspondingly. So, SLM extraction is appropriate for ionizable compounds and providing selective enrichments (Chimuka et al., 2010; Ncube et al., 2016). The selectivity can be modified by fine-tuning the settings in the three phases as seen in **Figure 1.3**.

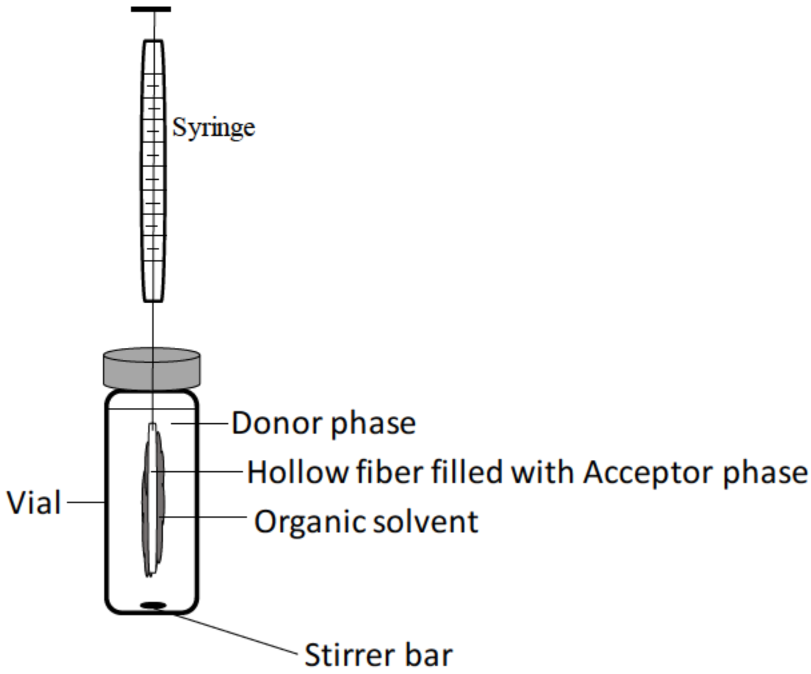


Figure 1.3: Hollow fiber supported liquid membrane extraction.

Enrichment factors in the HF-LPME technique which represent extraction efficiency (E) can be described using **Equation 1.1**;

$$E = C_A/C_D \quad (1.1)$$

The extraction efficiency of HF-LPME technique can also be defined using **Equation 1.2**;

$$E = (m_A/m_D)*100\% = (C_A*V_A/(C_D*V_D))*100\% = E*(V_A/V_D)*100\% \quad (1.2)$$

where, C_A and m_A represents the concentration and mass of the analyte at equilibrium in the acceptor phase, respectively. C_D and m_D represents the concentration and analyte mass at initial stage in the donor phase, respectively. v_A and v_D are the volumes of AP and DP, respectively (Es'hagi and Fasihi-Rad, 2016).

1.3.4 Critical parameters of HF-LPME

Since sample preparation is reliant on analyte and matrix effects, an appropriate optimization procedure on preparation parameters is essential. A proper understanding of the desired extraction sequence during a HF-LPME process allows one to focus on optimizing essential parameters that lead to a successful extraction. Chimuka et al. 2010 clearly scrutinized the parameters that are deemed critical and need to be optimized when analysing ionizable compounds using an SLM extraction technique. The parameters are derived from the mass transfer kinetics associated with HF-LPME (Chimuka et al., 2010). The aqueous phase pH needs to be optimized so that the analyte preserves its electrical neutrality in the DP and be present as an ionized compound in the AP to avoid back-extraction (Chimuka et al., 2010; Ebrahimzadeh et al., 2011; Hadjmohammadi and Ghambari, 2012; Płotka-Wasylka et al., 2016). To maintain the neutrality of a basic compound that ionizes at low pH, its solubility within the DP is reduced and the DP pH is thus attuned to basic conditions (Chimuka et al., 2011; Lee et al., 2008; Payán et al., 2011). The latter is applied for acidic compounds where the DP must be acidic while the AP is basic. If the pKa value of the analyte is known, the pH value of the AP that presents the maximum extraction can be estimated. Similarly, the pH value of the DP that improves transfer to the AP can also be predicted (Chimuka et al., 2011; Runfola et al., 2018)

For efficient extraction of acidic analytes, the AP pH should be kept well above (3.3 units higher) the least pKa value, causing the analytes to be deprotonated. This will enforce only neutral species to diffuse through the membrane and become trapped as well as enriched in the AP (Ncube et al., 2016). The pH of the sample (DP) must be adjusted to 2.2 units below of the most acidic compound and 2.2 units above the pKa of the most basic compound

(Chimuka et al., 2010). These predictions allow for a focussed optimization that is merely meant to formally verify the best pH of the DP and AP.

The nature of supported liquid phase is also essential in HF-LPME depending on the polarity of the analyte and thinness of the supporting membrane. The embedded solvent must be immiscible in the DP, have low solubility in water and the AP and be easily immobilized in the HF pores. Most studies have used dihexyl ether (Al Azzam et al., 2010; Ncube et al., 2016; Saaid et al., 2009) and n-decane (Al Azzam et al., 2010; Alguacil et al., 2009; González et al., 2018) as a solvent of choice for efficiency extraction. Also, Chimuka et al. 2010 outlined these solvents as the most effective SLM (Chimuka et al., 2010). Stirring of the aqueous solution has shown to increase the extraction efficiency and reduce the extraction time by continuously exposing the extraction and diffusion surfaces of the membrane to fresh aqueous sample in the DP and the small volume of the AP, respectively. The sample solution is continually stirred for a specific time in order to initiate the mass transfer of analytes. Whereas, an increase in the stirring speed is attributed to fast diffusion of analytes. However excess vigorous shaking can lower extraction efficiencies because of loss of the SLM, solvent evaporation or creation of air bubbles that accumulate on fiber surface (Al Azzam et al., 2010; Chimuka et al., 2010; Pena-Pereira et al., 2010). Extraction can also be affected by several non-vital factors which include salting out effect and extraction temperature (Bello-López et al., 2012; Chimuka et al., 2010; Saaid et al., 2009). Overall, for efficient extraction the optimization of several parameters is carried out. This can be done by optimizing one parameter at a time while other experimental conditions are kept constant. Also, a multivariate approach (applied in this study and discussed in the following section) has been applied for several analytes (Alsharif et al., 2019; Ncube et al., 2016; Nomngongo et al., 2014; Tajabadi et al., 2016).

1.4 MULTIVARIATE DESIGN OF EXPERIMENTS

Multivariate statistical techniques allow the simultaneous study of several experimental variables and the development of mathematical models that allow the evaluation of the relevance and statistical significance of factors being studied (Abulhassani et al., 2010). Also, multivariate experiments minimize the amount of work a researcher has to conduct by learning and predicting the interrelation of the variables that might affect the process output (Nomngongo et al., 2014). Unlike one-factor-at-a-time optimization approach, which involves optimizing only a single factor while keeping the other factors constant, multivariate approach allows for interaction between two or more factors using a trial and error tactic (Ncube et al., 2016).

A multivariate strategy involves two important steps: initial screening of all factors and optimization of significant factors. In this study, Minitab 17; a universal purpose statistical analysis tool was used for experimental design and analysis.

1.4.1 Factorial and Fractional designs

A factorial design is used to determine the simultaneous interaction of numerous factors and their combined effect on the outcome of the experiment, an initial screening is conducted using factorial design (Atkinson et al., 2007; Franceschini and Macchietto, 2008). Fractional design aim to evaluate the significance of each factor on the outcome of the experiment. The researcher can either choose to run a full factorial or rather a fraction of the factorial designs. A full factorial design is a design where the response of all combinations of the factor levels are measured by the researcher (Chadly et al., 2019). Minitab offers two types of full factorial designs, a 2-level factorial design denoted by 2^k, where k is the number of factors. For example, when a number of factors to be measured equals 7 that requires 128 runs. Whereas a half-fraction, a half-factorial would require half of those runs. A fractional design conducts only a selected fraction of the runs in the full factorial design. This design saves time and also should be the primary choice when there are limited resources because it uses fewer runs. In a fractional factorial design, some of the main factor effects and 2-way interactions are confounded thus cannot be separated from effects of higher order interactions (Sahu et al., 2018; Tajabadi et al., 2016). In this study, the focus was on the 2-level half-fractional factorial design where each factor has only two levels. The 2-level factorial designs provide useful information about the factor effects and also can identify major trends for relatively fewer runs and thus gives space for any additional experiments that might be needed (Sahu et al., 2018).

In this regard, experimental variables and their levels in chemometric design are predicted according to literature or the nature of the optimized method. These levels are denoted by (- and +) which are lower and upper value, respectively for a two-level design. Another design known as a three-level design includes, (-, 0 and +) which are upper, central and lower value, respectively. The limits are investigated by the researcher during preliminary studies. For example, the investigation of effect of time in a 2-level design could be 60 and 180; whereas a three-level would be 60, 120 and 180.

1.4.2 Design generators for 2-level designs and resolution in a factorial design

The design generators control just how the fraction (or subset of runs) is carefully chosen from the full set of runs in a fractional factorial design. Usually, when a researcher does a fractional factorial design, some of the factors are confounded as such they cannot be estimated separately from each other. Therefore, a highest possible design resolution for the amount of fractionation is required. A design resolution describes how much the effects in a fractional factorial design can be effectively predicted with other effects. Usually, a fractional factorial design with the highest possible resolution for the amount of fractionation is required. So, a design where the main effects are confounded with 3-way interactions (Resolution IV) instead of a design where main effects are confounded (meaning, they cannot be estimated separately from each other) with 2-way interactions (Resolution III) is mostly utilised (Sahu et al., 2018) whereas Resolution V has no main effects but 2-factor interactions which are aliased with 3-factor interactions . The most common resolutions are III, IV and V (Nageeb El-Helaly et al., 2018).

1.4.3 Optimization of main factors using response surface designs

To better understand and optimize the responses, a response surface design (RSD) is used in this regard. RSD is an advanced design of experiments that are often used to refine models after vital factors have been determined during screening (Myers et al., 2016). The difference between equations of the RSD and factorial design is the addition of the quadratic term that allow for modelling of the curvature in the response. This makes them useful for understanding the region of the surface response and thus how changes in variables affects the response of interest (Bezerra et al., 2008; Carley et al., 2004). Also, the curvature in the response allows for selection of the operating conditions for each factor to meet specifications and finding the levels of factors that optimize a response.

There are two main types of RSD, the central composite designs (CCD) and the Box-Behnken designs. CCD is the mostly used design as it can fit a full quadratic model up to 5 levels per factor (Veljković et al., 2018). A CCD needs to be rotatable and spherical. This is vital because, if the level points are equidistant from the centre of the design and thus the axial points then the rotatability of the responses from levels becomes constant. The number of levels per variable depends solely on an alpha (α) value (Mertler and Reinhart, 2018). The alpha value represents positions of some star (or axial) points on both axis of the design as shown in **Figure 1.4**. Rotatability requires that $\alpha > 1$ while sphericity is defined by **Equation 1.3**; $\alpha = \sqrt{k}$, where k is the number of vital factors (Atkinson et al., 2007). For example, when there are 4 factors, $\alpha = \sqrt{4} = \pm 2$. This therefore gives factor level of 5 per factor at -2, -1, 0, 1 and 2 with zero the mid-range value. This implies that if time was set to have a lower and upper limit of 20 and 60, then the level would be 20,30,40,50 and 60. The same approach is used for all factors.

The CCD is investigated experimentally by allowing for the pairing of vital factors according to the extent of their response or effect (Alsharif et al., 2019). The interaction of effects between these factors is investigated using response surface models. In order to visualize the response surface, contour plots, optimization plots and surface plots are used. Therefore, estimation of the optimum factor values for each paired factor plots are thus predicted using the empirical quadratic response surface by computing **Equation 1.4**.

$$y = b_o + b_1 x_1 + b_2 x_2 + b_{11} x_1^2 + b_{22} x_2^2 + b_{12} x_1 x_2 + \varepsilon \qquad (1.4)$$

where y is the average enrichment factor, b_0 the intercept parameter, b_i are the regression parameters for linear factor effects, b_{12} are the regression parameters for interaction factor effects, b_{11} and b_{22} are the regression parameters for quadratic factor effects, x_1 and x_2 are the paired factors and ε is the residual linked to the experiments (Sahoo and Gupta, 2012).

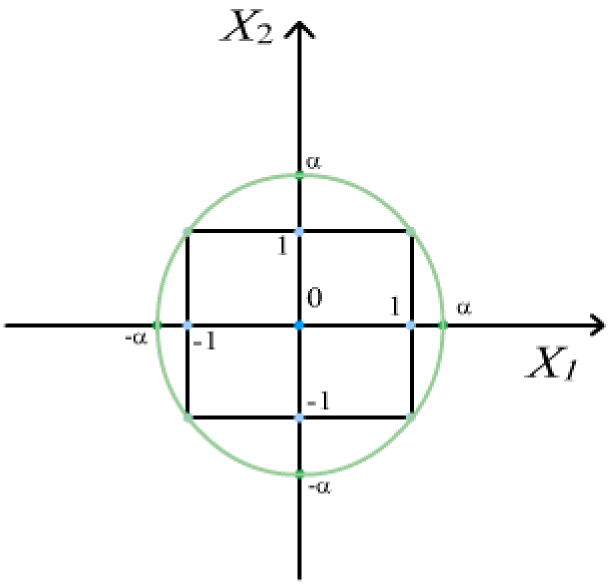


Figure 1.4: Star points for a 22 factorial as given by ±α on the axial lines. Modified from https://onlinecourses.science.psu.edu/stat503/node/59

The point of curvature shows the optimum value of the effects and can be considered as a stationary point where the partial derivatives ${}^{\delta y_1}/_{\delta x_1} = 0, {}^{\delta y_2}/_{\delta x_2} \dots\dots\dots {}^{\delta y_i}/_{\delta x_i} = 0$. The optimum response can be a saddle point, a minimum point or a maximum point as given away in **Figure 1.5.**

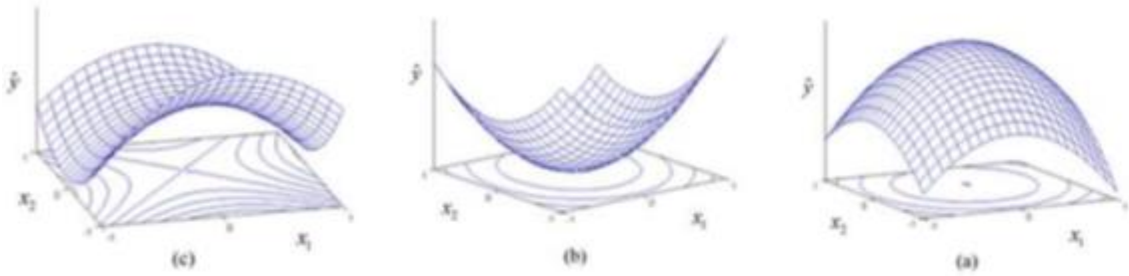


Figure 1.5: Mesh contour plots showing a saddle point (a), a minimum point (b) and a maximum point (c). Modified from https://onlinecourses.science.psu.edu/stat503/node/59

1.4.4 Desirability functions

A desirability function is a utility function that is used to determine the accuracy of the response. Also, the model is designed to measure how the optimized factor value satisfies the targeted response. In desirability studies, a response output is assigned a desirability function denoted by d_i y_i where y_i is the ith response. The d_i y_i values range from zero to one. A d_i y_i value of one denotes an ideal situation while zero implies unacceptable settings. This range is dependent on setting a lower limit and a target value, or a target value and an upper limit, or both for the ith response depending on the goal of the method as shown in **Figure 1.6**.

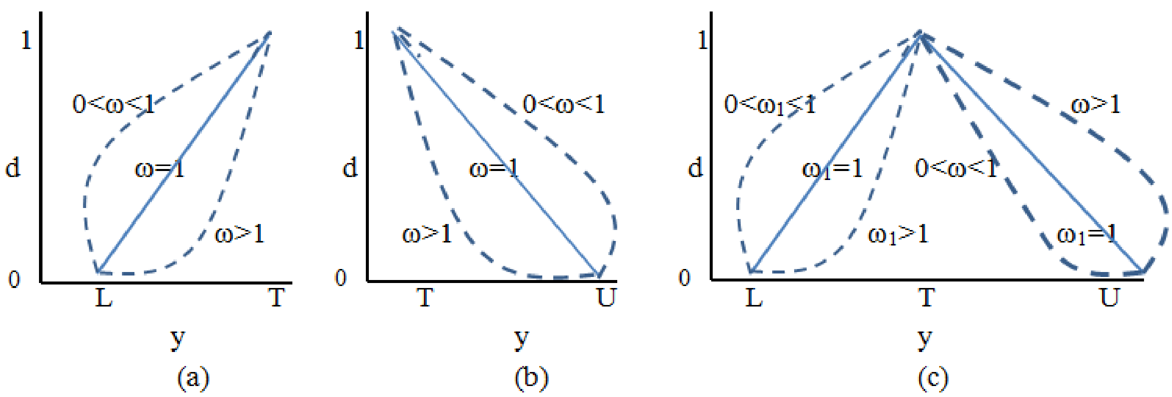


Figure 1.6: Plots of desirability functions when the goal is to maximize the set response value (a), the goal is to minimize the set response value (b) or the goal is to set a target value for the response (c).

Each plot has its own mathematical definition. When the goal is to maximize the response and the desirability was defined as shown in **Equation 1.5**.

$$d_i y_i = \begin{cases} 0 \\ [(y_i - L)/(T - L)]^{\omega} \\ 1 \end{cases} \qquad y_i < L,\ L \le y_i \le T \text{ and } y_i > T \qquad (1.5)$$

Here, T is the target value, L the set lower limit, y_i the i^{th} response and ω the weight of the factor. For a vital factor, ω is set to one and the d_i y_i function is linear. Almost all optimizations follow the $\omega<1$ route where emphasis is on getting a value close to the optimum. The $\omega>1$ approach requires that the target be achieved at all costs. In cases where d_i y_i, the response y_i is below the set limit. Most desirability values are acceptable when d_i y_i. A desirability function in which the effectiveness of an optimum point of two vital points is evaluated is called an individual desirability function because a single response is affected. A problem arises where the effect of several factors and factor levels on multiple responses are to be investigated.

Each response output will have its own optimum factor values different from the optimum values for the other responses. This creates a practical concern as what is optimum for extraction of one compound cannot be optimum for the other compounds. This leads to a conflict of optimum settings considering that the aim of this research was to simultaneously optimize extraction of three compounds with different physicochemical properties. A balanced scenery that would give the most appropriate response values for all the analytes has to be found. The composite desirability approach is used to compromise the factor values in order to satisfy an optimized response output.

A composite desirability function, D(Y) evaluates how the overall universal settings affect a set of responses. It gives an estimate of having a single factor value on multiple responses. It is therefore a function of the responses under a single compromised value. The choice of universal main factor levels is dependent on the importance of each response and the purpose of the design experiment. The acceptability of the universal experimental conditions is confirmed by using a compound desirability function calculated as a geometric mean of the individual desirabilities **(Equation 1.6)**.

$$D(Y) = (d_1\, y_1 . d_2\, y_2 .... d_m\, y_m)^{1/m} \quad (1.6)$$

Where D(Y) is the compound desirability, $d_i y_i$ is the individual desirability as the optimum factor value is changed and m is the number of responses.

1.5 PROBLEM STATEMENT AND MOTIVATION

There is currently an excessive disposal of pharmaceuticals that include ARVDs and NSAIDs into water resources. As shown in **Figure 1.2**, pharmaceuticals are transported into various forms of water bodies such as wastewater, surface water, etc. Unlike other organic pollutants of emerging concern, ARVDs are least monitored in the aquatic environment with few cases reported on their presence in South African water resources compared to other pharmaceuticals such as NSAIDs (Abafe et al., 2018; Mosekiemang et al., 2019; Mtolo et al., 2019; Rimayi et al., 2018; Schoeman et al., 2017, 2015; Wood et al., 2015; Wooding et al., 2017). It is of importance for more monitoring of ARVDs in the South African environment as this is a country with the largest antiretroviral treatment program in the world (Ncube et al., 2018). Furthermore, South African rivers receive high loads of pharmaceuticals that are discharged as part of effluents from WWTPs (Madikizela et al., 2017; Schoeman et al., 2017; Zunngu et al., 2017).

In literature, pharmaceuticals have been described as a group of compounds that can be easily taken up by plants including vegetables through the application of contaminated water for irrigation or the plantation of crops using sludge as the fertilizer (Muchuweti et al., 2006; Rahube et al., 2016). This poses health risks to humans and animals that consume these crops. The plant uptake of pharmaceuticals from contaminated water shows the potential of using plants for the reduction of water pollutants through the process of phytoremediation. In a review article presented by Madikizela et al. (2018), plant species that have the ability to take-up pharmaceuticals from water bodies have been discussed. The review article also presented the various pharmaceuticals that have been reported in literature to be taken-up by plant species. In the context of South African water resources, water hyacinth which is scientifically known as *Eichhornia crassipes* has been reported to be capable of reducing NSAIDs (ibuprofen, naproxen and diclofenac) from contaminated water (Sibeko et al., 2019). Water hyacinth is a plant species that is invading several water resources in South Africa. The plant grows quickly with its roots floating freely in water and covers several dams and rivers in the country, thereby, blocking out sunlight and cause stress in most aquatic animals. Thus far, there is only one South African study available in literature which reported the plant uptake of NSAIDs from contaminated rivers in KwaZulu-Natal (Sibeko et al., 2019). Therefore, due to recent reports that indicated the occurrence of ARVDs in KwaZulu-Natal environmental waters (Abafe et al., 2018; Rimayi et al., 2018), there is a strong need to investigate the ability of water hyacinth to reduce the quantity of ARVDs in the aquatic environment.

The development and application of sensitive analytical procedures is required in order to accurately monitor the occurrence of ARVDs in aquatic environments and plants. This is important as the concentrations of ARVDs in the environment is low, which requires their isolation and pre-concentration prior to the identification and quantitation on a suitable analytical technique. This was addressed in the current study by isolating ARVDs from aquatic plants using microwave assisted extraction technique. ARVDs were then pre-concentrated using HF-LPME prior to their quantitation on LC-MS. Accordingly, ARVDs were extracted and enriched from water samples using HF-LPME. Thereafter, LC-MS analysis was performed for chromatographic separation, identification and quantitation of ARVDs and NSAIDs present in environmental samples.

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2. CHAPTER TWO: AIMS AND OBJECTIVES

2.1 AIM OF THE STUDY

The aim of this study was to develop and optimize an analytical technique for analysis of selected ARVDs and NSAIDs in water samples and aquatic plants.

2.2 SPECIFIC OBJECTIVES

The objectives of the study are as follows:

- To develop a HF-LPME technique for the isolation and preconcentration of ARVDs and NSAIDs in aqueous samples and aquatic plants.
- To optimize a HF-LPME technique for efficient isolation and enrichment of selected ARVDs from aqueous samples using fractional designs and surface response methods.
- To apply the optimized HF-LPME technique in combination with LC-MS for analysis of target compounds in wastewater samples obtained from Durban, KwaZulu Natal and surface water samples obtained from Hartbeespoort dam, North of Johannesburg.
- To optimize a MAE technique for extraction of target analytes from *Eichhornia crassipes* followed by isolation and preconcentration using HF-LPME.
- To apply the optimized MAE-HF-LPME technique for extraction and pre-concentration of target analytes in *Eichhornia crassipes* of Hartbeespoort dam, Mbokodweni River and Springfield followed by quantitation using LC-MS.

2.3 RESEARCH STRUCTURE

This research expedition started with a literature search on ARVDs and NSAIDs to identify all the research studies that have been done. With various studies reported in literature and quite a number of reviews available, our approach was to write a review on adsorbents and removal strategies of NSAIDs in water resources. This has been published in Journal of Environmental Chemical Engineering and is given in this dissertation as Paper 1 in Section

3.1. This was followed by development of a hollow fiber-based liquid phase microextraction technique for analysis of the selected ARVDs and NSAIDs in various matrices. The optimization and application of HF-LPME and MAE-HF-LPME for analysis of ARVDs in both surface water and hyacinth plants is presented as Paper 2 in Section 3.2. This manuscript has been accepted by the Journal of Hazardous Materials. Paper 3 in Section 3.3 presents the preconcentration of NSAIDs in wastewater samples and aquatic plant materials. This manuscript has been submitted to in a peer review journal with impact factor. All the papers have been formatted to maintain a continuous structure of the dissertation. Each paper except for the review article (Paper 1), has its own introduction, chemicals and materials, sample collection and pre-treatment methods, extraction techniques, method optimization, results and discussion and lastly, conclusion then references.

3. CHAPTER THREE: RESEARCH PAPERS

3.1 PAPER 1

This paper summarizes the data on the different adsorbents and removal strategies of NSAIDs in contaminated water bodies around the world. In this review, the toxicity of NSAIDs after long term exposure in both human and animals have been outlined. Their occurrence in various water resources such as WWTPs and constructed wetlands has been carefully looked at. This has led for major investigation on the adsorbents that have been reported for their ability to remove pollutants from contaminated water at a laboratory scale. In addition, advanced oxidation processes (AOPs) which includes sonochemical and electrochemical advanced oxidation processes have been carefully discussed as they have the ability to remove pollutants from contaminated water. AOPs are categorized by the formation of non-selective and highly reactive hydroxyl radicals which are able to mineralize almost all organic compounds. This review highlights the ability of different adsorbents to remove NSAIDs for contaminated water.

Adsorbents and removal strategies of non-steroidal anti-inflammatory drugs from contaminated water bodies

Nomchenge Yamkelani Mlunguza[a], Somandla Ncube[b], Precious Nokwethemba Mahlambi[c], Luke Chimuka[d], Lawrence Mzukisi Madikizela[a*]

[a] Department of Chemistry, Durban University of Technology, P. O. Box 1334, Durban, 4000, South Africa

[b] Department of Chemistry, University of South Africa, Private Bag X6, Florida 1710, South Africa

[c] School of Chemistry, University of KwaZulu-Natal, Private Bag X01, Scottsville, Pietermaritzburg, 3209, South Africa

[d] Molecular Sciences Institute, University of Witwatersrand, Private Bag X3, Johannesburg, 2050, South Africa

Corresponding Author: LM Madikizela, lawrencem2@dut.ac.za, +2731 373 2315

Abstract

In the past few decades, there has been a rapid growth in the number of published articles that have focused on the environmental monitoring of non-steroidal anti-inflammatory drugs (NSAIDs). This is due to their extensive usage for the treatment of various diseases such as arthritis, musculo-skeletal pain and other various acute pains, because of their availability without a medical prescription. NSAIDs consumption is followed by excretion through fecal matter and urine which increases their concentration in the aquatic environment. Review articles focusing on the fate, occurrence and removal of pharmaceuticals in the water environment have been reported. This review focusses on adsorbents and various ways of NSAIDs reduction in the environment that include activated carbon, ligninolytic enzymes, graphene-based adsorbents, molecularly imprinted polymers, electrochemical methods, sonochemical processes and photocatalytic degradation. The applicability of each adsorbent in removing NSAIDs from environmental surface water are deliberated in this review. Generally, it is observed that many adsorbents and processes are yet to be investigated for removal of NSAIDs in the large scale such as wastewater treatment plants. Other remedial approaches such as constructed wetlands have shown great potential for elimination of NSAIDs in wastewater effluent and are also discussed in this review. Also, the attainments and challenges, as well as views for future studies, are outlined and discussed in the current review.

Keywords

Non-steroidal anti-inflammatory drugs; wastewater; adsorbents; removal efficiency; adsorption capacity

3.1.1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are an extensive range of medication used to treat and alleviate pain as well as inflammation in different arthritic and post-operative situations. Their three main therapeutic actions can be described as either anti-inflammatory, analgesic or antipyretic (Kress et al., 2016; Modi et al., 2012; Smith, 2014). NSAIDs can be purchased over the counter, without medical prescription from healthcare professionals. Therefore, tons of these pharmaceuticals are used gradually and consumed daily due to the increasing number of the general population and moreover invention of new drugs with better therapeutic efficacy (Daughton, 2003). As shown in **Figure 3.1.1**, after consumption these pharmaceutically active compounds leave the body as intact substances or metabolites through urine and feces. These metabolites or unmetabolized form of the parent compounds make way to the wastewater treatment plants (WWTPs) and raw sewerage after excretion (Jelic et al., 2012). It has been reported that extreme disposal of expired drugs in trash cans and sewers leads to NSAIDs being continuously released to the environment in large quantities (Escher et al., 2011). NSAIDs undergo several processes during the wastewater treatment of which they are not completely removed from water. Hence, several studies have reported their occurrence in WWTP effluents which is an indication of their incomplete elimination during the wastewater treatment process (Ben et al., 2018; Kermia et al., 2016; Li et al., 2013; Petrie et al., 2014; Shraim et al., 2017; Tran et al., 2018). This contributes to the occurrence of high levels of NSAIDs in aquatic environments reaching as high as $\mu g\ L^{-1}$ concentrations at multiple locations worldwide (Jelic et al., 2011; Luo et al., 2014; Sun et al., 2016; Tran et al., 2018; Wang and Wang, 2016). Poor control of NSAIDs in the environment can result in their uptake by crops through farming activities as indicated in **Figure 3.1.1**.

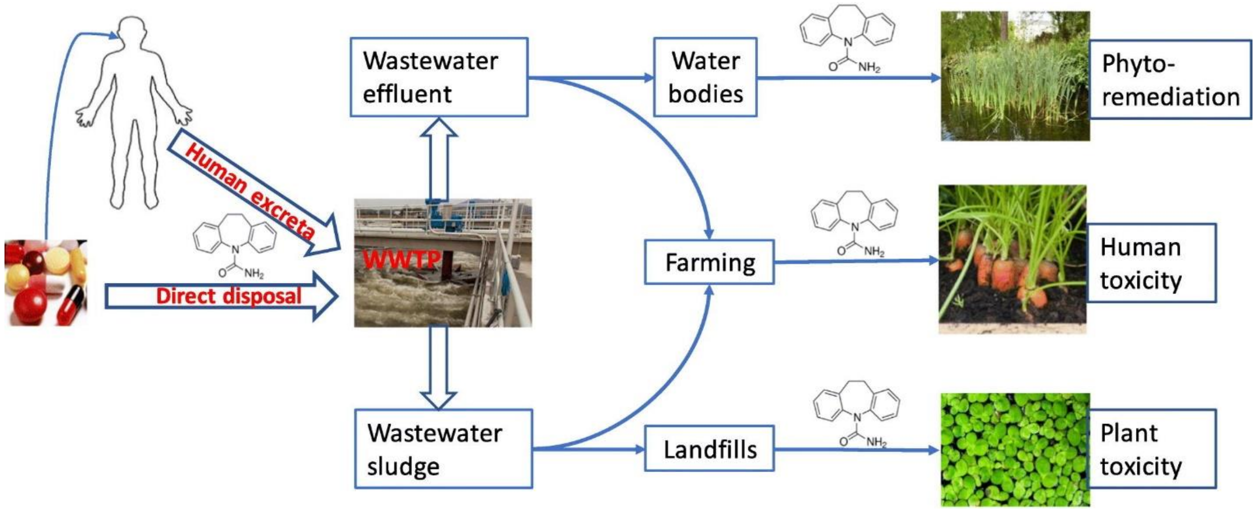


Figure 3.1.1. Sources of pharmaceuticals in the environment. Adapted from Madikizela et al. (2018) (Madikizela et al., 2018a) with permission from Elsevier.

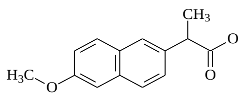
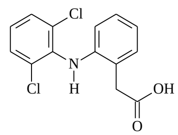
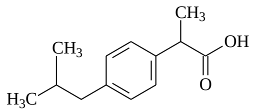
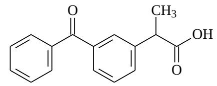
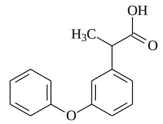
Based on literature, the removal efficiency of NSAIDs from WWTPs varies from -174 to 99% (Kermia et al., 2016; Zorita et al., 2009). Gao et al. (2016) evidenced that some pharmaceuticals are acknowledged as highly refractory and stable pollutants in WWTPs. After sewerage treatment, their concentrations are increased instead of being reduced which results in negative removal efficiency (Gao et al., 2016). Other possible explanations for the negative removal rates is the influent-effluent mismatching, or the creation of conjugated compounds during the wastewater treatment steps (Ratola et al., 2012). The negative removal efficiency can also be explained by the fact that some pharmaceuticals are excreted with feces and remain bounded in fecal particles in the raw influent wastewater and become released during wastewater treatment which makes them more concentrated in the effluent. In addition, the day-to-day concentration instabilities during the sampling period, the analytical uncertainty, and desorption of molecules from sludge and suspended particulate matter has been ascribed to the negative removal efficiency (Clara et al., 2004; Köck-Schulmeyer et al., 2013).

Some review papers have focused on the occurrence and removal of a variety of pharmaceuticals from drinking water and WWTPs (Gogoi et al., 2018; Kanakaraju et al., 2018; Madikizela et al., 2017; Sophia et al., 2016; Yang et al., 2017; Zhang et al., 2008). However, NSAIDs being a group of pharmaceuticals that are predominantly identified in water bodies across the world, this review paper focuses specifically on NSAIDs, their removal from contaminated water resources which include WWTPs, drinking water, river water, dam and lake water. Several studies have provided evidence of presence of NSAIDs in water bodies implying that the drugs could be consumed un-intentionally through the consumption of drinking water and food sources (Gumbi et al., 2017a; Husk et al., 2019; Madikizela and Chimuka, 2017a; Shanmugam et al., 2014). The current review will therefore look at remedial strategies that have been applied to alleviate the presence and impact of NSAIDs in contaminated water resources that include WWTPs, rivers, dams, lakes and drinking water. The focus is on adsorbents and some remedial processes such as constructed wetlands; that involve electrolysis of the parent compounds to by-products with less ecotoxicological and human health effects. Constructed wetlands have an advantage of the sorption and oxidation potential which provides remedial opportunities for any size of WWTP effluent. Application of constructed wetlands can be as a stand-alone mechanism or as a polishing step following both conventional or advanced treatment technologies (Ávila and García, 2015). Other adsorbents and processes that were critically reviewed in this work are activated carbon, ligninolytic enzymes, graphene-based adsorbents, molecularly imprinted polymers, electrochemical methods, sonochemical processes and photocatalytic degradation.

3.1.2 Toxicity of non-steroidal anti-inflammatory drugs in the environment

NSAIDs produce their therapeutic effects in humans by precluding various prostaglandin substances involved in the development of pain and inflammation as well as control of body temperature (Bellomo et al., 2017; Modi et al., 2012). NSAIDs taken in high dosages for longer periods may result in disruption of the body's endocrine system leading to toxicity and unpleasant effects (Sacher et al., 2008). The health effects summarized in Table 1 show that the effects may be rapid and fatal. For example, it has been reported that the consumption of 24 - 36 g of fenoprofen can lead to metabolic acidosis, hypotension, coma, and respiratory depression within 4 hours after its oral consumption (Kolodzik et al., 1990). Furthermore, it has been projected that 1 in 5 chronic users of NSAIDs will develop gastric impairment (Modi et al., 2012). Moreover, NSAIDs such as diclofenac have been linked to the deterioration of vulture population in Asia (Oaks et al., 2004; Taggart et al., 2007)

Table 3.1.1. Chemical structures, physicochemical properties and health effects of NSAIDs.

NSAID	Chemical structure	Log K_{OW}	pKa	Water solubility (mg L^{-1})	Health effects
Naproxen		3.18	4.19	44	Drowsiness, heartburn, indigestion, nausea, and vomiting.
Diclofenac		4.51	4.00	10	Loss of consciousness increased intracranial pressure and aspiration pneumonitis.
Ibuprofen		3.97	4.91	58	Peripheral edema and fluid retention.
Ketoprofen		3.12	4.45	51	Gastro intestinal tract, abdominal pain, constipation and flatulence in greater than 3% of patients.
Fenoprofen		4.05	4.50	81	Gastrointestinal and central nervous systems.

Information on this table was acquired from the literature cited in this document and drugbank website (https://www.drugbank.ca/) assessed in the period between March and April 2018.

3.1.3 Physicochemical properties of non-steroidal anti-inflammatory drugs

NSAIDs are weak organic acids with a carboxylate moiety present in them (Gundogdu-Hizliates et al., 2014; Narsinghani and Sharma, 2014). Their acid dissociation constants (pKa) range from 4.00 to 4.91 while their octanol-water partition coefficients (Kow) range from 1.10 to 3.97, implying that NSAIDs exist as dissolved neutral species under normal environmental conditions (Behera et al., 2011; Lindqvist et al., 2005). Their physicochemical properties relevant to their existence in water bodies are given in **Table 3.1.2**. Their high water solubility and polar nature could lead to difficulty in their removal efficiency in WWTPs (Dahane et al., 2013; Koutsouba et al., 2003; Larsson et al., 2009). To date, there are several adsorbents and procedures that have been proposed for the effective removal of NSAIDs from the aquatic environment.

3.1.4 Occurrence of non-steroidal anti-inflammatory drugs in water bodies

NSAIDs are regarded as emerging pollutants in water bodies and they are among the most detectable organic pollutants in the aquatic environment. Emerging pollutants are chemicals that have been found globally in drinking water supplies at trace levels and for which the hazard to the aquatic environment and human health is not yet understood. While these contaminants have been present in our drinking water for as long as people have been using them, advances in analytical technology and instrumentation have only recently made it possible to detect them (Geissen et al., 2015; Sun et al., 2015). It has been reported that NSAIDs find their way into drinking water through surface run-off and WWTP effluents (Carmona et al., 2014; Leal et al., 2010; Szymonik et al., 2017). Effluents from WWTPs that have an effect on receiving water bodies make up the main source of pharmaceuticals in surface waters which may possibly be used for drinking water supply. Also, the discharge of pharmaceuticals to groundwater from sources such as pipes and sewerage leaks could contribute to NSAIDs found in drinking water. A large number of articles have focused on the occurrence of NSAIDs in water bodies. This is important as it provides awareness on the status of pollution in the aquatic environment which could lead to un-monitored consumption of NSAIDs by humans. In Spain, the average concentrations detected for naproxen, diclofenac and ibuprofen in tap water were 11, 39 and 18 ng L^{-1}, respectively (Carmona et al., 2014). In Iran, the maximum detected concentrations in tap water for ibuprofen, diclofenac and naproxen were 39, 47 and 24 ng L^{-1}, respectively (Eslami et al., 2015). The problem with the occurrence of pharmaceuticals in drinking water may be associated with adverse effects on human health due to long-term exposure. According to Madikizela et al. (2017), the mean concentrations of naproxen detected in African wastewater influent and effluent, as well as surface water ranged from 1.1 – 55 µg L^{-1}, 0.33 – 20.4 µg L^{-1} and non-detection to 0.68 µg L^{-1}, respectively (Madikizela and Chimuka, 2017c). The amounts reported in the African continent are summarized in Table 2. In their review paper, it is presented that the maximum concentration of ibuprofen that has been detected in wastewater influent from South Africa was 221 µg L^{-1}. In comparison with well-developed countries such as Europe, the amounts of NSAIDs detected in their water systems are lower. For example, diclofenac concentration detected in WWTPs located in Turkey did not exceed 1.4 µg L^{-1} (Sari et al., 2014), while as shown in Table 2, the maximum concentration of diclofenac reported in South African WWTP influent was 104 µg L^{-1} (Madikizela and Chimuka, 2016b). The variations in NSAIDs levels in the environment across different countries could be explained by differences in the sanitation systems. For example, the lack of proper infrastructure in many African countries leads to the direct disposal of NSAIDs into surface water. Hence, the concentration of the most widely used NSAID, ibuprofen in the African continent reached a maximum of 85 µg L^{-1} in surface water (Matongo et al., 2015a). Whereas, in studies conducted in Brazil and China, the maximum ibuprofen concentrations in surface water were 20 µg L^{-1} (Fujimaki and Bernardo, 2017) and 5.4 µg L^{-1}, respectively (Peng et al., 2017). In a study conducted by Pereira et al. (2017), ibuprofen was not detected in Portuguese rivers (Pereira et al., 2017).

Table 3.1.2. Mean concentrations of NSAIDs found in various water matrices from Africa. Adapted from Madikizela et al. (2017) (Madikizela et al., 2017) with permission from Elsevier.

Sample	Compound	Mean concentrations or concentration ranges (μg L^{-1})
Influent	Naproxen	9.6[a], 1.2[a], 55[b], 52[b], 1.1[c], 2.3[c], 1.22–39.6[h], 2.2[k]
	Ibuprofen	1.6[a], 8.6[a], 39.8[b], 111.9[b], 5.2[c], 7.2[c], 62.8[f], 5.8[g], 6.02–221[h], 6.46–10.6[j], 1.36[k]
	Diclofenac	2.3[a], 0.99[a], 22.3[d], 3.72–104[h], 0.93–1.51[j], 0.85[k]
	Ketoprofen	0.57[a], 3.15[d], 1.7–6.4[e], 0.31[k]
Effluent	Naproxen	0.33[a], 13.5[b], 20.4[b], 0.4[c], 0.8[c], <LOQ-5.34[h], 0.098[k]
	Ibuprofen	0.34[a], 0.43[a], 12.6[b], 24.6[b], 1.1[c], 1.6[c], 58.7[f], 12.9[g], 3.87–67.9[h], nd-2.1[j], nd[k]
	Diclofenac	1.6[a], 2.7[a], 19.0[d], <LOQ-20.8[h], 0.03–0.06[j], 0.74[k]
	Ketoprofen	1.0[a], 0.90[d], 1.2–4.3[e], 0.16[k]
Surface water	Naproxen	<LOQ-0.68[h], 0.02–0.03[i], nd- < LOQ[k]
	Ibuprofen	0.31[a], 85[f], 0.23–6.2[g], <LOQ-11.4[h], 0.04–8.84[i], nd- 17.4[j], nd- < LOQ[k]
	Diclofenac	nd[a], 12.4[d], 0.03–0.27[i], nd- 0.73[j], nd-0.036[k]
	Ketoprofen	0.27[a], 0.38[d], <0.26–2.0[e], nd[k]

Reference/Country/Sampling month and year - [a]Kermia et al., 2016/Algeria/November 2014; [b]Amdany et al., 2014/South Africa/August and September 2012; [c]Amdany et al., 2015/South Africa/August and October 2012; [d]Agunbiade and Moodley, 2016/South Africa; [e]Madikizela et al., 2014/South Africa/August–October 2013; [f]Matongo et al., 2015a/South Africa/September 2013; [g]Matongo et al., 2015b/South Africa/September 2013; [h]Madikizela and Chimuka, 2016a/South Africa/January–March 2016; [i]Olarinmoye et al., 2016/Nigeria/August–September 2013; [j]K'oreje et al., 2016/Kenya/September 2012 and July 2013; [k]Dahane et al., 2013/Spain.

nd-the compound was not detected; <LOQ – the concentration of the compound was below the quantification limit.

3.1.5 Removal of non-steroidal anti-inflammatory drugs from water during purification

In most countries, wastewater treatment systems such as WWTPs and constructed wetlands were not originally designed to entirely prevent NSAIDs from entering the aquatic environment. High pharmaceutical loads together with other organic pollutants enter the water treatment facilities through sewage discharge from households, hospitals and other sources. Depending on the design of the treatment facility and the properties of NSAIDs, several compounds are removed efficiently from contaminated water using the conventional water treatment facilities. In this study, the removal efficiencies of NSAIDs from contaminated water achieved in WWTPs and constructed wetlands are examined.

3.1.5.1 Wastewater treatment plants

The removal of compounds from WWTPs can be determined based on the concentrations detected in both influent and effluent by using **Equation (3.1.1)**.

$$R = (C_{infl} - C_{effl})/C_{infl} \times 100 \qquad (3.1.1)$$

where C_{infl} and C_{effl} are the concentrations measured in the WWTP influent and the effluent, respectively. As shown in Table 3, the removal efficiency for NSAIDs from wastewater varies widely (Table 3). In some cases, negative values for removal efficiencies are reported due to the increase of concentrations for target pharmaceuticals in the WWTP effluents when compared to the loads of similar compounds found in the influents (Zorita et al., 2009)

Table 3.1.3. Removal efficiencies of NSAIDs from various wastewater treatment processes.

Treatment process	NSAID	Removal efficiency (%)	Reference
Mechanical, biological and chemical	Naproxen	94	(Zorita et al., 2009)
	Diclofenac	-105	
	Ibuprofen	99	
Mechanical and biological	Naproxen	73	(Kermia et al., 2016)
	Diclofenac	-174	
	Ibuprofen	95	
	Ketoprofen	-83	
Mechanical, biological and chemical	Naproxen	96	(Behera et al., 2011)
	Diclofenac	81	
	Ibuprofen	98	
	Ketoprofen	94	
Biological and chemical	Naproxen	25 – 98	(Kosma et al., 2014)
	Diclofenac	93.8	
	Ibuprofen	63 – 97	
Biological	Naproxen	>50	(Sun et al., 2016)

	Diclofenac	-50	
	Ibuprofen	84	
	Ketoprofen	-50	
Mechanical and biological	Naproxen	71	(Quintana et al., 2005)
	Diclofenac	23	
	Ibuprofen	97	
	Ketoprofen	62	
Mechanical, biological and chemical	Diclofenac	~60	(Sari et al., 2014)

Based on the results summarized in **Table 3.1.3**, it is shown that NSAIDs are not completely removed during wastewater treatment which results in their high loads entering surface water bodies with WWTP effluent. As evidenced in **Table 3.1.3**, even though NSAIDs are sometimes efficiently removed during wastewater treatment, they are also ubiquitous and present at substantial concentrations in water bodies receiving effluents from WWTPs. This could also be due to the fact that even though they are efficiently removed, concentrations in the influents are so high that the levels left over in the effluent are still significant (Jelic et al., 2012). High removal of NSAIDs is important as there is evidence that some of these drugs have negative effects on humans and aquatic species. Furthermore, although these drugs are present in trace amounts in surface water, the pseudo-persistence due to continuous disposal of these drugs by humans could result in health-related problems.

The removal efficiency of NSAIDs depends on their biodegradability and other physicochemical properties such as the likelihood of adsorption or not getting adsorbed by activated sludge, water solubility and their tendency to volatilize (Kosma et al., 2014). Also, the design of WWTPs and treatment processes employed in each WWTP can influence the removal efficiency of target compounds (Kermia et al., 2016). A typical wastewater treatment process involves sedimentation (mechanical treament), anaerobic digestion (biological treatment) and tertiary treatment (chemical treatment). Sedimentation is the process which allows particles in the wastewater effluent (suspension) to settle out of the suspension under the influence of gravity, thereby proving some degree of purification. The particles settle out from the suspension and thus become a sludge. The secondary treatment is the anaerobic digestion which is also known as the sludge treament. Here, the sludge is reduced without the use of air or elemental oxygen. In anerobic digestion, organic pollutants are converted by anaerobic micro-organisms to gaseous products which include methane gas that has a potential to be reused. The final step of the wastewater trament is the tertiary treament which consists of removing the organic load left over from the secondary step. Effluent from the secondary treatment plants contain phosphorus and nitrogen which are ingredients in all fertilizers. When excess amount of phosphorus and nitrogen are discharged, plant growth in the receiving waters (lakes, dams and rivers) maybe accelerated which results in eutrophication in the water body receiving such water. The purpose of this stage is to alleviate the treatment water quality to an extent where it is suitable for its intended reuse. Different types of organic pollutants such as NSAIDs are removed at high levels. Wastewater becomes even cleaner at this stage through the use of more advanced treatment systems such as sedimentation, coagulation, filtration of particulate phosphorus, ion-exchange, activated carbon adsorbtion, and membrane processess (Ahmed et al., 2017; Zorita et al., 2009).

NSAIDs are not easily adsorbed onto activated sludge due to their polar and hydrophilic properties. This is also evident in the results presented in **Table 3.1.3**, where there are variations in the removal efficiencies of each NSAID. In this context, it has been reported that the main removal of diclofenac in WWTPs is caused by biological treatment (Sari et al., 2014). Among other NSAIDs, diclofenac shows the least removal efficiency in most cases **(Table 3.1.3)** which has been the common trend in most studies. For example, the reported removal efficiencies for diclofenac in studies conducted in France (Thiebault et al., 2017), Spain (Martín et al., 2012) and Sweden (Bendz et al., 2005) are -20 - 50%, 14% and 17 - 69%, respectively. Whereas, in the same studies the reported removal efficiency for other NSAIDs (ibuprofen, ketoprofen, and naproxen) was above 40% (Martín et al., 2012; Thiebault et al., 2017). In fact, in some cases, diclofenac concentrations have been observed to increase in treated wastewater when compared to the raw influent (Kasprzyk-Hordern et al., 2009). Zorita et al. (2009) and Martin et al. (2012) associated the poor removal of diclofenac to the combination of its degradation in wastewater together with the discharge of supplementary diclofenac molecules by de-conjugation of glucuronidated or sulfated diclofenac and/or its desorption from particles (Martín et al., 2012; Zorita et al., 2009). Thiebault et al. (2017) reported that the wide variability could be caused by changes in the chemical parameters of the influent water that could potentially affect the water treatment efficiency (Thiebault et al., 2017). The low removal efficiency of diclofenac might also be due to its low water solubility and its inability to adsorb onto sludge. This augmentation is probably due to the deconjugation of conjugated metabolites during the treatment process; an underestimation of the current amount may be due to particulate matter with adsorbed pharmaceuticals being filtered out during the sample preparation, and/or the desorption of diclofenac from the particulate phase during the wastewater treatment. For these reasons, diclofenac is not expected to adsorb significantly to the sludge (Kermia et al., 2016; Sui et al., 2010). Under normal wastewater treatment pH, diclofenac is at its ionized state and thus existing in aqueous phase hence the removal of NSAIDs cannot be explained by sorption onto sludge but by biodegradability in the aqueous phase.

The effect of disinfection by UV method throughout the wastewater treatment process has been reported to contribute to the removal efficiency of diclofenac by at least 27% (Sari et al., 2014). Similarly, Madikizela and Chimuka (2017) reported a decrease in diclofenac concentration from 5.5 µg L^{-1} in water (prior to disinfection in WWTP) to 2.0 µg L^{-1} in WWTP effluent (after disinfection by chlorination) which correspond to 36% removal in a single treatment stage (Madikizela and Chimuka, 2017b). In the same study (Madikizela and Chimuka, 2017), the effect of chlorination during WWTP process had a minimal contribution to the removal efficiency of naproxen and ibuprofen, which is a case that needs further investigation.

The highest removal rate (94 – 99%) for NSAIDs in the study reported by Zorita et al. (2009) was achieved in the biological process except for diclofenac. Elsewhere, high removal efficiencies for naproxen, diclofenac, ibuprofen and ketoprofen ranged from 81-94% (Behera et al., 2011). In the same study, the removal of most NSAIDs occurred in the biological treatment, the average removal efficiency for different compounds ranged from −38% to 100% (Behera et al., 2011). Furthermore, a critical review on the biological and chemical processes of WWTPs has been presented elsewhere (Ahmed et al., 2017).

3.1.5.2 Constructed wetlands

Constructed wetlands (CWs) are suitable wastewater treatment systems for regions where sewer networks and WWTPs are not economical. Wetlands are capable of efficiently removing conventional pollutants and meeting secondary treatment standards for municipal wastewater treatment. These wetlands utilize complex natural processes, including bio- and photo-degradation, sorption, plant uptake and sedimentation for the removal of wastewater constituents. In addition, they offer economically viable treatment, and typically require less operation and maintenance effort than other decentralized treatment technologies (Kadlec and Wallace, 2009; Vymazal, 2011).

The performance of CWs in the removal of NSAIDs has been investigated (Ávila et al., 2010; Sochacki et al., 2018; Vymazal, 2011; Vystavna et al., 2017; Zhang et al., 2011). Several geochemical properties of CWs responsible for the remediation of NSAIDs have been identified. In a study that investigated the removal of NSAIDs in constructed wetlands, an injection process was employed (Ávila et al., 2010). In this process, water was spiked with ibuprofen, naproxen, diclofenac and other targeted compounds. The mixture was normalized and injected into the circulation pipes of the system. Approximately, 99% removal efficiency was achieved for naproxen, ibuprofen and diclofenac(Ávila et al., 2010). High removal efficiency was ascribed to the high injected influent concentrations of these NSAIDs as well as high temperatures in spring at the period the experiment was conducted. This was an indication that removal efficiency was related to the amount of analyte in the influent while higher temperatures enhanced their biodegradability and plant uptake. Elsewhere, Avila et al. (2013) have identified redox potentials as one of the most interesting parameters for evaluating the ability of a CW to remove NSAIDs

(Ávila et al., 2013). In their study, the influence of redox potentials was investigated for the removal efficiencies of ibuprofen and diclofenac in a CW. The removal efficiencies observed for ibuprofen and diclofenac were 52% and 32%, respectively (Ávila et al., 2013). However, they observed lower removal efficiencies in 2013 compared to their previous study reported in 2010, where removal efficiencies for NSAIDs were from 98 to 99% (Ávila et al., 2010).

The removal of diclofenac in CW through phytoremediation has been reported in literature (Zhang et al., 2012). The uptake and build-up of diclofenac by the macrophyte *Scirpus validus* has been measured by Zhang et al. (2012) in hydroponic solutions containing 0.5 – 2.0 mg L^{-1} of diclofenac over the maximum exposure period of 21 days (Zhang et al., 2012). Their findings showed that diclofenac could be reduced significantly (80%) by phytoremediation which appeared to be the main pathway for its removal. Zhang et al. (2011) reported that the removal efficiency of 55% for diclofenac in the beds planted with *Typha angustifolia* (55%) showed a significant enhancement compared to those in the unplanted beds (41%) (Zhang et al., 2011). The findings of Zhang et al. (2011; 2012) further indicate that the removal efficiency of NSAIDs also depend on the plant species as 55% removal of diclofenac was observed when *Typha angustifolia* was employed which increased to >80% when *Scirpus validus* was used (Zhang et al., 2012, 2011). Table 4 shows the removal efficiency of NSAIDs from CWs using different plant species. This evidence suggests that aquatic plants could play a significant role in the diclofenac removal from CWs.

Table 3.1.4. Removal efficiencies of NSAIDs in constructed wetlands by various plant species.

NSAID	Plant species	Removal efficiency (%)	Reference
Diclofenac	*Scirpus validus*	>80	(Zhang et al., 2013)
Diclofenac	*Typha angustifolia*	55	(Zhang et al., 2011)
Ibuprofen	*Typha spp*	96	(Dordio et al., 2009)
Naproxen	*Scirpus validus*	98	(Zhang et al., 2013)

3.1.6 The removal of non-steroidal anti-inflammatory drugs from water by adsorption

Adsorption is the most widespread physical procedure, which is often used for removal of trace organic pollutants in water and as such has also been reported for the removal of NSAIDs in the environmental water samples. The adsorption process has the ability to remove both soluble and insoluble organic pollutants with the removal of some compounds almost going to completion (Rostvall et al., 2018a). Various strategies and adsorbents reported in literature for the adsorption or removal of pharmaceuticals from water include activated carbon (Ali et al., 2019; Altmann et al., 2014; Andrea et al., 2018; Bahamon et al., 2017; Katsigiannis et al., 2015; Mestre et al., 2007; Nam et al., 2014; Rigobello et al., 2013; Rostvall et al., 2018a; Sophia and Lima, 2018), ligninolytic enzymes (Naghdi et al., 2018; Stadlmair et al., 2018; Vasiliadou et al., 2016), graphene-based adsorbents (Al-Khateeb et al., 2017; Banerjee et al., 2016; Nodeh et al., 2018; Sarker et al., 2018; Sophia and Lima, 2018), molecularly imprinted polymers (MIPs) (Madikizela and Chimuka, 2016b; Samah et al., 2018; Sun et al., 2008; Zunngu et al., 2017), electrochemical methods (Ensano et al., 2017; Murugananthan et al., 2010), sonochemical processes

(Adityosulindro et al., 2017; Ince, 2018) and photocatalytic degradation (Akkari et al., 2018; Eslami et al., 2016; Jallouli et al., 2018; Strbac et al., 2018). Some of these materials and methods including activated carbons (Ahmed, 2017), ligninolytic enzymes (Naghdi et al., 2018), photocatalytic degradation (Kaur et al., 2016), sonochemical process (Chu et al., 2017), electrochemical advanced oxidation process (Feng et al., 2013; Moreira et al., 2017) and graphene-based adsorbents (Hiew et al., 2018) have already been reviewed elsewhere. This section therefore focusses more on MIPs since they have not been reviewed for removal of NSAIDs while important points on the adsorbents that have already been reviewed are mentioned in the current review.

3.1.6.1 Activated carbon

It is utmost important to mention that activated carbon (AC) has been widely explored for adsorption of NSAIDs where most work focused on the application of commercially available powdered activated carbon (PAC) and granulated activated carbon (GAC). GAC has a relatively larger particle size compared to PAC and consequently, presents a smaller external surface area for adsorption. Activated carbon has a large internal surface area of up to 1 500 $m^2 g^{-1}$ which makes it highly suitable for adsorption of organic compounds. Most NSAIDs have pKa values below the normal environmental pH conditions **(Table 3.1.2)** implying they exist in their anionic state. The capability of AC depends upon contact time, dose, the molecular structure as well as the behavior of the compound of interest (Ahmed, 2017; Mestre et al., 2007; Rostvall et al., 2018b). In this context, Nourmoradi et al (2018) achieved a maximum sorption capacity of 96.15 mg g^{-1} for ibuprofen on AC from oak corn treated with phosphoric acid. In this case, the optimum experimental conditions were the contact time of 120 min at pH 3, the adsorbent was 1 g L^{-1} of solution and the initial concentration of ibuprofen was 150 mg L^{-1}. The authors (Nourmoradi et al., 2018) indicated that the surface of the adsorbent at pH 3 was negatively charged while ibuprofen was in its non-ionized form, hence stronger adsorbate-adsorbent interactions could have happened. Further work also indicated that the removal efficiency of NSAIDs from water using AC depends largely on the pH of aqueous solutions with most studies suggesting the acidic conditions for favourable adsorption (Baccar et al., 2012; Behera et al., 2012; Larous and Meniai, 2016; Mestre et al., 2007). This was demonstrated when the removal efficiency higher than 90% was achieved for ibuprofen at sample pH between 2 and 4 (Mestre et al., 2007). This suggest that the adsorption is influenced by hydrogen bonding, van der Waals interactions and π - π interactions (Baccar et al., 2012). At a higher dosage, activation sites are increased producing higher removal efficiencies with NSAIDs having moderate to high log Kow values experiencing an almost complete removal (Ahmed, 2017). Also, increasing contact time for the adsorbent to interact with the NSAIDs can result in a more complete adsorption equilibrium as activated carbon binds well with the NSAIDs. As much as GAC has been found to be highly efficient and effective, water-soluble contaminants can break from the GAC surface more hastily than strongly bound hydrophobic pollutants (Snyder et al., 2007). Generally, reports have shown that the removal efficiencies of NSAIDs from various water matrices by activated carbon-based adsorbents can reach up to 100% (Nam et al., 2014; Nourmoradi et al., 2018; Yu et al., 2008).

3.1.6.2 Graphene-based adsorbents

Graphene is a carbon allotrope (Sophia and Lima, 2018) which can be modified into different forms thereby resulting in its numerous applications such as adsorption of water pollutants.

Various forms of graphene such as those given in **Figure 3.1.2** have been studied for removal of several pollutants from water. It has been noted that nanoparticles such as nanographene plateletes seem to be better adsorbents due to their good working capabilities, excellent electrical and optical properties as well as good chemical/physical stability (Hiew et al., 2018). Nanographene is known for its high surface area which subsequently result in high adsorption capacities. For example, nano-graphene that had a specific surface area of 677.5 $m^2 g^{-1}$ resulted in maximum adsorption capacities of 16.6, 17.8, 19.3 and 11.9 mg g^{-1} towards ketoprofen, naproxen, diclofenac, and ibuprofen, respectively (**Table 3.1.5**) (Al-Khateeb et al., 2017; Hiew et al., 2018). In one study, graphene oxide-doped polysulfone membrane was used for the removal of diclofenac from water where the removal of the target compound was greater than 90% (Zambianchi et al., 2017). Zambianchi et al. (2017) observed better removal of diclofenac at pH 3 while the performance of graphene-based adsorbent was poorly affected by sample pH in the adsorption of other organic contaminants including ofloxacin, benzophenone-3, rhodamine b and triton X-100 (Zambianchi et al., 2017). This implied that the removal efficiency of NSAIDs using graphene-based adsorbent was greatly related to the chemical species rather than the adsorbent (Zambianchi et al., 2017). However, a different view was presented for adsorption of ibuprofen from water on graphene oxide nanoplatelets where the % removal was observed to increase from 60 to 98% as water solution pH varied from 2-6 due to electrostatic interactions (Banerjee et al., 2016). This meant that the pH of the solution has the ability to influence the surface chemistry of the adsorbent. In their study, Nam et al., 2015 observed hydrophobic and π–π EDA interactions as the main binding mechanisms for the adsorption of diclofenac into graphene oxide from aqueous solution (Nam et al., 2015). Elsewhere, greater than 94% of NSAIDs were removed from water contaminated with 20 mg L^{-1} mixture of ketoprofen, naproxen, diclofenac and ibuprofen, using 40 mg of nano-graphene, with adsorption equilibrium being reached within 5 min at pH 2 (Al-Khateeb et al., 2017). Recently, Jothinathan and Hu (2018) reported a study on the kinetic evaluation of graphene oxide (GO)-based heterogeneous catalytic ozonation for the removal of ibuprofen where the degradation of ibuprofen was found to be 85% for the O_3/GO/Fe_3O_4 suspensions followed by O_3/GO (76%) and O_3 alone (55%) (Jothinathan and Hu, 2018). These results correspond well with the data reported by Liu et al. 2016, where N, N-diethyl-m-toluamide degradation rate was significantly accelerated through the combined effect of GO and ozonation which yielded abundant hydroxyl radical, compared to pure ozone condition (Liu et al., 2016). According to the reported results, GO has a future as an adsorbent for micropollutants. This is due to graphene having a high surface area which means it has the ability to extract more compounds and is not easily saturated by pollutants. This means that graphene-based adsorbents can adsorb plenty pollutants at once.

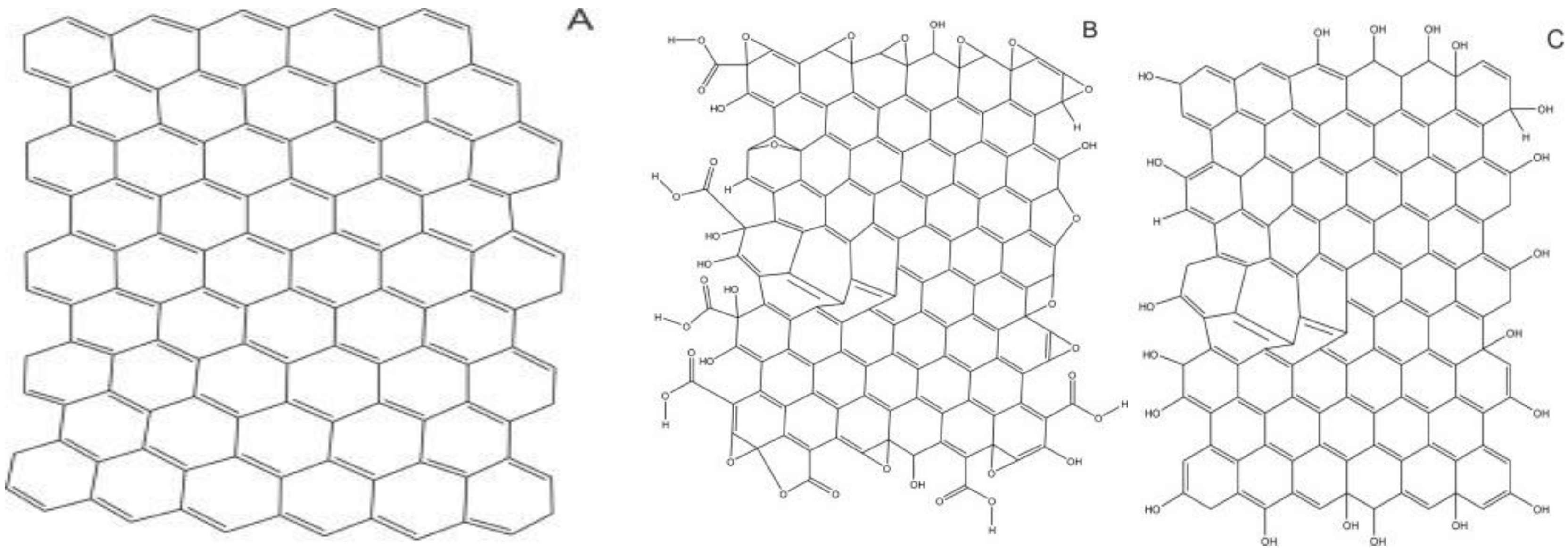


Figure 3.1.2. Chemical structures of graphene (A), graphene oxide (B) and reduced graphene oxide (C). Adapted from Sophia and Lima (2018) (Sophia and Lima, 2018) with permission from Elsevier.

Table 3.1.5. Various adsorbents applied for removal of NSAIDs from water bodies.

Adsorbent	Surface area (m^2 g^{-1})	Adsorption medium	Adsorption capacity (mg g^{-1})	Reference
Multi-template MIP	282	Ultra-pure water	4.4[a], 5.5[b] and 3.6[c]	(Madikizela and Chimuka, 2016a, 2016b)
Nanographene	678	Wastewater	17.8[a], 19.3[b],11.9[c] and 16.6[d]	(Al-Khateeb et al., 2017)
Activated O-biochar	1151	Ultra-pure water	228[a], 214[b] and 286[c]	(Jung et al., 2015)
Activated N-biochar	1360	Ultra-pure water	290[a], 372[b] and 311[c]	(Jung et al., 2015)
Carbonaceous material (carbon black-2000)	1443	River water	517[a] and 400[d]	(Cuerda-Correa et al., 2010)

[a]naproxen, [b]diclofenac, [c]ibuprofen and [d]ketoprofen

3.1.6.3 Molecularly imprinted polymers

Molecular imprinting is a technique for the creation of selective recognition sites in synthetic polymers (Caro et al., 2004; Saloni et al., 2011; Samah et al., 2018). As shown in **Figure 3.1.3**, molecularly imprinted polymers (MIPs) are prepared by polymerization of functional monomers using a cross-linker in the presence of a template (target molecule). The imprinting molecule(s) is then removed from the polymer by washing with a suitable organic solvent to create cavities with complimentary binding site(s) (Haginaka et al., 1999). Thereafter, molecular recognition by MIP is based on the size, shape and position of functional groups of the target compound.

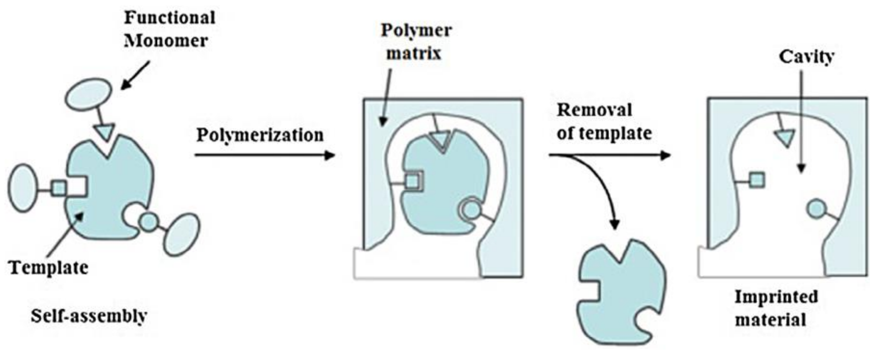


Figure 3.1.3. Synthesis of molecularly imprinted polymer. Adapted from Sarafraz-Yazdi et al. (2015) (Sarafraz-Yazdi and Razavi, 2015) with permission from Elsevier.

Over the years, MIPs have shown great potential for selective adsorption of NSAIDs from water bodies (Ansari and Karimi, 2017; Madikizela et al., 2018b; Pichon, 2007). However, there is lack of evidence for the production of MIPs in large scales which can result in their application as adsorbents in water treatment. Hence, MIPs have been largely utilized as selective sorbents in sample preparation. To date, MIPs have been synthesized for all NSAIDs (Madikizela et al., 2018b), with fenoprofen being imprinted most recently (Mbhele et al., 2018). Most of these MIPs have been applied as selective solid-phase extraction sorbents in the analysis of NSAIDs in water and biological samples (Caro et al., 2004; Olcer et al., 2017; Sun et al., 2008; Zunngu et al., 2017).

In adsorption experiments, MIPs have been shown to be able to adsorb NSAIDs from lake water (Dai et al., 2012), river water (Caro et al., 2005; Madikizela and Chimuka, 2016b) and wastewater (Madikizela and Chimuka, 2016b; Sun et al., 2008). It has been shown that adsorption depends on the pH of the polluted water (Dai et al., 2012). High extraction efficiency is achieved in acidic conditions where the NSAIDs are neutral at the carboxylic group. This allows for hydrogen bonding to occur between the hydrogen atom of the carboxylic group in the NSAID and the basic nitrogen atom of 2-vinylpyridine or 4-vinylpyridine mostly used as functional monomers in the polymerization. Furthermore, studies have shown the ability to synthesize multi-template MIPs that can extract more than one NSAID. Multi-template MIPs have been reported to be able to remove a group of NSAIDs selectively from aqueous solutions (Dai et al., 2012; Madikizela and Chimuka, 2016a). In the same context, a multi-template MIP which had a surface area of 282 m^2 g^{-1} resulted in maximum adsorption capacities of 4.4, 3.6 and 5.5 (mg g^{-1}) for naproxen, ibuprofen and diclofenac, respectively **(Table 3.1.5)** (Madikizela and Chimuka, 2016a, 2016b). The experimental conditions employed to achieve such adsorption capacities were 50 mg of MIP, extraction time of 10 min, sample pH of 4.6, volume of 10 mL and the initial concentration for each NSAID was 50 mg L^{-1} (Madikizela and Chimuka, 2016b).

Surface adsorption for NSAIDs onto MIPs has been explained better using Langmuir isotherm model rather than Freundlich model (Dai et al., 2012; Madikizela and Chimuka, 2016b). This implies the occurrence of a monolayer adsorption on the surface of MIP adsorbents. Furthermore, when the results fit Langmuir isotherm best, the binding sites in the MIP are considered to be homogeneous (Madikizela and Chimuka, 2016b). In the same studies, the sorption of target compounds onto MIP has been found to be influenced by chemical adsorption (Dai et al., 2012; Madikizela and Chimuka, 2016b). Chemical adsorption is likely to occur due to hydrogen bonding between NSAIDs and basic nitrogen atom of vinylpyridine used as the functional monomer in the synthesis of MIP.

3.1.6.4 Other novel adsorbents for removal of NSAIDs from water

There are several other strategies that have been reported for the removal of NSAIDs from water bodies as shown in Tables 5 and 6. These include the application of composite iron nano adsorbent for the removal of ibuprofen from water (Ali et al., 2016). This nano-adsorbent was regenerated by treating with dilute (0.50 mol L^{-1}) hydrochloric acid and used up to 8 times yielding removal capacities for ibuprofen from 85 - 92% (Ali et al., 2016). This was achieved using the following experimental conditions; 60 μg L^{-1}, 30 min, 7.0, 1.0 g L^{-1}, and 25.0 °C as ibuprofen concentration, contact time, pH, adsorbent amount and temperature, respectively (Ali et al., 2016). Elsewhere, a porous carbon organic framework (zeolitic-imidazolate framework-8) derived from coating carbon using prepared nitrogen-containing organic linker (2-methylimidazole) and Zn clusters, is attractive for its high porosity, thermal/chemical stability, and hydrophobicity as a functional moiety has shown the ability to adsorb ibuprofen and diclofenac via hydrogen bonding (Bhadra et al., 2017). Their adsorbent yielded the adsorption capacity greater than 225 mg g^{-1} for ibuprofen and maintained its efficiency even after 4 extraction cycles (Bhadra et al., 2017). Most recently, persulfate-based advanced oxidation was employed for the removal of ibuprofen using recycled and reused rusted iron particles containing core-shell Fe-FeOOH (iron III oxide hydroxide) for ibuprofen removal (Yin et al., 2018). In this instance, the adsorption of ibuprofen increased from 10% to 85% with increasing reused rusted iron particles dosages. Subsequently, other materials that include functionalized strong nano-clay composite (Rafati et al., 2018) and activated biochar with much higher surface areas led to extremely high adsorption capacities **(Table 3.1.5)** for NSAIDs. Such adsorbents as they showed the potential to remove NSAIDs in water (Ocampo-Perez et al., 2019) are expected to be explored for all NSAIDs in the near future.

3.1.7 Other methods for removal of non-steroidal anti-inflammatory drugs from water

Various processes including ozonation, photocatalytic degradation, enzymatic treatment, sonochemical processes and advanced oxidation processes have been applied for the reduction of NSAIDs from contaminated water. These processes remove NSAIDs from water bodies by converting these pharmaceuticals into smaller organic molecules. The application of these procedures should produce compounds that are environmentally friendly or less toxic than the parent compounds. The work presented by various researchers in this aspect is presented in this section.

3.1.7.1 Ozonation

Removal of pharmaceuticals including NSAIDs from municipal wastewater using the ozonation process has been reviewed by Petrie et al. (2013) (Petrie et al., 2013). Various removal efficiencies reported in their review for NSAIDs were 46 – 62% (ibuprofen), 92 – 99% (diclofenac), 50 – 99% (naproxen), 73 – 98% (ketoprofen) (Petrie et al., 2013). Beyond 2013, other studies have reported advanced applications of ozonation with the aim of enhancing its efficiency in the removal of pharmaceuticals. In a study by Ikhlaq et al. (2014), ibuprofen removal from water using the ozonation process alone was 0 - 60% at different pH levels (Ikhlaq et al., 2014). The highest removal was observed at pH 13 and the lowest being at pH 3. Whereas in the presence of a zeolite catalyst up to 80% removal of ibuprofen was reported, with the highest removal at pH 3 and lowest at pH 13 (Ikhlaq et al., 2014). This is an indication that at acidic pH ibuprofen shows higher adsorption on zeolite surface and at pH 13 ibuprofen is negatively charged which results in weak interactions with zeolite. The addition of a catalyst is therefore known as catalytic ozonation. Ikhlaq et al. (2015) reported on the removal of ibuprofen using catalytic ozonation from water on alumina (Al_2O_3), high removal of 80% was observed as compared to when ozonation process was solely used resulting at 60% removal efficiency (Ikhlaq et al., 2015). Elsewhere, ozonation was combined with ultra-violet radiation (O_3/UV) to decompose ketoprofen from river water and thermal water (Illés et al., 2014). In their study, the removal of ketoprofen was almost to completion (O_3/UV) and 80% was achieved when ozonation was used alone (Illés et al., 2014). This removal was due to the direct influence of UV light, nevertheless ozone contributed to the mineralization of small carboxylic groups towards the end of the treatment process. Using both methods, four major aromatic transformation products were formed:3-(1-hydroxyethyl)benzophenone, 3-(1-hydroperoxyethyl)benzophenone,1-(3-benzoylphenyl)ethanone and 3-ethylbenzophenone and toxicity tests conducted showed that these by-products were rather toxic to the aquatic ecosystem (Illés et al., 2014). Another process known as photocatalytic ozonation for the removal of organic pollutants which utilizes photocatalysts such as TiO_2 based and non-based materials, magnetic materials based on magnetite and ZnO to mention a few has already been critically reviewed (Xiao et al., 2015). In the removal of organic pollutants (diclofenac and ketoprofen) from municipal wastewater, a complete removal (100%) was observed when solar light (SL) and Fe (III) were combined with ozone (SL/O_3/Fe (III)) (Gimeno et al., 2016). However, the intermediates detected showed no toxicity towards the aquatic ecosystem (Gimeno et al., 2016). Ozonation alone shows the inability to remove NSAIDs without the addition of a catalyst to advance the treatment process.

3.1.7.2 Photocatalytic degradation

Photocatalytic degradation has been reviewed by Kaur et al. (2016) (Kaur et al., 2016) and as such this subsection summarizes the major findings and also looks at current advances on its application since 2016. In their evaluation, they concluded that TiO_2 photocatalysis was an efficient and effective method for the removal of NSAIDs from wastewater compared to conventional treatment methods such as filtration, flocculation, coagulation, and sedimentation. They also mentioned that adsorption is an alternative method for the degradation of drugs but not for all prescription drugs. Beyond 2016, Bilgin Simsek, (2017) has iterated that degradation of NSAIDs in the environment is accelerated by the introduction of a suitable catalyst where TiO_2 is frequently used due to its relatively high reactivity (Bilgin Simsek, 2017; Ohtani et al., 2010). In addition to the introduction of TiO_2, molecularly imprinted photocatalyst have been reported as responsible for the improvement of selectivity in photocatalytic process (de Escobar et al., 2018). Most recently, Jallouli et al. (2018) have converted ibuprofen from ultrapure water, municipal and pharmaceutical industry wastewaters into environmentally friendly chemicals, namely; 1-(4-isobutyl-phenyl)-ethanol and 2-[4-(hydroxyl-2-methylpropyl)phenyl] propionic acid, in the presence of titanium dioxide (TiO_2) under ultraviolet radiation (Jallouli et al., 2018). Furthermore, it has been shown that the application of reduced graphene oxide-based TiO_2-zinc oxide nanostructures as a catalyst results in better photoactivity than bare TiO_2 and zinc oxide (Bilgin Simsek et al., 2018). An interesting study mentioned in the review by Kaur et al. (2016) was conducted by Mendez-Arriaga et al. (2008) who reported that there were no common tendencies found for the photolytic degradation or thermo-degradation of ibuprofen, naproxen, and diclofenac with TiO_2 and simulated solar irradiation (Kaur et al., 2016; Fabiola Méndez-Arriaga et al., 2008). A strong photolytic influence was observed in the case of naproxen and diclofenac where highest degradation was achieved for experiments carried out at 40 C. In all instances, an improvement was reached on the total organic carbon reduction when TiO_2 loading was increased. Nonetheless, the by-products generated for diclofenac and naproxen were not recommended for a post-biological treatment due to the low biodegradability index reached (sometimes equal to the original one). Only ibuprofen had an imperative increase in its removal and biodegradability index reached after a photocatalytic process. The photocatalytic process exhibited a higher efficiency in degradation at low initial concentrations of ibuprofen. Its higher biodegradability index could be related to the high oxidation level reached by the by-products generated. In another study, results showed that degradation of ibuprofen and diclofenac by photocatalytic oxidation was somewhat moderate (Hama Aziz et al., 2017). The disappearance of the target pollutant does not give assurance for the successful water treatment method since the degradation by-products might be more harmful than the initial pollutant. Therefore, in order to achieve a maximum degree of mineralization, Hama et al. (2017) have proposed that prolonged treatment time is necessary (Hama Aziz et al., 2017). In their study, mainly short chain acids such as acetate, oxalate and to a minor extent, maleate and malonate succinate were the final end-products of decomposition of diclofenac.

3.1.7.3 Enzymatic treatment

Biocatalytic conversion using living organisms or their enzymes is an environmentally friendly alternate method in remediation of organic pollutants in the environment. This treatment process needs lower energy input, works under moderate conditions and produces less or no toxic by-products compared to other conventional technologies (Asif et al., 2017). Enzymes are biologically-made catalysts that facilitate biochemical reactions at a rapid rate and can play a critical role in preventing pollution (Arora and Sharma, 2010). Lignin is a high molecular complex oxyphenyl propanoid polymer, discovered in all vascular plants including herbaceous species, which provides stiffness, provision, and shielding to the plants (Norgren and Edlund, 2014). A ligninolytic enzyme laccase immobilized onto biochar was employed for the degradation of diclofenac in water, 73% degradation was achieved after 8 hours (Taheran et al., 2017). Elsewhere, the degradation of selected pharmaceutically active compounds by whole fungal culture, trametes versicolor, culture filtrates and commercial laccase preparation was conducted (Tran et al., 2010). A removal efficiency of 5 – 99% for the selected pharmaceuticals (ibuprofen, diclofenac, ketoprofen, naproxen and fenoprofen) was reported. This removal was attributed to the presence of the enzymes such as laccase in the fungal culture. It was noted that pharmaceuticals with nitrogen-containing structure and negative charge(s) were easily removed by laccase activity. The key concept suggested by Stadlmair et al. (2018) was due to a key effect of functional groups and their electron retreating or donating properties on the susceptibility to biodegradation (Stadlmair et al., 2018). As such, Tran et al. (2010) noted that diclofenac and naproxen could be efficiently removed by the cell-free extract (crude laccase) and the commercial laccase, although ibuprofen, ketoprofen, and fenoprofen showed poor degradation. On the other hand, whole fungal culture evidenced considerably higher degradation for ibuprofen, ketoprofen, and fenoprofen which could be completely removed (Tran et al., 2010).

3.1.7.4 Sonochemical processes and advanced oxidation processes

Advanced oxidation processes (AOPs) are amongst the most competent treatments for the removal of pharmaceutical pollutants in water (Rivera-Utrilla et al., 2013; Saeid et al., 2018). The performance of these processes in the remedial of variety of pharmaceuticals has been reviewed by Chu et al. (2017) (Chu et al., 2017). AOPs are characterized by the formation of highly reactive and non-selective hydroxyl radicals (˙OH) which can mineralize virtually all organic compounds. Among these, Fenton oxidation is very interesting due to its ease of producing ˙OH radicals. Ultrasound is also an additional promising AOP since it does not require any addition of chemicals and it is able to degrade organic pollutants through direct thermolysis in case of volatile compounds.

3.1.7.5 Sonolysis and sono-Fenton process

Sonolysis is an AOP, the most important parameters for its application are the applied power (higher power yields higher degradation rates) and frequency used. Depending on the ultrasound degradation pathway of the parent pollutant, there is an optimum frequency (200 - 400 kHz) for each process. For example, Mendez-Arriaga et al. (2008) demonstrated that degradation of ibuprofen by sonolysis at a frequency of 300 kHz and 80 W applied power led to 98% removal of ibuprofen (Chu et al., 2017; Méndez-Arriaga et al., 2008). The increased removal efficiency of ibuprofen was mainly due to the tendency to concentrate in the interface of the cavitation where the highest amount of ˙OH radicals is reached. In a study by Adityosulindro et al. (2017) on the removal of ibuprofen from wastewater by sonolysis and coupled ultrasound/ Fenton oxidation process, degradation of ibuprofen was low in wastewater (24%) compared to 48% in deionized water (Adityosulindro et al., 2017). The effectiveness of the sonolysis process was reduced in wastewater matrix, due to higher pH increasing the molecule solubility (Adityosulindro et al., 2017). In the same context, the degradation of ibuprofen using Fenton reaction in the presence of homogeneous catalyst has been reported to reach 99% (Chu et al., 2017; Marković et al., 2015). While in a different study, bio-electro-Fenton oxidation of NSAIDs reached 61-97% in 5 hours of reaction time (Nadais et al., 2018).

3.1.7.6 Sonocatalytic degradation

The combination of sonochemistry with catalysis is used to achieve a number of chemical reactions with suitable workup conditions (e.g. shorter reaction times) in contrast to more conventional methods (Chu et al., 2017; Gawande et al., 2014). In sonocatalytic degradation, the ultrasonic waves have stronger penetrating power as a result of sonoluminescence and hotspot which are very effective in degrading complex contaminants. Ultrasonic treatment is another advanced treatment process which has shown several advantages including energy saving, cleanliness, safety, and negligible or no secondary pollution products (Chu et al., 2017). Removal of NSAIDs is influenced by water quality and sonication parameters such as temperature, pH, background common ions, and promoters/scavengers which have been discussed by Chu et al. (2017). Of late, sonocatalytic degradation of ibuprofen has also been studied where higher removal (97%) was observed at acidic conditions (Al-Hamadani et al., 2017). Most recent work reported was that of sonocatalytic degradation of diclofenac which was performed in the presence of graphene oxide in aqueous solution (Al-Hamadani et al., 2018). The presence of graphene oxide during the degradation of diclofenac resulted in an increase in cavitational bubbles, which in turn led to the increased production of hydroxide radical and enhanced adsorption due to dispersion, which caused an increase in active adsorption sites of the graphene oxide. Sonocatalytic degradation is promising to be a viable method since it yields higher removal of NSAIDs from water. However, further studies as recommended by Chu et al. (2017) need to be conducted in order to ensure the viability of the process. These studies include the need for identification of the intermediates produced during ultrasonic treatments for different NSAIDs both in terms of toxicity and biodegradability to clearly evaluate the sonodegradation of NSAIDs (Chu et al., 2017).

3.1.7.7 Electrochemical advanced oxidation process

Electrochemical advanced oxidation processes (EAOPs) have been critically reviewed in the past (Feng et al., 2013; Moreira et al., 2017). EAOPs are a green technology for wastewater treatment due to the dispensable agents used in the process. A suitable anode material such as platinum (Pt) nano-particles and boron doped diamond, multi-walled carbon nanotubes (MWCNTs), and platinum-ruthenium (PtRu) nano-alloy are essentially required to effectively degrade and mineralize NSAIDs under suitable conditions (Chang et al., 2017; Feng et al., 2013; Moreira et al., 2017). Chang et al. (2017) highlighted that usage of PtRu electrocatalysts effectively enhanced the surface activity and thus degradation and mineralization efficiencies revealed that the EAOPs with platinum-ruthenium fluorine-doped tin oxide conductive glass (PtRu-FTO) anode were very effective due to advantages of the higher capacitance, carbon monoxide tolerance, catalytic ability at less positive voltage and stability (Chang et al., 2017). In order to achieve an affordable degradation process for ibuprofen, multi-walled carbon nanotubes and platinum nanoparticles were used to synthesize cheap and effective anodes based on commercial conductive glass. The potentially cytotoxic intermediate, 1-(1-hydroxyenthyl)-4-isobutylbenzene was completely mineralized as the reaction time reached 60 min (Chang et al., 2017). An alternative treatment, the bio-electro-Fenton process, has received increasing attention in past years. In this process the strong oxidant OH radical was formed using the electrons derived from bacterial oxidation of organic substrates (Nadais et al., 2018). In a recent study conducted by Nadais et al. (2018) using this approach, removal efficiencies for ketoprofen, diclofenac, ibuprofen and naproxen were in ranges of 59 – 61%, 87 – 97%, 80 – 86% and 75 – 81%, respectively (Nadais et al., 2018). This greater removal of pharmaceuticals was due to electrocoagulation phenomena at higher pH which was observed only at the end of the batch tests which may be explained by the high initial pH which coupled the natural pH increase at the end of the reaction period due to H^+ consumption to produce hydroxyl radicals. This is a viable method commercially as it utilizes low energy when compared to ozonation and UV which requires high energy usage.

3.1.8 Re-usability of adsorbents in the removal of NSAIDs from water

Reuse of adsorbents is one of the significant purposes for the high cost-effectiveness of adsorption method in practical water treatment applications. Some of the adsorbents mentioned in Section 6 such as MIPs and nanographene are re-usable **(Table 3.1.6)**. Therefore, these adsorbents can be applied repeatedly without losing their efficiency. Re-usability has been evident in a study reported by Banerjee et al. (2016) where graphene oxide nanoplatelets yielded 96% extraction efficiency after 10 cycles of adsorption-desorption process (Banerjee et al., 2016). For MIPs, a polymer that was selective for diclofenac removal from water gave constant removal efficiency of over 90% up to 12 cycles of adsorption and desorption processes (Dai et al., 2011). Other adsorbents that have shown the ability to be re-used are magnetic chitosan derivatives (Zhang et al., 2016), composite iron nano-adsorbent (Ali et al., 2016), nickel ferrite nanoparticles (Springer et al., 2018) and metal-organic frameworks (Hasan et al., 2013; Lin et al., 2018) (Table 6). In the case of magnetic chitosan derivatives, the extraction efficiency for diclofenac was >80% after 5 cycles (Zhang et al., 2016). The composite iron nano-adsorbent was regenerated up to 8 times, yielding removal capacities from 85 – 92% of ibuprofen (Ali et al., 2016). Hasan et al. (2013) observed a steady decrease in the adsorbed amounts of naproxen from 120 – 100 mg g^{-1} within 4 cycles (Hasan et al., 2013). Investigation and re-usability potentials of these adsorbents are highly essential for the removal of NSAIDs in large quantities repeatedly.

Table 3.1.6. Re-usability of several adsorbents for adsorption of NSAIDs from water.

Adsorbent	Target compound	Number of adsorption-desorption cycles	Extraction efficiency (%)	Reference
Graphene oxide nanoplatelets	Ibuprofen	10	96	(Banerjee et al., 2016)
	Ibuprofen	3	≥98	(Akkari et al., 2018)
	Naproxen	4	>98	(Sarker et al., 2018)
	Diclofenac	3	~35	(Zambianchi et al., 2017)
MIPs	Diclofenac	12	≥90	(Dai et al., 2011)
	4 NSAIDs	15	≥90	(Dai et al., 2012)

Chitosan derivatives	Diclofenac	5	>80	(Zhang et al., 2016)
Iron nano-adsorbent	Ibuprofen	8	85-92	(Ali et al., 2016)
Activated biochar	Ibuprofen	4	>67	(Chakraborty et al., 2018)
Metal-organic frameworks	Naproxen	4	*120 – 100	(Hasan et al., 2013)

4 NSAIDs were ketoprofen, naproxen, diclofenac, and ibuprofen. *Extraction efficiency was not reported; only the adsorption capacity (mg g^{-1}) was reported.

3.1.9 Challenges and future opportunities

In general, the ability of certain WWTPs to remove NSAIDs during the wastewater purification has been investigated. Most of the reported studies estimate the removal efficiency based on the concentrations detected in raw influent and treated effluent. This standard practice makes it difficult to understand which treatment stage or process is most efficient and thus allows for maximum removal of these drugs. A better understanding can be achieved by monitoring the occurrence of NSAIDs in all stages of wastewater treatment process.

The initiative to apply plant species such as *Scirpus validus*, *Typha spp* and *Scirpus validus* in constructed wetlands **(Table 3.1.4)** for removal of NSAIDs from contaminated water has yielded promising results. However, this approach has been mostly investigated for single analytes, whereas, in most cases, NSAIDs are simultaneously detected in water bodies. Therefore, future studies should focus on the application of a wide variety of plant species for the simultaneous uptake of NSAID groups from water.

While MIPs have a potential to adsorb NSAIDs from water, these materials have not been thoroughly investigated for water purification on a large scale. Instead, most MIP applications for NSAIDs have been centered around sample preparation for analytical determination. Also, the synthesis of MIPs involves the use of large volume of organic solvents which could impact negatively on the environment at their disposal. Furthermore, the usage of MIPs in large scale is expected to be expensive due to the high costs that maybe associated with MIP production and large-scale operation.

Various adsorbents that have the potential to remove pollutants from water bodies other than NSAIDs have been reported in literature. Such adsorbents which include amine functionalized carbon nanotubes (Zhang et al., 2015) and MoS_2 based polymer composites (Huang et al., 2017a) have been successfully applied for removal of inorganics and organic dyes from water. The ability of these adsorbents for removal of NSAIDs from contaminated water should be investigated prior to their usage in water treatment. Some of these interesting adsorbents were prepared based on mussel inspired chemistry that is based on the self-polymerization of dopamine (Huang et al., 2017b; Zhang et al., 2017).

Degradation studies including photocatalytic degradation (Strbac et al., 2018), UV/persulfate degradation (Fu et al., 2019) and biodegradation (Apriceno et al., 2019) as well as the oxidation process (Adityosulindro et al., 2018) for NSAIDs in water have the potential to reduce these drugs from the environment. In this respect, several applications have been documented (Bilgin Simsek et al., 2018; Jallouli et al., 2018; Ohtani et al., 2010). However, in this approach NSAIDs are converted into other organic compounds. Hence, it is not clearly understood if the degradation products are environmentally friendly. Further understanding of TiO_2 photocatalytic degradation processes have been provided and should be taken into consideration during the planning or design of such systems for the treatment of NSAIDs in water matrices.

Overall, several studies have focused on removal of NSAIDs from water where the application was based on water matrices such as river water, tap water, and ultra-pure water. However, the main source of NSAIDs in an aquatic environment such as river water is WWTP effluents. Therefore, most future studies should be directed towards the adsorption of NSAIDs from wastewater. Also, the recent work reported on removal of NSAIDs from water which include the application of nanoclay/PVA/PSf nanocomposite membrane (Bojnourd and Pakizeh, 2018), multiwalled carbon nanotube adsorbents (Gil et al., 2018), water-soluble protein extracted from *Moringa stenopetala* seeds (Kebede et al., 2018), biodegradation

(Apriceno et al., 2019) and heterogeneous photocatalysis using Bi_2S_3/TiO_2–Montmorillonite nanocomposites under simulated solar irradiation (Djouadi et al., 2018) is expected to be well explored in the future.

Conclusion

In recent years, there has been an increase in investigations focusing on removal of NSAIDs from contaminated water bodies. Various adsorbents reported in several studies include among others activated carbon, graphene-based adsorbents, and MIPs. Some adsorbents such as MIPs, graphene oxide nanoplatelets, composite iron nano adsorbent and metal-organic frameworks can be re-used many times which could result in their classification as low-cost adsorbents. It has been observed that the adsorbents with high surface areas result in higher adsorption capacities towards the removal of several NSAIDs from contaminated water. On the other hand, some plant species including *Scirpus validus*, *Typha spp,* and *Scirpus validus* have been reported to have the ability to remove greater than 80% of selected NSAIDs from contaminated water.

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3.2 PAPER 2

This paper was based on method development for the extraction, pre-concentration, isolation, identification and quantitation of three ARVDs namely emtricitabine, tenofovir disoproxil and efavirenz in water samples and different segments of *Eichhornia crassipes*. The article focused on the development and optimization of HF-LPME for aqueous samples and MAE for plant samples. A multivariate approach through factorial designs was used for the screening of vital factors in the HF-LPME of the selected ARVDs.

Determination of selected antiretroviral drugs in waste water, surface water and aquatic plants using hollow fiber liquid phase microextraction and liquid chromatography - tandem mass spectrometry

Nomchenge Yamkelani Mlunguza[a], Somandla Ncube[b], Precious Nokwethemba Mahlambi[c], Luke Chimuka[d], Lawrence Mzukisi Madikizela[a*]

[a] Department of Chemistry, Durban University of Technology, P. O. Box 1334, Durban, 4000, South Africa

[b] Department of Chemistry, University of South Africa, Private Bag X6, Florida 1710, South Africa

[c] School of Chemistry, University of KwaZulu-Natal, Private Bag X01, Scottsville, Pietermaritzburg, 3209, South Africa

[d] Molecular Sciences Institute, University of Witwatersrand, Private Bag X3, Johannesburg, 2050, South Africa

Corresponding Author: LM Madikizela, lawrencem2@dut.ac.za, +2731 373 2315

Abstract

This work describes a simple and sensitive method for the simultaneous isolation, enrichment, identification and quantitation of selected antiretroviral drugs; emtricitabine, tenofovir disoproxil and efavirenz in aqueous samples and plants. The analytical method was based on microwave extraction and hollow fiber liquid phase microextraction technique coupled with ultra-high-pressure liquid chromatography-high resolution mass spectrometry. A multivariate approach via a half-fractional factorial design was used focusing on six factors; donor phase pH, acceptor phase concentration, extraction time, stirring rate, supported liquid membrane carrier composition and salt content. The optimal enrichment factors for emtricitabine, tenofovir disoproxil and efavirenz from aqueous phase were 78, 111 and 24, respectively. The analytical method yielded recoveries in the range of 86 to 111%, and quantitation limits for emtricitabine, tenofovir disoproxil and efavirenz in wastewater were 0.033, 0.10 and 0.53 µg L^{-1}, respectively. The three drugs were detected in most samples with concentrations up to 37.6 µg L^{-1} recorded for efavirenz in wastewater effluent. Roots of the water hyacinth plant had higher concentrations of the investigated drugs ranging from 7.4 to 29.6 µg kg^{-1}. Overall, hollow fiber liquid phase microextraction proved to be an ideal tool for isolating and pre-concentrating the selected antiretroviral drugs from environmental samples.

Keywords:

Hollow fiber liquid phase microextraction; antiretroviral drugs; water hyacinth; wastewater; surface water

3.2.1 Introduction

Statistics South Africa has reported over 7 million people who are infected with human immunodeficiency virus-1 (HIV-1) as of 2018 (*Mid-year population estimates*, 2018). The number of infected patients increases yearly, which therefore leads to a significant escalation in the production and consumption of antiretroviral drugs (ARVDs). The history of antiretroviral therapy dates to the late 1980's with the first clinical trial of zidovudine conducted and administered to patients with HIV-1 in 1987 (Broder, 2010; Warnke et al., 2007). To date, there are over 30 antiretroviral medications available for the treatment of HIV.

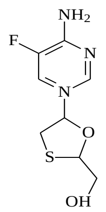
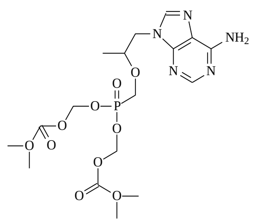
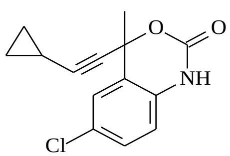
Like most pharmaceuticals, ARVDs are not completely metabolized in the human body when ingested for promotion of health and are excreted through fecal matter or urine (Swanepoel et al., 2015). Their excretion leads to their introduction into the aquatic environment. In certain instances, unused and expired drugs are disposed into the environment and reach surface water through the run-off. Incomplete removal of pharmaceuticals during water purification in wastewater treatment plants (WWTPs) has been identified as the main source of ARVDs in rivers (Halling-Sørensen et al., 1998; Ncube et al., 2018). As a result, recent work has shown the occurrence of ARVDs in the aquatic environment with most of the studies conducted in the African continent (Abafe et al., 2018; K'oreje et al., 2016, 2012; Mosekiemang et al., 2019; Mtolo et al., 2019; Ngumba et al., 2016; Rimayi et al., 2018; Schoeman et al., 2017, 2015; Sophia A. and Lima, 2018; Wood et al., 2015; Wooding et al., 2017).

Unlike other organic pollutants of emerging concern, ARVDs are least monitored in the aquatic environment with few cases reported on their presence in South African water resources compared to other pharmaceuticals such as non-steroidal anti-inflammatory drugs (Abafe et al., 2018;

Mosekiemang et al., 2019; Mtolo et al., 2019; Rimayi et al., 2018; Schoeman et al., 2017, 2015; Wood et al., 2015; Wooding et al., 2017). It is of importance for more monitoring of ARVDs in the South African environment as this is a country with the largest antiretroviral treatment program in the world (Ncube et al., 2018). Furthermore, South African rivers receive high loads of pharmaceuticals that are discharged as part of effluents from WWTPs (Madikizela and Chimuka, 2017; Schoeman et al., 2017; Zunngu et al., 2017). In addition, most pharmaceuticals are easily taken up by plants from water resources (Madikizela et al., 2018) hence there is a need to also monitor the occurrence of pharmaceuticals in aquatic plant species.

This study presents a hollow fiber liquid phase microextraction technique for isolation and preconcentration of selected ARVDs in various surface water samples (wastewater effluents and influents, as well as dams) and in water hyacinth (*Eichhornia crassipes*) plants followed by quantitation using ultra high pressure liquid chromatography-high resolution mass spectrometry (UHPLC-HRMS). The study targeted the three Atripla components; emtricitabine, tenofovir disoproxil and efavirenz. Their relevant physicochemical properties are given in Table 1. Atripla is the most common ARVD combination therapy recommended by World Health Organization as a first-choice combination therapy for people diagnosed with HIV-1 infection due to their manageable side effects (Meintjes et al., 2017). However, their potential human and eco-toxicity due to their presence in surface water is of concern hence the need for monitoring and/or remediation studies. The water hyacinth is a highly problematic invasive species in South African dams and rivers but its presence might be of benefit as a natural remediation tool for polluted water by accumulating pollutants. Its potential to accumulate ARVDs from water samples was investigated for the first time in this study.

Table 3.2.1. Molecular structures and physicochemical properties of the selected antiretroviral drugs

Compound	Class	Structure	Molecular weight (g mol^{-1})	Water solubility (mg mL^{-1})	pKa		Human health side effects
					Strongest Acidic	Strongest Basic	
Emtricitabine	Nucleoside reverse transcriptase inhibitor		247.248	112	14.29	-3.1	Nephrogenic diabetes insipidus, Fanconi syndrome, nephrotoxicity and renal failure
Tenofovir disoproxil	Nucleoside reverse transcriptase inhibitor		519.443	13.1	18.59	4.13	Nephrogenic diabetes insipidus, Fanconi syndrome, nephrotoxicity, renal failure and bone loss
Efavirenz	Non-nucleoside reverse transcriptase inhibitor		315.675	0.00855	12.52	-1.5	Lipoatrophy, central nervous system adverse effects, hypertriglyceridemia, rash and hepatotoxicity

3.2.2 Experimental

3.2.2.1 Chemicals and materials

High purity (98%) ARVDs; tenofovir disoproxil, efavirenz and emtricitabine were procured from Sigma-Aldrich (Johannesburg, South Africa). Di-(2-ethylhexyl)phosphoric acid, dihexyl ether, 37% (v/v) hydrochloric acid (HCl) and formic acid (≥ 98%) were also purchased from Sigma-Aldrich (Johannesburg, South Africa). HPLC-grade acetonitrile (≥ 99.9%) and methanol (≥ 99.5%) were obtained from Merck Chemicals (Pty) Ltd (Johannesburg, South Africa). Sodium chloride was purchased from Associated Chemical Enterprise (Johannesburg, South Africa). Deionized water used as a solvent for the extraction of analytes and dilution was purified from a Milli-Q-RO4 system (Millipore, Bedford, USA). A 100 mg L^{-1} stock solution (mixture of three target compounds) was prepared by dissolving the respective chemicals in 100 mL acetonitrile. The stock solution was stored at 4 °C in a refrigerator for not more than one month and used to prepare working standards on a daily basis. Q 3/2 Accurel 200/600 Accurel®PP polypropylene hollow fiber tubing with 200 µm wall thickness, 0.2 µm pore size and 600 µm internal diameter sourced from Membrana GmbH (Wuppertal, Germany) were utilised. The hollow fibers were cut using a scalpel with a detachable size 10 Swann-Morton surgical blade into 8 cm long strips with an internal volume of 22.6 µL.

3.2.2.1 Liquid chromatography-mass spectrometry conditions

Identification and quantitation of selected ARVDs were performed using a Dionex Ultimate 3000 UHPLC system (Thermo Scientific, Sunnyvale, California, USA) coupled to a quadrupole time of flight mass spectrometric (QTOF-MS) detector from Bruker Daltonics (Bremen, Germany) operated in the positive electrospray ionization mode. In each case, 20 μL of each extract or standard solution was injected into the chromatographic system using an autosampler and separated using a Luna® Omega C_{18} column (50 mm x 4.6 mm x 3 μm) from Phenomenex (California, USA). The separation was achieved by utilizing a mobile phase which consisted a mixture of 0.1% (v/v) formic acid in water (solvent A) and 0.1% (v/v) formic acid in acetonitrile (solvent B). A multi-step gradient programme was initiated by using 10% solvent B in the first 5 min and ramped to 90% in the next 3 min and re-equilibrated after each analysis. Data acquisition was performed using Data Analysis 4.3 software from Bruker Daltonics (Bremen, Germany).

3.2.2.2 Collection of samples and pre-treatment

Wastewater samples were collected in the influent and effluent of WWTPs (Amanzimtoti, Northern, Umbilo, Shallcross, Marrianridge and Umhlathuzana) located around Durban city in South Africa. All the WWTPs receive and treat water from both domestic sources and industrial activities to a lesser extent. Surface water was sampled from Hartbeespoort dam located next to the city of Pretoria, the capital city of South Africa. This dam is found downstream of the largest WWTP in Johannesburg (Northern Works) and it is considered as one of the important dams in the country as its water is largely used for agricultural activities as well as domestic use (Rimayi et al., 2018). All these aqueous samples were collected and stored in pre-cleaned brown glass bottles. The collected samples were kept in cooler boxes with ice, transported to the laboratory, where they were immediately filtered to remove the particulate matter, and stored in a refrigerator at 4°C prior to extraction of target compounds and analysis.

Water hyacinth which is periodically available floating in surface water was collected near the outfall of the Northern WWTP effluent in Springfield Business Park (Durban, South Africa). In this work, this sampling point is identified as Springfield. Other set of plants were collected from Hartbeespoort dam. Plant samples were placed in re-sealable plastic bags and transported to the laboratory. On arrival, they were rinsed with deionized water and divided into different plant segments (roots, stems and leaves). These were placed in a freezer set at –80 °C for at least 2 h prior to freeze drying using ALPHA 1-2 plus freeze drier from Lasec (Cape Town, South Africa). Freeze dried samples were milled using a pulverrisette from Fritsch (Darmstadt, Germany) and extracted using the optimized microwave assisted extraction technique.

3.2.2.3 Extraction and pre-concentration of target compounds

The extraction procedures were optimized prior to their application. Therefore, this section explains the optimized procedure. This involved cutting the hollow fiber into 8 cm long segments followed by their ultra-sonication in acetone for 15 min. Acetone was then allowed to evaporate at room temperature. One end of the hollow fiber was heat-sealed. Thereafter, water acidified to pH 0.4 with HCl was transferred into the lumen of the hollow fiber using a 50 µL syringe until bubbles of the solvent were visible on the walls of the fiber. The bubbles were wiped off with clean paper towel and the syringe was replaced with a wire as a hook to hang the fiber into the aqueous donor solution. Thereafter, the fiber was submerged into an organic solution of di-(2-ethylhexyl)phosphoric acid in dihexyl ether (4.5 (%w/w)) for 10 s in order to embed the pores of the hollow fiber with the organic solution. This was followed by immersing the hollow fiber in deionized water for about 3 s. The hollow fiber containing the acceptor phase was then placed inside a 15 mL glass vial containing 10 mL of the aqueous sample (the donor solution) at pH 4 for 60 min. Thereafter, the acceptor solution now containing the targeted analytes was drawn from the fiber and transferred to a vial insert with bottom-spring (Sigma Aldrich, Johannesburg South Africa. The acceptor solution was diluted with deionized water to make 50 µL total volume and injected into UHPLC.

For extraction from the water hyacinth plant, a pulverized plant sample (0.1 g) was transferred into a microwave vessel followed by the addition of 20 mL of deionized water as an extracting solvent. The vessel was sealed, and the microwave extraction was carried out using a Multiwave Go (Anton Paar, GmbH, Austria). The power of the microwave was kept at 100% throughout the extraction. Thereafter, the obtained liquid extracts were treated as water samples and the analytes extracted using the hollow fibers as described earlier.

3.2.3 Optimization of extraction techniques

3.2.3.1 Hollow fiber liquid phase microextraction

A multivariate approach for the optimization of the hollow fiber liquid phase microextraction (HF-LPME) was performed using Minitab 17 (Pennsylvania, USA). In this case, a half-fractional factorial design was used for screening of six potential factors that can affect the extraction efficiency. The investigated factors were donor phase pH (DP pH), acceptor phase HCl (AP HCl) concentration, supported liquid membrane (SLM) carrier composition, stirring rate, extraction time and salt content. In each case, the enrichment factors were used to quantify the extent of extraction. The significant factors were further optimized using a central composite design.

3.2.3.2 Microwave assisted extraction

The main parameters influencing microwave assisted extraction (MAE) performance, temperature and extraction time were optimized in the 90 – 150°C and 10 – 20 min ranges, respectively. Optimization was done in order to transfer the target compounds from plant samples into aqueous samples. Prior to microwave extraction, 1 mL of 0.1 µg L^{-1} mixture of standard solution in acetonitrile was added into 0.1 g of pulverized plant samples resulting in a spiking concentration of 100 µg kg^{-1}.

3.2.4 Results and discussion

3.2.4.1 Optimization of hollow fiber liquid phase microextraction

3.2.4.1.1 Half-fractional factorial design

A two-way half-fractional factorial design was used to screen six parameters; DP pH, AP HCl concentration (mM), stirring rate (rpm), SLM carrier composition (%w/v), extraction time (min) and salt content (%w/w) for their potential effect in the extraction of the target analytes. A total of 32 runs with design resolution of VI was done. As shown in both the Pareto charts and the Normal plots of effects **(Figure. 3.2.1)**, the significant factors for the HF-LPME of emtricitabine, tenofovir disoproxil and efavirenz from aqueous samples were the AP HCl concentration, extraction time and stirring rate. The significance of the interactive effects between these effects is also observed. The Pareto charts of effects **(Figure. 3.2.1 (a) & (c))** also show the enhanced interactive effect of extraction time and SLM carrier composition (emtricitabine, tenofovir disoproxil) as well as that of the AP pH, stirring rate and SLM carrier composition (efavirenz). In addition, the DP pH and its interactive effects with AP HCl concentration and with stirring rate also appear just below the response average for efavirenz **(Figure 3.2.1(e))**. In this regard, both the SLM carrier composition and the DP pH were therefore included in the list of significant effects. The factors screened in this study have also been reported in carrier mediated HF-LPME of organic compounds (Ebrahimzadeh et al., 2011; Ncube et al., 2016; Payán et al., 2011).

3.2.4.1.2 Central composite design

A spherical rotatable central composite design with alpha set at 2 (alpha = $\sqrt{k}$ = ±2.2 when k = 5) was created to measure the degree of effect on the response output of each analyte. The factor levels of the design for the target analytes are presented in **Table 3.2.2**. Results in **Figure 3.2.2 a** & **c** show that the interactive effect between DP pH and stirring rate had the greatest effect on the extraction of emtricitabine and efavirenz. This was followed by the AP HCl concentration x SLM composition interactive effect. For tenofovir disoproxil, the SLM composition x extraction time was the most effective interactive effect. However, DP pH x stirring rate and the AP HCl concentration x SLM composition interactive effects were also above the response average. Thus, the DP pH was paired with stirring rate for further optimization while AP HCl concentration was paired with SLM composition. Extraction time which only affected the transfer of tenofovir disoproxil was maintained at 60 min during optimization of paired factors. Extraction time of 60 min has been reported in various studies (Han and Row, 2010; Ncube et al., 2016; Zeng et al., 2015). The paired factors in the current study have also been reported by Ncube et al., 2016 whose target compounds were alkaloids containing a basic nitrogen like our study analytes (Ncube et al., 2016).

Table 3.2.2. Factor levels of the target antiretroviral drugs

		Alpha (α) values				
Factor labels	Significant factors	-2	-1	0	+1	+2
A	AP HCl concentration (mM)	0.3	0.5	0.7	0.9	1.1
B	DP pH	4	5	6	7	8
C	SLM carrier comp. (%w/w)	0	1.5	3	4.5	6
D	Stirring rate (rpm)	600	700	800	900	1000
E	Extraction time	20	30	40	50	60

3.2.4.2 Optimization of paired factors

The results of optimization of the paired effect of DP pH and stirring rate are summarized in form of contour and optimization plots of enrichment factors as shown in **Figure 3.2.3**. These plots are visual representations of the empirical quadratic response surface model for paired factors as given by **Equation 3.2.1**. A rising ridge pattern with minima at its centre was observed for the enrichment of emtricitabine. An initial decrease in response is observed when both DP pH and stirring rate are increased. This was an indication that optimum extraction of emtricitabine could be achieved when the sample solution is acidic with minimum stirring rate. In strongly acidic media, emtricitabine is in its charged state which is essential in carrier mediated HF-LPME. However, the response reaches a minimum with further increase in factor values resulting in increase in the response again. At higher pH values, emtricitabine exist in its neutral form and it is predicted that vigorous stirring might strip the carrier from the pores of the membrane leading to free transfer of the analyte. For tenofovir disoproxil, the model gave a minimax pattern characterized by a saddle point near the center of the design. Increasing both factors results in decrease in the response. The saddle point is relatively stationary indicating that at this DP pH region, stirring rate does not affect the enrichments. As observed for emtricitabine, at DP pH values above this region and high stirring rates, the response rises again. For efavirenz, high enrichments were obtained at low DP pH values with high stirring rates. The optimum factor values predicted as points of curvature shown in the optimization plots of effects **(Figure. 3.2.3(b), (d) & (f))** for extraction of the target compounds are given in **Table 3.2.2**. The experimental enrichment factor (EF) values were either within the predicted range, except for efavirenz, which was slightly higher than the predicted range. The estimation of the optimum factor values for each paired factor plots were predicted using the quadratic response surface models by computing **Equation 3.2.1**.

$$y = b_o + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 + \varepsilon \qquad (3.2.1)$$

where y is the average enrichment factor, b_0 the intercept parameter, b_i are the regression parameters for linear factor effects, b_{12} are the regression parameters for interaction factor effects, b_{11} and b_{22} are the regression parameters for quadratic factor effects, x_1 and x_2 are the paired factors and ε is the residual linked to the experiments.

The interaction effects of AP HCl concentration and SLM carrier composition are visualized in **Figure 4**. Minimax response surfaces were observed for enrichment of emtricitabine and tenofovir disoproxil. The presence of a saddle point near the center of the design is an indication that the enrichment of these analytes decreases if both factors are increased simultaneously. High AP HCl concentration and SLM carrier composition led to increased enrichment of efavirenz **(Figure 3.2.4 (e)).** The predicted optimum factor values using optimization plots of effects **(Figure3.2.4 (b), (d) & (f))** for extraction of the target compounds are summarized in **Table 3.2.2**.

Table 3.2.3. Predicted and applied optimum factor values

	Emtricitabine			Tenofovir disoproxil			Efavirenz		
	Predicted	Applied	Desirability	Predicted	Applied	Desirability	Predicted	Applied	Desirability
AP HCl concentration (mM)	0.5	0.4	0.8962	0.2	0.4	0.8569	0.31	0.4	0.5689
DP pH	6	4		4	4		4	4	
Stirring rate (rpm)	1000	1000	0.9425	936.64	1000	0.7568	987.52	1000	0.6845
SLM carrier composition (% w/w)	1.5	4.5		4.5	4.5		4.5	4.5	
Predicted enrichment factor	72 – 95	-		96 – 145	-		9 – 12	-	
Enrichment factor under universal conditions	-	78		-	111		-	24	

3.2.4.3 Simultaneous extraction of emtricitabine, tenofovir disoproxil and efavirenz

Each analyte had its own optimum factor values as shown in **Figures 3.2.3 & 3.2.4 and Table 3.2.3**. However, in any analysis, the target is to extract analytes simultaneously under universal conditions. In this regard, the universal extraction conditions for a simultaneous HF-LPME of emtricitabine, tenofovir disoproxil and efavirenz were assigned by manually changing the optimized individual factor levels on the optimization plots given in **Figures 3.2.3 & 3.2.4**. The acceptability of the universal experimental conditions was confirmed using a compound desirability function calculated as a geometric mean of the individual desirabilities **(Equation 3.2.2)**.

$$D(Y) = (d_1 y_1 . d_2 y_2 .... d_m y_m)^{1/m} \qquad (3.2.2)$$

Where $D(Y)$ is the compound desirability, $d_i y_i$ is the individual desirability as the optimum factor value is changed and m is the number of responses.

The individual desirabilities are obtained from the optimization plots as the optimum values are manipulated to universal conditions. The overall optimum HF-LPME conditions were found to be DP pH of 4, AP HCl concentration of 200 mM (pH = 0.4) with SLM carrier composition set at 4.5 (%w/w) and stirring at 1000 rpm. Under these conditions, the compound desirability was 0.7144. The ARVDs were then extracted under these universal conditions with enrichments of 78, 111 and 24 obtained for emtricitabine, tenofovir disoproxil and efavirenz, respectively.

3.2.4.4 Optimization of microwave-assisted extraction

The main factors that could influence the performance of a microwave assisted extraction are the extraction temperature, irradiation time, nature of the solvent and its volume as well as sample weight. The optimization was carried out by varying one parameter at a time while all others were kept constant. After extraction, the extract was filtered and subjected to HF-LPME technique described for water samples. As shown in **Table 3.2.1**, all target compounds are water soluble and contain polar functionalities in their molecular structures; therefore, water was pre-selected for extraction of analytes from plant samples. Previous work has shown that water is a good extracting solvent (Jin et al., 1999; Lopez-Avila et al., 1995; Srogi, 2006). The most important factors that were optimized in this study were the extraction temperature and irradiation time.

During the optimization of temperature, irradiation time was kept at 20 min. In this case, heating was essential to enable efficient extractions to be performed (Camel, 2001). Results **(Table 3.2.4)** showed a considerable loss of all target ARVDs when the extraction temperature reached 110ºC. Recoveries for all compounds were poor in the temperature range of 110 to 150ºC; therefore, 90ºC was selected as the optimum temperature. At higher temperatures, there is a possibility of mutilation of the analyte molecules in the microwave field (Varga et al., 2010). Although tenofovir disoproxil decomposes at 60ºC ((EMA), 2017), it remained stable at 90ºC used for the extraction. Both emtricitabine and efavirenz decompose at 105ºC ((EMA), 2017)

Table 3.2.4. Effect of temperature on microwave assisted extraction of selected antiretroviral drugs from plant samples (n = 3)

	% Recovery (% ± RSD)		
Temperature (ºC)	Emtricitabine	Tenofovir disoproxil	Efavirenz
90	93 ± 0.01	92 ± 0.14	98 ± 0.63
110	58 ± 9.3	62 ± 1.2	51 ± 1.1
130	53 ± 2.3	54 ± 3.3	46 ± 2.5
150	33 ± 5.5	45 ± 0.93	26 ± 2.2

Irradiation time was one of the important factors to optimize as it could allow sufficient time for migration of analytes from plant samples into the aqueous phase. Irradiation time was varied from 10 to 20 min while keeping all other experimental conditions constant including the extraction temperature of 90 ºC. Maximum extraction of selected ARVDs occurred in 20 min **(Table 3.2.5)** which was taken as the optimum time. Shorter irradiation times have also been reported in other studies (Azzouz and Ballesteros, 2012; Camel, 2001; Madej, 2009) and prolong the analysis time. Longer irradiation times tend to diminish the signal of analytes due decomposition while shorter irradiation times are associated with the redistribution of the adsorbed species between the solid and the aqueous phases under the effect of the microwave field (Azzouz and Ballesteros, 2012).

Table 3.2.5. Effect of irradiation time on microwave assisted extraction of selected antiretroviral drugs from plant samples (n = 3)

	Irradiation time (min)	% Recovery ± % RSD		
		Roots	Stem	Leaves
Emtricitabine	10	76 ± 1.1	91 ± 7.0	98 ± 2.3
	15	80 ± 0.9	89 ± 0.3	96 ± 1.1
	20	89 ± 0.15	92 ± 2.2	99 ± 0.2
Tenofovir disoproxil	10	80 ± 1.3	79 ±1.6	98 ± 1.7
	15	85 ± 2.2	84 ± 0.5	91 ± 0.5
	20	91 ± 0.63	83 ± 2.2	96 ± 3.3
Efavirenz	10	66 ± 0.01	75 ± 3.0	83 ± 2.4
	15	63 ± 0.02	80 ± 5.1	81 ± 3.6
	20	78 ± 0.1	85 ± 5.1	87 ± 4.2

3.2.4.5 Validation of the proposed analytical technique

The proposed analytical method which involved microwave assisted extraction, HF-LPME and liquid chromatographic analysis for the three selected ARVDs was validated for accuracy, precision, sensitivity and linearity of the analytical method. This was done by spiking wastewater and surface water at 10 µg L^{-1} while the plant samples were spiked at 100 µg kg^{-1}. The summarized results are given in **Table 3.2.6**. In all spiked samples, recoveries ranged from 92 to 111% which indicates that the analytical method was highly accurate. Furthermore, the relative standard deviations obtained in triplicate analysis not exceeding 2.2% indicated good precision. Limits of detection (LOD) and quantitation (LOQ) measured as concentrations at 3 and 10 S/N respectively were used to measure the sensitivity of the proposed analytical method. The results in **Table 3.2.6** imply that the trace amounts of targeted ARVDs could be easily extracted and isolated in environmental water samples using a HF-LPME and from plant material using MAE followed by HF-LPME.

Table 3.2.6. Performance of analytical method in aqueous samples and water hyacinth (n = 3, SD)

Target Compound	Linearity (r^2)	Calibration			Wastewater		Surface water		Water hyacinth	
		LOD (µg L^{-1})	LOQ (µg L^{-1})	Recovery	LOD (µg L^{-1})	LOQ (µg L^{-1})	Recovery	LOD (µg kg^{-1})	LOQ (µg kg^{-1})	Recovery
Emtricitabine	0.994	0.01	0.033	96 ± 0.02	0.169	0.56	96 ± 2.2	0.65	0.93	95 ± 0.9
Tenofovir disoproxil	0.998	0.03	0.10	92 ± 0.4	0.018	0.060	93 ± 0.3	0.39	1.35	93 ± 0.3
Efavirenz	0.997	0.16	0.53	99 ± 1.2	0.113	0.38	111 ± 0.1	6.01	10.29	102 ± 0.9

3.2.4.6 Application of the analytical method in environmental monitoring

The optimized analytical method was applied in the determination of selected ARVDs in wastewater influent and effluent, surface water from the dam as well as in different segments of the water hyacinth plant. In this regard, the study investigated whether the selected WWTPs could remove the selected compounds from influents during the treatment process. The treatment process used in most South African WWTPs have various stages including screening for grit removal, settling tanks for sludge production and removal, aeration tanks and chlorination for disinfection (Madikizela and Chimuka, 2017). In terms of water hyacinth, plant species were collected from a river and dam that have been previously reported to be contaminated by pharmaceuticals including ARVDs (Matongo et al., 2015b; Rimayi et al., 2018). Therefore, these study areas served as good starting points for the application of the developed and optimized method due to the probability of detecting the target ARVDs.

3.2.4.6.1 Monitoring of emtricitabine, tenofovir disoproxil and efavirenz in water samples

Results illustrated in **Table 3.2.7** show that the three ARVDs were detected in most samples. At Hartbeespoort dam, emtricitabine and efavirenz were detectable but could not be quantified as they were below their quantitation limits. The average concentration found in Hartbeespoort dam for tenofovir disoproxil was 0.11 µg L^{-1}. Compared to other studies done at Hartbeespoort dam, efavirenz was the only ARVD recently detected (Rimayi et al., 2018), while in another previous study reported in 2015 by Wood et al., 2015, all three target compounds were either not detected or below the quantitation limit (Wood et al., 2015) in water from Hartbeespoort dam. The observed deviations from results among the studies reporting ARVs at Hartbeespoort dam could be related to different sampling times and the extraction techniques used. It is worth noting that the maximum concentrations of emtricitabine and efavirenz that have been previously detected in South African surface water were 0.36 and 0.70 µg L^{-1}, respectively (Wooding et al., 2017) whereas this is the first study to detect tenofovir disoproxil in surface water from South Africa.

Among the investigated ARVDs in WWTPs, efavirenz was the most abundant drug having its concentration reaching an average of 37.3 µg L^{-1} in Northern WWTP effluent water **(Table 3.2.7)**. Its concentration in the influent water was 26.3 µg L^{-1}. This was an interesting observation because efavirenz has lower water solubility than other analytes **(Table 3.2.1)** which could easily lead to its adsorption onto solid particles during sludge removal. This contrast has also been reiterated by Schoeman et al., 2017 who observed that a significant amount of efavirenz is not eliminated from water purification and enters the surface water (Schoeman et al., 2017). Similarly, efavirenz has been found to be one of the most frequently detected pharmaceuticals in the influent and effluent water in WWTPs located in Kenya (K'oreje et al., 2018). Consequently, the differences in consumption rates could have triggered these observations. For example, the formulation of Atripla comprises of 600 mg of efavirenz, while the masses used for emtricitabine and tenofovir disoproxil are 200 and 245 mg, respectively. Generally, the efavirenz results are similar to those previously reported in the same WWTP where efavirenz concentrations in the influent and effluent were 24 and 33 µg L^{-1}, respectively (Abafe et al., 2018). In other studies, the concentrations reported for efavirenz in influent and effluent of a WWTP located in Gauteng province were 17.4 µg L^{-1} and 7.1 µg L^{-1} respectively (Schoeman et al., 2015), while in a WWTP in the Western Cape province, 15.4 µg L^{-1} was reported in the influent, and the effluent concentration decreased to 1.93 µg L^{-1} (Mosekiemang et al., 2019).

Emtricitabine and tenofovir disoproxil are rarely monitored in South African surface water. A recent South African work has reported the occurrence of emtricitabine in WWTPs located in the Western Cape province (Mosekiemang et al., 2019). In this case, the concentrations found in the influent and effluent of one WWTP were 172 and 4.23 µg L^{-1} respectively whereas in another WWTP the influent concentration was 31.3 µg L^{-1} and decreased to below the quantitation limit in the effluent. In this study, traces of both emtricitabine and tenofovir disoproxil were detected in most studied WWTPs with concentrations decreasing from the influent to the effluent. This was an indication that a certain amount of these ARVDs are removed during the wastewater treatment process.

Table 3.2.7. Average concentrations of target antiretroviral drugs found in aqueous samples (n =3)

	Average concentration (µg L^{-1}) ± %RSD		
Sampling site	Emtricitabine	Tenofovir disoproxil	Efavirenz
Hartbeespoort dam	<LOQ	0.11 ± 2.0	<LOQ
Amanzimtoti WWTP influent	3.10 ± 3.1	0.25 ± 2.4	1.37 ± 3.7
Amanzimtoti WWTP effluent	0.22 ± 2.1	<LOQ	3.63 ± 2.0
Northern WWTP influent	0.30 ± 0.3	0.17 ± 2.6	26.3 ± 0.08
Northern WWTP effluent	0.22 ± 0.001	nd	37.3 ± 0.10
Umbilo WWTP influent	1.47 ± 0.10	<LOQ	1.67 ± 2.5
Umbilo WWTP effluent	0.35 ± 0.10	<LOQ	3.27 ± 1.6
Shallcross influent	nd	<LOQ	1.02 ± 3.1
Marrianridge influent	<LOQ	0.10 ± 1.1	2.22 ± 0.8
Umhlathuzana effluent	0.11 ± 3.0	<LOQ	3.64 ± 0.02

nd: not detected; <LOQ: the compound was detected but its concentration was below the quantitation limit

3.2.4.6.2 Phytoremediation of antiretroviral drugs by water hyacinth plants

The ability of aquatic plants to uptake pharmaceuticals from water sources through mass flow and diffusion of the dissolved compounds into the roots of the plants (Bartrons and Peñuelas, 2017) and their eventual translocation to aerial parts has been reviewed (Madikizela et al., 2018). In this regard, a diversity of pharmaceuticals with the exception of ARVDs have been detected in plant tissues (Madikizela et al., 2018) and their uptake mechanisms as well as translocation in a variety of plants have been explained (Wu et al., 2015). In this study, the bio-accumulation and bio-translocation of emtricitabine, tenofovir disoproxil and efavirenz in water hyacinth was monitored. This was done to understand whether these invasive species could assist in the elimination of these pharmaceuticals from surface water. Bio-accumulation was defined as the plant's ability to uptake ARVDs and calculated as the ratio of the ARVD concentration in water to its concentration in the whole plant. Bio-translocation was defined as the hyacinth plant's ability to translocate the ARVDs from the roots to the aerial parts of the plant (stem and leaves).

Generally, in both sampling sites all the three ARVDs were detected in plant roots, stems and leaves **(Table 3.2.8)** with bio-accumulation factors well above one indicating that the hyacinth plant has the ability to effectively accumulate the ARVDs from polluted water sources. In all cases, the highest concentration for each pharmaceutical was observed in plant roots with emtricitabine, tenofovir disoproxil and efavirenz reaching concentrations of 13.4, 8.7 and 29.6 µg kg^{-1} respectively. As a percentage of ARVDs in the whole plant, the roots had 65, 76 and 53% of emtricitabine, tenofovir disoproxil and efavirenz respectively. As such, the bio-translocation factors were quite low **(Table 3.2.8)**. The detection of these ARVDs in the water hyacinth plants serves as evidence that aquatic plants can accumulate organic pollutants including pharmaceuticals in polluted water bodies. In this regard, although water hyacinth plants are considered a nuisance to the aquatic environment, this study presents a different perspective that these plants might be playing a significant role in remediation of water pollution.

Table 3.2.8. Average concentrations of the antiretroviral drugs found in different segments of water hyacinth (n = 3)

			Concentration in plant samples (µg kg^{-1})				Biotranslocation Factor	
Sampling point	Target compound	Concentration in water (µg L^{-1})	Roots	Stem	Leaves	Bioaccumulation Factor (kg L^{-1})	Roots to stem + leaves	Roots to leaves
Hartbeespoort dam	Emtricitabine	< LOQ (0.56)	11.7 ± 0.52	1.05 ± 0.24	3.91 ± 0.002	*30	0.42	0.33
	Tenofovir disoproxil	0.11	7.4 ± 0.582	0.97 ± 0.80	0.98 ± 0.005	85	0.26	0.13
	Efavirenz	< LOQ (0.38)	17.2 ± 0.14	9.63 ± 0.05	8.91 ± 0.36	*94	1.1	0.52
Springfield	Emtricitabine	0.22	13.4 ± 0.118	3.08 ± 0.004	6.2 ± 0.63	103	0.69	0.46
	Tenofovir disoproxil	< LOQ (0.10)	8.65 ± 0.58	1.35 ± 0.94	1.96 ± 0.58	*119	0.38	0.22
	Efavirenz	37.3	29.6 ± 0.17	11.42 ± 0.24	9.98 ± 0.73	1.4	0.72	0.34

*Value predicted using LOQ (limit of quantitation)

Conclusion

A convenient extraction process based on microwave assisted extraction and hollow fiber liquid phase microextraction of emtricitabine, tenofovir disoproxil and efavirenz from water and aquatic plants followed by their quantitative analysis using LC-QTOF/MS was developed. The analytical technique allowed for trace quantitation of emtricitabine, tenofovir disoproxil and efavirenz in surface water, wastewater and various plant tissues of *Eichhornia crassipes*. The three ARVDs under investigation were detected in all sample matrices which indicates that they are discharged into surface water from WWTPs. Results further showed that these ARVDs are taken by plant roots, and also get translocated to aerial tissues. Efavirenz was the most abundant compound in all samples. The occurrence of emtricitabine, tenofovir disoproxil and efavirenz in various water samples analyzed in this study is a cause for concern hence the need to conduct more investigation on their presence in water resources in South Africa and other countries affected by the HIV/AIDs epidemic. More studies can be done to evaluate their bioaccumulation in other aquatic plants as well as to evaluate their mechanism of uptake.

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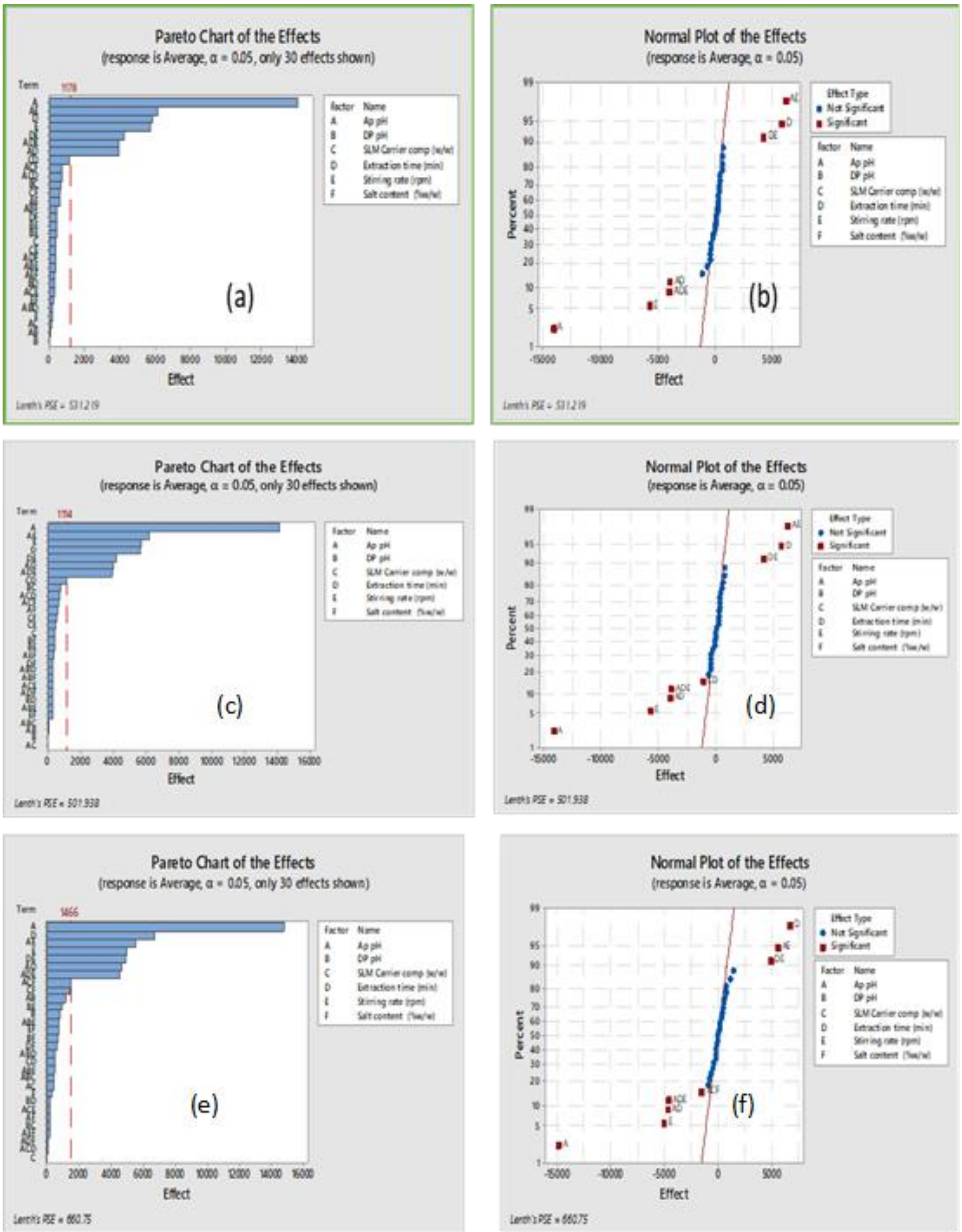
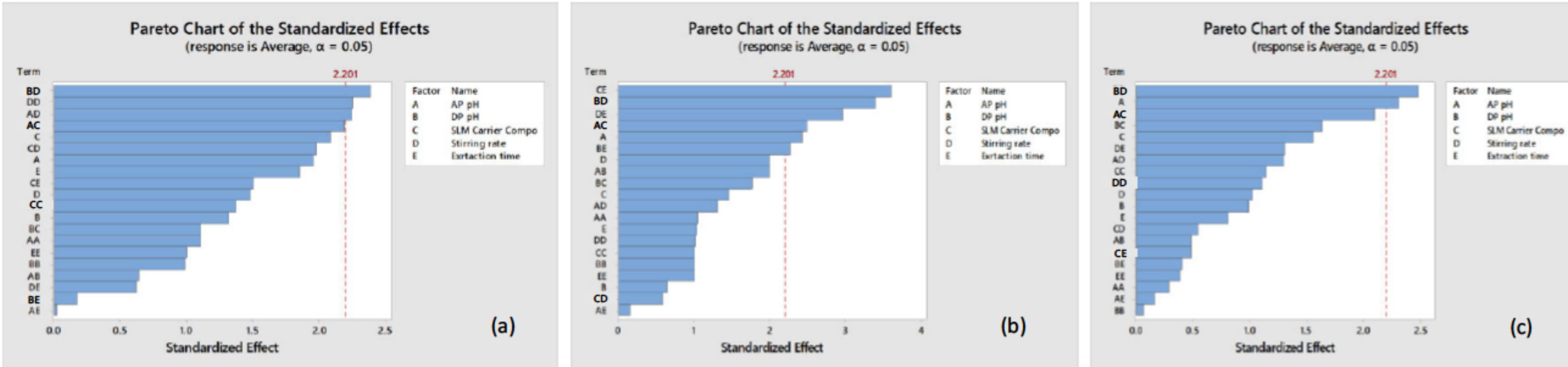
Annexures

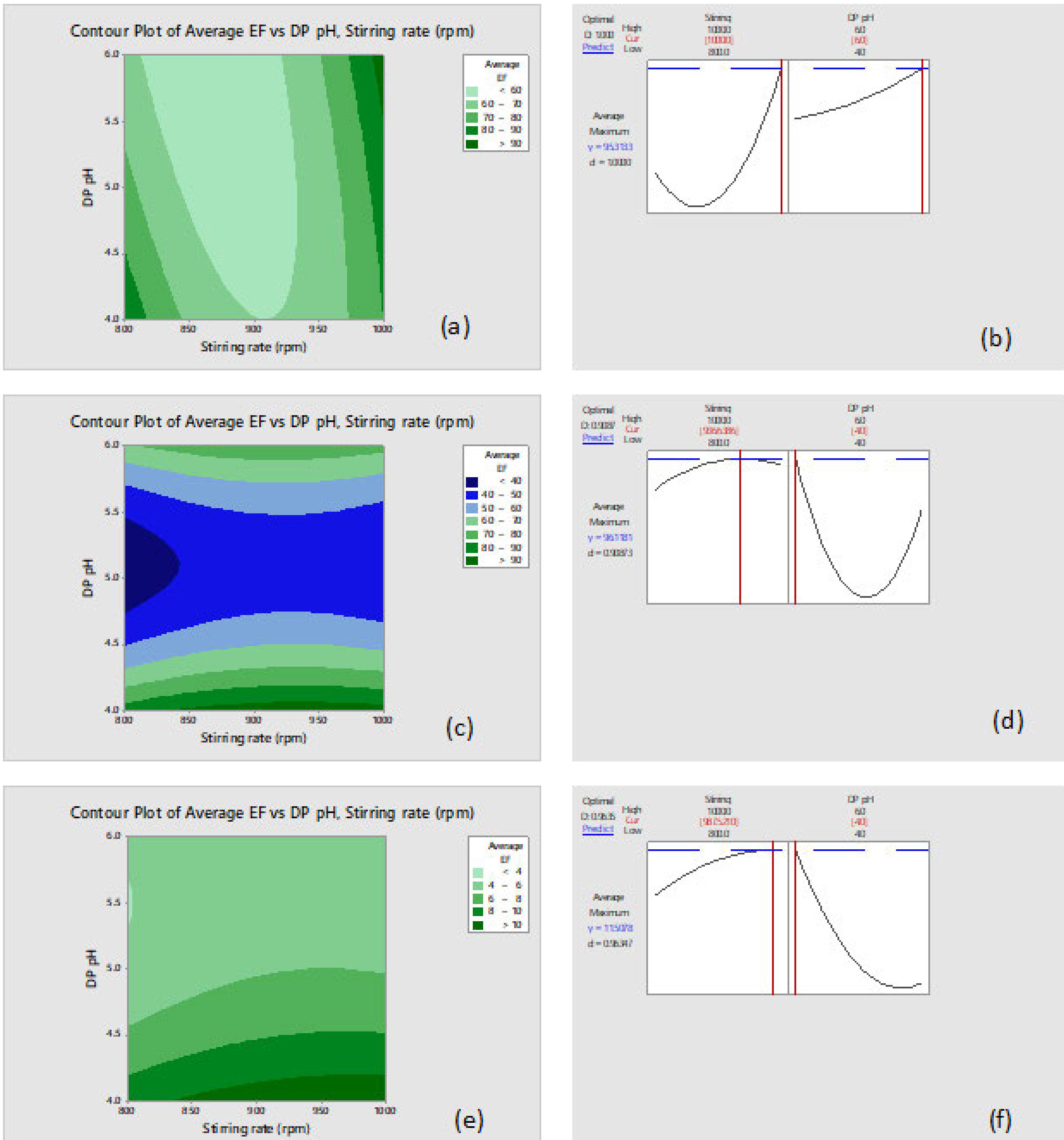


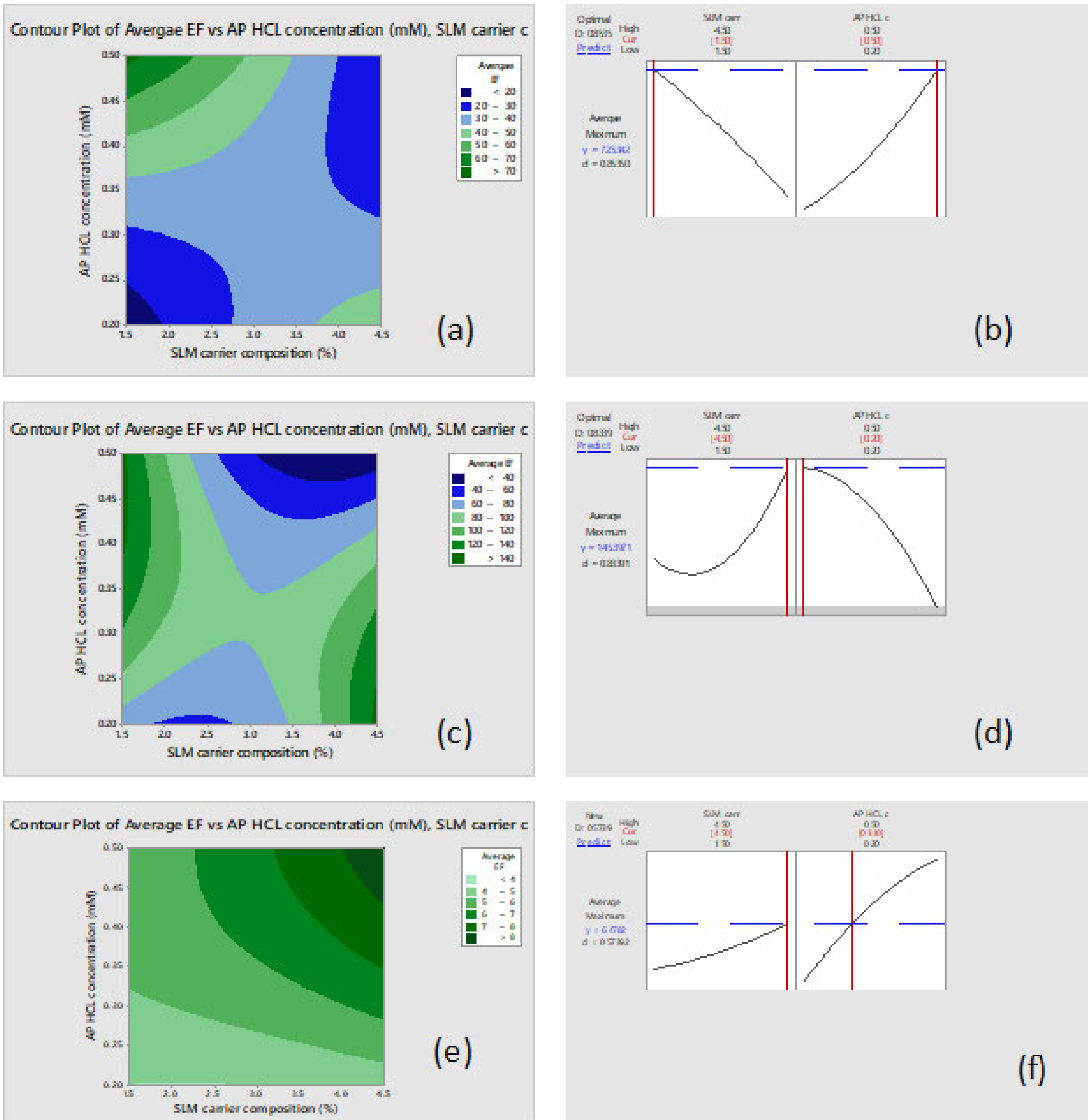
Annexure A: Pareto charts ((a), (c) and (e)) of standardized effects for factors affecting the extraction of emtricitabine, tenofovir disoproxil and efavirenz, respectively. Figure 4.1 (b), (d) and (f) represent the normal plots (α = 0.05 at 95 % confidence intervals) for emtricitabine, tenofovir disoproxil and efavirenz, respectively.



Annexure B: Pareto charts of standardized effects of the main factors of emtricitabine (a), tenofovir disoproxil (b) and efavirenz (c).

Annexure C: Contour plots and optimal plots of average enrichment factors (a), (c) and (e) and optimal plot of average enrichment factors (b), (d) and (f) for the pairing of DP pH and stirring rate of emtricitabine, tenofovir disoproxil and efavirenz, respectively





Annexure D: Contour plots and optimal plots of average enrichment factors (a), (c) and (e) and optimal plot of average enrichment factors (b), (d) and (f) for the pairing of SLM carrier composition and AP HCl concentration of emtricitabine, tenofovir disoproxil and efavirenz, respectively.

3.3 PAPER 3

This paper outlines the HF-LPME-MAE-UHPLC-MS method optimization and application for the extraction, pre-concentration, isolation, identification and quantitation of NSAIDs from wastewater and *Eichhornia crassipes* plant. The NSAIDs studied in this paper were naproxen, fenoprofen, diclofenac and ibuprofen. These drugs are amongst the mostly detected pharmaceuticals in South Africa.

Optimization and application of hollow fiber liquid phase microextraction and microwave assisted extraction for the analysis of non-steroidal anti-inflammatory drugs in aqueous and plant samples

Nomchenge Yamkelani Mlunguza[a], Somandla Ncube[b], Precious Nokwethemba Mahlambi[c], Luke Chimuka[d], Lawrence Mzukisi Madikizela[a*]

[a] Department of Chemistry, Durban University of Technology, P. O. Box 1334, Durban, 4000, South Africa

[b] Department of Chemistry, University of South Africa, Private Bag X6, Florida 1710, South Africa

[c] School of Chemistry, University of KwaZulu-Natal, Private Bag X01, Scottsville, Pietermaritzburg, 3209, South Africa

[d] Molecular Sciences Institute, University of Witwatersrand, Private Bag X3, Johannesburg, 2050, South Africa

Corresponding Author: LM Madikizela, lawrencem2@dut.ac.za, +2731 373 2315

Abstract

Human consumption of non-steroidal anti-inflammatory drugs (NSAIDs) is increasing, which poses a great risk of pollution by these pharmaceuticals on the aquatic environment. Therefore, this study reports the optimization of microwave assisted extraction using water as a green solvent and hollow fiber liquid microextraction (HF-LPME) methods followed by ultra-high-performance liquid chromatography-high resolution mass spectrometry analysis of NSAIDs in wastewater and an aquatic plant, *Eichhornia crassipes*. The optimized MAE resulted in efficient transfer of selected NSAIDs from plant samples into the aqueous phase yielding recoveries ranging from 91 to115%. A multivariate approach based on half fractional factorial and central composite design was used for the optimization of HF-LPME. Under optimized conditions, the maximum enrichment factors for naproxen, fenoprofen, diclofenac and ibuprofen were 49, 126, 93 and 156, respectively. The analytical method recoveries for waste water samples ranged from 86 – 116% while the limits of quantification for wastewater and plant samples ranged from 0.09 – 0.59 µg L^{-1} and 0.11 – 0.59 µg kg^{-1}, respectively. The precision of the proposed analytical method which was measured in terms of RSD values did not exceed 5%. Naproxen was the most abundant compound in both wastewater and the *Eichhornia crassipes* plant samples with concentrations of up to 3.30 µg L^{-1} and 10.97 µg kg^{-1} respectively. The detection of NSAIDs in *Eichhornia crassipes* means this plant has the ability to bioaccumulate pharmaceutical load in surface water.

Keywords: Non-steroidal anti-inflammatory drugs; aquatic plants; wastewater; hollow fiber liquid phase microextraction, microwave assisted extraction

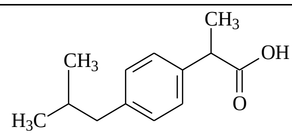
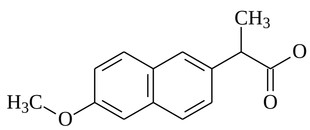
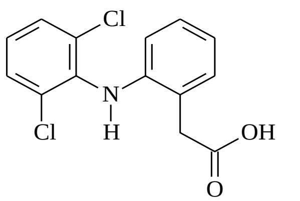
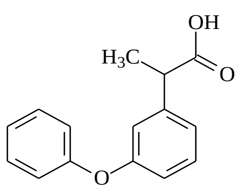
3.3.1 Introduction

Numerous reports on the occurrence of non-steroidal anti-inflammatory drugs (NSAIDs) in South African aquatic environment have emerged over the past five years (Agunbiade and Moodley, 2016, 2014; Amdany et al., 2014; Gumbi et al., 2017b; Madikizela et al., 2017; Madikizela et al., 2014; Madikizela and Chimuka, 2017a; Matongo et al., 2015a, 2015b; Mbhele et al., 2018; Ngubane et al., 2019; Sibeko et al., 2019; Zunngu et al., 2017). NSAIDs are described as pharmaceuticals that are extensively consumed for their therapeutic effect towards rheumatoid arthritis, inflammation and fever in humans (Mahkam and Poorgholy, 2011; Patrolecco et al., 2013). The widespread presence of pharmaceuticals in the aquatic environment is linked to their excretion as un-metabolized drugs which are swept as part of sewage into the domestic wastewater treatment plants (WWTPs). The NSAIDs investigated in this study (naproxen, fenoprofen, diclofenac and ibuprofen) contain polar groups making them water soluble **(Table 3.3.1)**. Due to these features, high amounts of NSAIDs are discharged into surface water as part of the WWTP effluent. This has been verified in few South African cases where NSAIDs have been detected in WWTP effluents and the receiving surface waters (Gumbi et al., 2017b; Madikizela et al., 2018b; Madikizela and Chimuka, 2017a; Matongo et al., 2015a, 2015b; Mbhele et al., 2018; Ngubane et al., 2019; Zunngu et al., 2017). In most of these studies, solid-phase extraction (SPE) has been used as a sample preparation method for the extraction and pre-concentration of NSAIDs in which either Oasis hydrophilic lipophilic balance (HLB) or molecularly imprinted polymers were used as the SPE sorbents. In this study, the occurrence of the selected NSAIDs in WWTP influents and effluents was investigated using a hollow fiber liquid-phase microextraction technique (HF-LPME). The HF-LPME technique was also combined with microwave assisted extraction (MAE) and used in the analysis of the selected pharmaceuticals in *Eichhornia crassipes* commonly known as the water hyacinth. HF-LPME is a greener approach when compared to SPE due to the reduction of organic solvents required for the analysis (Ncube et al., 2016). In addition, smaller sample volumes can still be accommodated in HF-LPME.

With several South African communities depending on untreated surface water as their only source of drinking water, it is imperative to conduct more frequent scientific research to assess the quality of the WWTP effluents. Furthermore, there is a need to investigate various ways that could be used to remediate water resources with a recent review by Madikizela et al., 2018 identifying aquatic plants as potential bio-accumulators of pharmaceuticals in aquatic systems. According to the review, various plants either growing naturally or under hydroponic conditions have shown great potential as phytoremediators of pharmaceuticals (Madikizela et al., 2018).

Investigation of NSAIDs in water hyacinth was used as an indication of the potential of these plants as phytoremediators of pharmaceuticals from contaminated water. *Eichhornia crassipes* is considered as the most invasive species which grows rapidly in a space of 7 - 14 days invading a wide range of freshwater ecosystems (Jafari, 2010). This has been the case in South Africa where the rapid growth of *Eichhornia crassipes* in rivers and important dams, which are identified as tourist destinations, has been observed. This is a threat to the tourism and economy of the country. On the contrary, if these plants that grow naturally in nutrient-rich water bodies can accumulate pharmaceuticals from wastewater effluents, then they may be considered as a solution to reduce pollution in wastewater effluents before they reach surface drinking water sources.

Table 3.3.1. Molecular structures and physicochemical properties of the selected non-steroidal anti-inflammatory drugs.

Compound	Structure	Solubility in water (mg L^{-1})	pKa	xlogP3
Ibuprofen		58	4.91	3.5
Naproxen		44	4.15	3.3
Diclofenac		10	4.15	4.4
Fenoprofen		81	4.5	3.3

3.3.2 Methods and materials

3.3.2.1 Chemicals and reagents

High purity NSAIDs (97-99%) (naproxen, ibuprofen, diclofenac and fenoprofen) as well as dihexyl ether (DHE), sodium hydroxide (NaOH) and hydrochloric acid (HCl) were purchased from Sigma-Aldrich (Johannesburg, South Africa). HPLC-grade Lichrosolv acetonitrile (MeCN) and methanol (MeOH) were obtained from Merk Chemicals (Pty) Ltd (Johannesburg, South Africa). Sodium chloride (NaCl) was purchased from Associated Chemical Enterprise (Johannesburg, South Africa). Deionized water that was used as a solvent for the extraction of the analytes from plant segments was produced from a Milli-Q-RO4 system (Millipore, Bedford, USA).

3.3.2.2 Sample collection and pretreatment

3.3.2.2.1 Wastewater samples

Wastewater samples were collected from four WWTPs located around Durban city (South Africa) during the spring season in the month of October in 2018. The exact location of each WWTP is described in **Table 3.3.2** using the Global Positioning System (GPS) coordinates. At each WWTP, approximately 500 mL of raw influent (domestic wastewater after screening for removal of debris) and final effluent (wastewater post chlorination stage) were collected using dark brown glass bottles that were previously cleaned with detergent solution followed by deionized water. Umhlathuzana WWTP has two influent streams which are known as Marrianridge and Shallcross influents. Therefore, in Umhlathuzana WWTP, two influent samples (Shallcross and Marrianridge influents) and one effluent (Umhlathuzana effluent) were collected. In each sampling site, sampling containers were rinsed with the wastewater prior to collection of samples. The collected samples were transported to the laboratory in cooler boxes with ice. On arrival in the laboratory, the suspended solids were removed from the water samples through filtration using a 0.45 µm membrane filter obtained from Pall Corporation (Michigan, United States). The pH of each wastewater sample was adjusted to pH 3 and refrigerated at 4ºC until analysis.

Table 3.3.2. Sampling sites and their corresponding GPS coordinates.

WWTP	GPS coordinates
Amanzimtoti	S30.00749˚, E30.91720˚
Umhlathuzana	S29.87692˚, E30.88397˚
Umbilo	S29.84558˚, E30.88991˚
Northern	S29.79635˚, E30.99630˚

3.3.2.2.2 Plant samples (water hyacinth)

The plant samples were collected from two rivers around the Durban city. In this study, these rivers are identified as Mbokodweni river (GPS coordinates: S30.00460˚, E30.90045˚) and Springfield (GPS coordinates: S29.80558˚, E30.99473˚). Both these rivers have been previously found to be contaminated by NSAIDs (Agunbiade and Moodley, 2014; Gumbi et al., 2017b; Madikizela et al., 2014; Sibeko et al., 2019). In Mbokodweni river, there were no plants found downstream of the nearby WWTP (Amanzimtoti WWTP) which discharges its effluent into the river. Generally, the plants were pulled out from the river water and kept in plastic bags during their transportation to the laboratory. On arrival in the laboratory, the plants were thoroughly rinsed with deionized water and divided into leaves, stems and roots prior to their storage at -80 ˚C in a freezer. This was followed by freeze-drying each plant segment using an ALPHA 1-2 plus freeze-drier from Lasec (Cape Town, South Africa) for 72 h. The freeze-dried samples were pulverized on a pulverrisette from Fritsch (Darmstadt, Germany) into fine powder followed by extraction using MAE.

3.3.2.3 Hollow fiber preparation and extraction procedure

The 8 cm long fibers were ultra-sonicated in acetone and left to dry through evaporation in a dust-free environment prior to the extraction. One end of the fiber was then heat-sealed. A 50 µL Hamilton syringe was used to transfer the acceptor phase into the fiber until bubbles were visible on the walls of the fiber. The bubbles were wiped with a clean paper towel and thereafter the fiber was immersed for about 15 s in dihexyl ether which acted as a supported liquid membrane that impregnated the pores of the fiber. Deionized water was used to wash the walls of the fiber for removal of the excess organic solvent. The syringe was replaced with a wire to hang the fiber in aqueous samples. The fiber-containing an acceptor phase was then immersed in a 6 mL vial containing donor solution (aqueous sample) and extraction allowed to take place while stirring the donor phase. The acceptor phase containing the analytes was retracted from the lumen of the hollow fiber using a 50 µL Hamilton syringe. This was transferred into 100 µL vial inserts and diluted to 50 µL and taken to ultra-high-pressure liquid chromatography-mass spectrometry (UHPLC-MS) for identification and quantification of the analytes.

3.3.2.4 UHPLC-MS system and conditions

Identification and quantitation of target NSAIDs were performed using a Dionex Ultimate 3000 UHPLC system, Thermo Scientific (Sunnyvale, California, USA) equipped with a quadrupole time of flight mass spectrometric (QTOF-MS) detector from Bruker Daltonics (Bremen, Germany) operated in the positive electrospray ionization mode. A volume of 5 µL of each extract or standard solution was injected into the chromatographic system using an autosampler and separated using a Luna® Omega C_{18} column (50 mm x 4.6 mm x 3 µm) from Phenomenex (California, USA). The elution was achieved by using a mobile phase which consisted a mixture of 0.1% (v/v) formic acid in water (solvent A) and 0.1% (v/v) formic acid in acetonitrile (solvent B). A multi-step gradient programme was initiated by using 5% solvent B in the first 0.5 min and ramped to 90% in the next 9 min and re-equilibrated after each analysis. Data acquisition was performed using Data Analysis 4.3 software from Bruker Daltonics (Bremen, Germany).

3.3.2.5 Optimization of hollow fiber-liquid phase microextraction

A half fractional factorial design was used to screen six potential factors (donor phase (DP) pH, acceptor phase (AP) pH, supported liquid membrane (SLM) composition, stirring rate, extraction time and salt content) for their degree of significance on the extraction of analytes. The experimental design was created on Minitab 18 (Pennsylvania, USA). The importance of each factor effect was quantified as an analyte enrichment factor (EF) value. A response surface methodology was used to characterize the significance of each factor. This was then followed by listing them according to their importance and finally pairing according to their significance. The optimum conditions for each paired factors for extraction of each analyte was then predicted separately using central composite design. For a simultaneous extraction of the analytes from samples, universal optimum conditions were predicted in-silico using Minitab by manually altering the optimum values in optimal plots of paired factor effects. The new desirability values were then used in calculating a composite desirability value to clarify the acceptability of the predicted universal factor values. Model adequacy testing for each analyte was performed using the predicted universal conditions in order to get true experimental EF values.

3.3.2.6 Extraction of analytes from water hyacinth using microwave assisted extraction

The MAE technique was used in extracting the target analytes from the plant samples. With consideration of green chemistry principles, water was used as the extracting solvent. Two essential MAE parameters; extraction temperature and the volume of the extraction solvent (Fernandez et al., 2013) were then optimized in the range of 80 - 110˚C and 10 - 25 mL, respectively. Optimization was done using pulverized plant samples spiked with a mixture of NSAIDs in acetonitrile at a concentration of 100 µg kg^{-1}. Prior to extraction, acetonitrile was allowed to evaporate from plant samples overnight at room temperature. The general MAE procedure involved placing 0.1 g of powdered plant sample into a digestion vessel followed by addition of 20 mL of deionized water as the extracting solvent. The microwave vessels were tightly sealed and inserted in the microwave rotor. When MAE was completed, the water extract was treated like water samples by isolating and pre-concentrating analytes from aqueous phase using the optimized HF-LPME technique.

3.3.3 Results and discussion

3.3.3.1 Selection of essential HF-LPME factors

The two-way half fractional factorial randomized design created and used in characterizing the six potential factors is summarized in **Table 3.3.3**. The upper and lower levels of the factors used in the design were selected based on literature. As shown in **Figure 3.3.1**, the most effective factors for the extraction of analytes from water samples were AP pH, DP pH, extraction time and stirring rate. The significant factors for extraction of all the target analytes were found to be the same. This is mainly because these compounds have the same functional groups and their pKa values are almost similar ranging from 4.10 – 4.91 **(Table 3.3.1)**. Therefore, one analyte (naproxen) was selected randomly and used as a representative analyte of all the other analytes during the optimization process.

According to **Figure 3.3.1**, the DP pH and the AP NaOH concentration had a very significant effect on the extraction of naproxen. Expectedly, their interactive effect was significant too. In addition, some interactive effects of DP pH and SLM composition as well as those for DP, SLM composition and stirring rate were observed. In this regard, SLM composition and stirring rate were also selected as important factors. The significant factors observed in this study have also been reported elsewhere for the HF-LPME of pharmaceuticals (Ramos et al., 2010; Villar-Navarro et al., 2013).

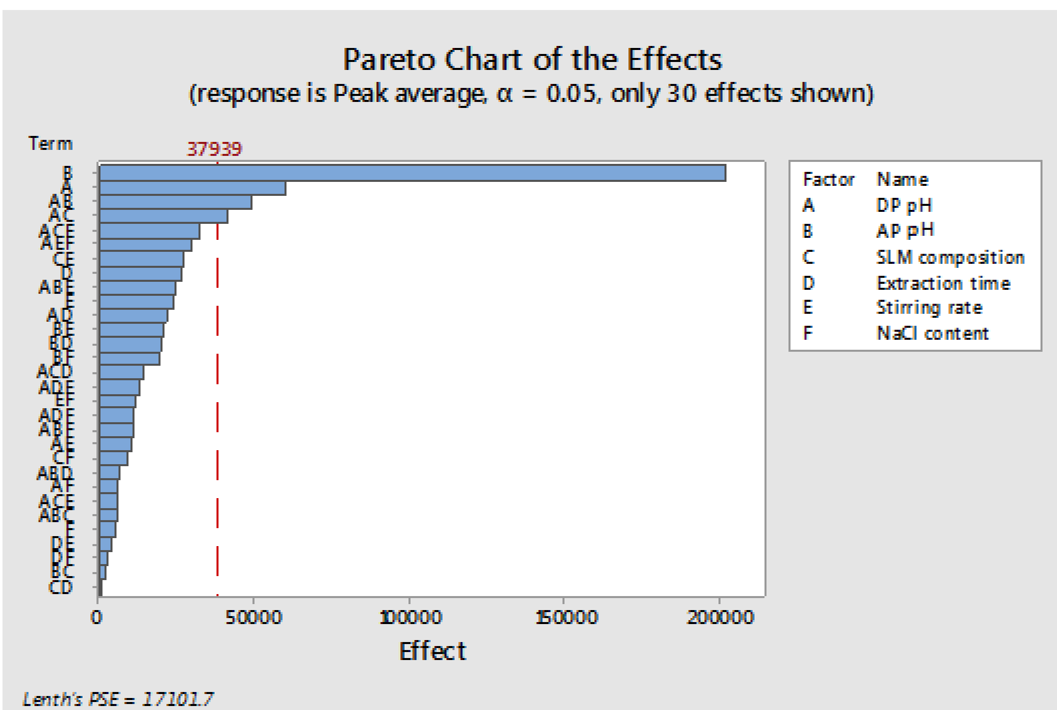


Figure 3.3.1. Pareto chart of the effects of the selected non-steroidal anti-inflammatory drugs.

Table 3.3.3. Design summary of the factor levels.

Factor	Factor name	Lower level	Upper level
A	DP pH	3	7
B	AP pH	7	11
C	SLM composition (%w/w)	5	15
D	Extraction time (min)	20	60
E	Stirring rate (rpm)	500	1000
F	NaCl content (%w/v)	0.001	0.01

3.3.3.2 Pairing of essential factors

The response surface methodology results for listing the four essential factors (AP pH, DP pH, extraction time and stirring rate) according to their extent of significance are shown in **Figure 3.3.2**. The results show that DP pH and the stirring rate were the driving forces in the extraction of NSAIDs. This was expected as the pH of the donor solution plays an important part in the extraction performance by altering the existing state of the analytes. The HF-LPME technique requires that analytes be in their non-ionized form in the donor phase for an effective transfer across the supported liquid membrane (Xiong and Hu, 2008). This ensures that the analytes are trapped by the acceptor phase where they must exist in their charged state to prevent back-extraction. The significance of the stirring rate could be explained by its influence in increasing the mass-transfer rate of the analyte to the surface of the hollow fiber. Thus, DP pH and stirring rate were paired and then central composite design was used to investigate their interactive effects on the extraction of all the study compounds. The less significant factors (AP pH and extraction time) were also paired together and their interactive effects investigated for the study compounds.

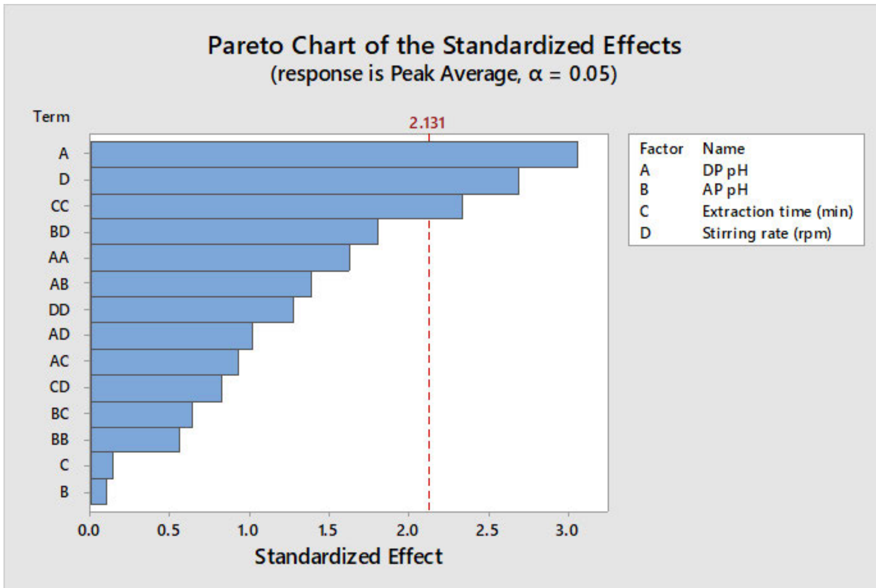


Figure3.3.2. Pareto chart of the standardized effects showing significant factors.

3.3.3.3 Optimization of the paired factors

Optimization of the paired factors was done individually for all the four study NSAIDs. The optimum factor levels were visualized in a form of contour and optimal plots of paired factor effects as shown in **Figure 3.3.3**. The summary of the optimum conditions of the paired factors for extraction of the four NSAIDs based on optimal plots **(Figure 3.3.3)** are summarized in **Table 3.3.4**. Notably, the optimum stirring rate and extraction time were the same for all analytes while the donor phase pH and AP pH were in the 2 – 4 and 7 – 11, respectively. Therefore, the next step was to predict the optimal pH conditions for both the acceptor and donor phases to enable the simultaneous extraction of the four NSAIDs. These universal conditions were predicted by manually changing the optimal values on the optimal plots of effects of each NSAID until desirable levels were met **(Table 3.3.4)**. As shown in **Table 3.3.4**, the universal optimum DP pH and AP pH were 3 and 10 respectively. At pH 3, all target NSAIDs are neutral or uncharged and thus can be adequately extracted from aqueous solutions while at pH 10 they are charged. The difference in charges of analytes in the donor and the acceptor is essential in HF-LPME. Under these conditions the compound desirability was 0.7735. These universal optimum conditions are in agreement with those reported elsewhere for compounds with hydroxyl groups (Tak et al., 2009) for the development of HF-LPME of nerve agent hydrolysis products from water. Also, these optimum conditions have been reported for the determination of NSAIDs in urine samples using a stir membrane liquid–liquid micro-extraction (Riaño and Lucena, 2012). More details on the significance of each optimum factor in the extraction of target NSAIDs are given in the following sections with summarized results shown in **Table 3.3.4**.

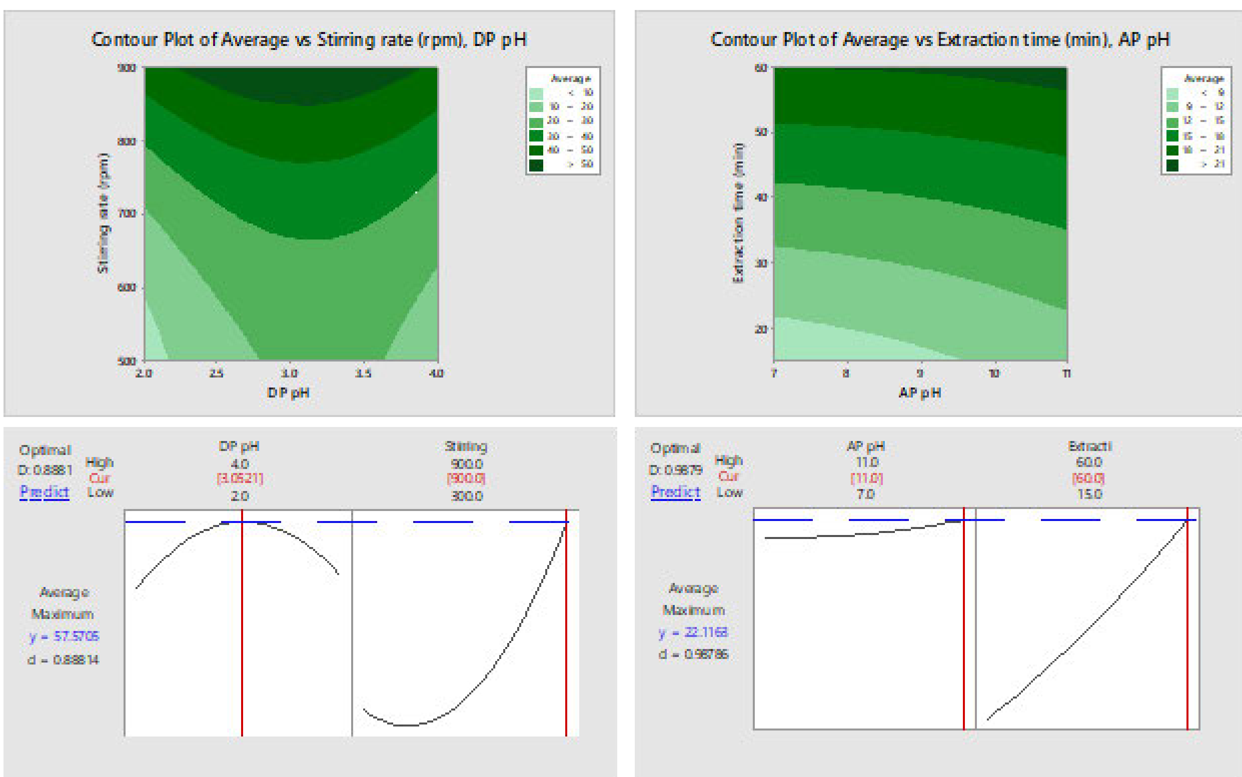


Figure 3.3.3. Contour and optimal plots of paired factor effects for naproxen.

Table 3.3.4. Summary of optimum results for all the analytes.

	Optimum factor levels				Universal optimum factor levels			
	Naproxen	Fenoprofen	Diclofenac	Ibuprofen	Naproxen	Fenoprofen	Diclofenac	Ibuprofen
DP pH	3	4	2	2.5	3	3	3	3
Stirring rate (rpm)	900	900	900	900	900	900	900	900
AP pH	11	9.3	11	7	10	10	10	10
Extraction time (min)	60	60	60	60	60	60	60	60
Minitab predicted EF	21 - 22	65 - 111	14 – 85	25 – 100	27 – 49	102 – 126	26 – 93	85 - 156
Maximum EF	-	-	-	-	49	126	93	156

3.3.3.4 Optimization of microwave assisted extraction method

During the optimization of irradiation temperature, the extraction solvent volume was kept constant at 20 mL. The recoveries of the analyte extracts obtained at different irradiation temperatures are shown in **Table 3.3.5**. The results show that the recoveries of the analytes increased from 66 to 113% with increasing irradiation temperature from 80˚C to 100˚C. In this instance, the optimum irradiation temperature was taken as 100˚C. A significant decrease in recoveries of all analytes was observed at 110˚C. This could be linked to photo-degradation of NSAIDs at high temperatures (Routray and Orsat, 2012).

Table 3.3.5. Effect of irradiation temperature on microwave assisted extraction of NSAIDs from E*ichhornia crassipes* (n = 3).

Temperature (°C)	% Recovery ± RSD values			
	Naproxen	Fenoprofen	Diclofenac	Ibuprofen
80	79 ± 0.1	66 ± 0.1	68 ± 5.0	86 ± 1.6
90	86 ± 1.7	82 ± 0.3	97 ± 3.2	99 ± 2.3
100	113 ± 0.6	100 ± 0.6	95 ± 1.9	96 ± 0.2
110	42 ± 3.6	47 ± 2.1	49 ± 3.3	54 ±1.4

During the optimization of the solvent volume, the extraction temperature, sample mass and extraction time were kept constant at 100˚C, 0.1 g and 20 min, respectively. As can be seen in **Table 3.3.6**, the analyte recoveries in different plant segments increased with increasing solvent volume until it reaches 20 mL. The reduction in analyte recoveries was observed when the solvent volume was 25 mL. It should be noted that 25 mL was the maximum capacity of the vessels used in this study which meant the combination of the 25 mL solvent and 0.1 g plant samples in a single vessel may have resulted in inadequate vibration of the water molecules by the microwaves. Therefore, 20 mL of the solvent volume was taken as optimum and used in subsequent experiments.

Table 3.3.6. Effect of solvent volume on microwave assisted extraction of selected non-steroidal anti-inflammatory drugs from plant samples (n = 3).

	Solvent volume (mL)	% Recovery ± RSD		
		Roots	Stem	Leaves
Naproxen	10	80 ± 0.6	93 ± 1.1	86 ± 3.3
	15	93 ± 1.5	88 ± 0.9	79 ± .0.7
	20	115 ± 0.1	96 ± 1.6	94 ± 3.3
	25	37 ± 0.4	28 ± 1.2	33 ± 2.6
Diclofenac	10	82 ± 4.1	86 ±2.8	92 ± 2.5
	15	91 ± 0.6	88 ± 4.4	90 ± 3.6
	20	96 ± 3.9	99 ± 1.8	101 ± 2.4
	25	48 ± 3.6	52 ± 0.4	35 ± 4.1
Fenoprofen	10	92 ± 1.5	87 ± 0.4	72 ± 2.6
	15	95 ± 2.1	91 ± 1.1	73 ± 0.9
	20	91 ± 0.5	93 ± 2.1	91 ± 3.8
	25	28 ± 1.5	34 ± 0.8	41 ± 1.6
Ibuprofen	10	96 ± 1.4	90 ± 0.2	79 ± 1.7
	15	99 ± 2.1	94 ± 1.9	92 ± 0.7

	20	106 ± 1.4	98 ± 3.7	104 ± 0.6
	25	23 ± 2.9	39 ± 2.4	26 ± 4.2

3.3.3.5 Competence of the analytical method

Method performance which involved MAE, HF-LPME and UHPLC-MS analysis for the four selected NSAIDs was validated by analysing the spiked samples. The analytical method validation involved the assessment of linearity, accuracy (recovery of analytes in both wastewater and plant sample media), repeatability and sensitivity (limits of quantification (LOQ) and detection (LOD)). The linearity of the method was evaluated by plotting the peak area of an analyte against the corresponding compound's concentration. The R^2 values determined from the regression curves of each NSAID were greater than 0.99 **(Table 3.3.7)** which indicated good linearity. Accuracy of the analytical method expressed as recoveries in the ranges of 96 - 99% for wastewater and 86 - 116% for plant samples indicates a reliable method that can be used in environmental monitoring of the target compounds. Relative standard deviation (RSD) values did not exceed 5% which is an indication of a precise method. LOD and LOQ values for plants samples were derived from the instrumental values with considerations of HF-LPME enrichment factors and sample extraction efficiencies. LOQ values obtained for wastewater samples ranged from 0.09 to 0.59 µg L^{-1} which is relatively similar to those reported in literature using SPE with LC-MS (Baranowska et al., 2013; Baranowska and Kowalski, 2012). The advantage of the proposed HF-LPME-based extraction and pre-concentration technique is the reduction of organic solvents used which aligns well to green chemistry principles. For identification of NSAIDs in wastewater and plants, fragmentation patterns and peak retention times were used. The chromatograms of the target analytes identified using standards and in real samples are given **Figure 3.3.4** while the fragmentation patterns are in **Figure 3.3.5**. The chromatograms and fragmentation patterns of real samples are characterized by matrix effects. It was noted that the major daughter fragment for naproxen (MR = 230) was 186.9 versus the expected 185.09 for pure standards, an indication of possible ionization in presence of matrix effects.

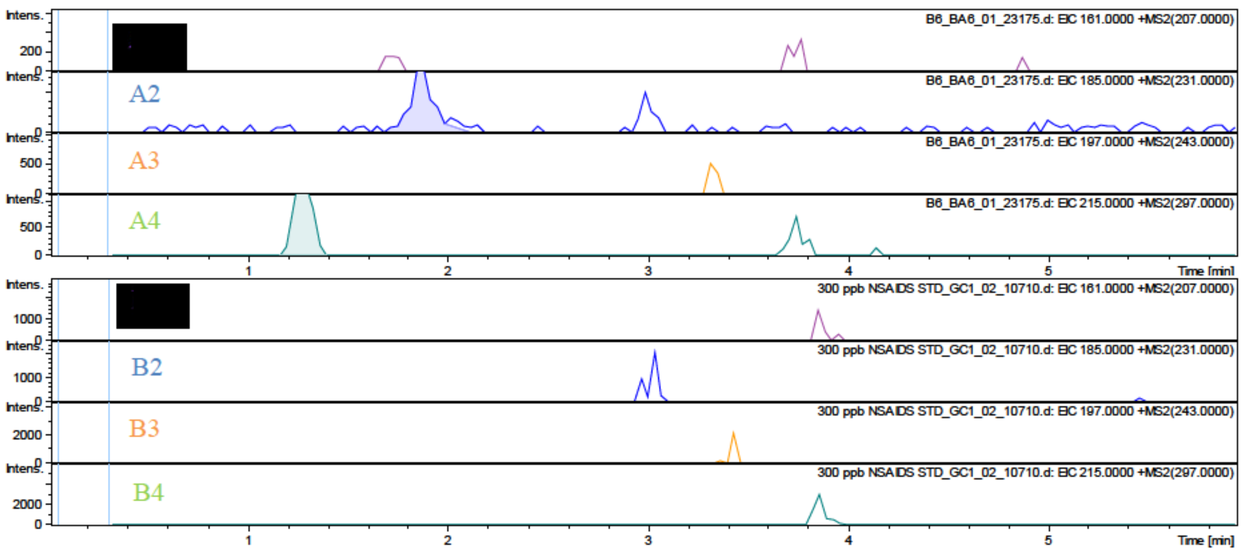


Figure 3.3.4. Chromatograms of NSAIDs in plant samples (A) and standards (B). Ibuprofen peaks (A1+B1), naproxen peaks (A2+B2), fenoprofen peaks (A3+B3) and diclofenac (A4+B4).

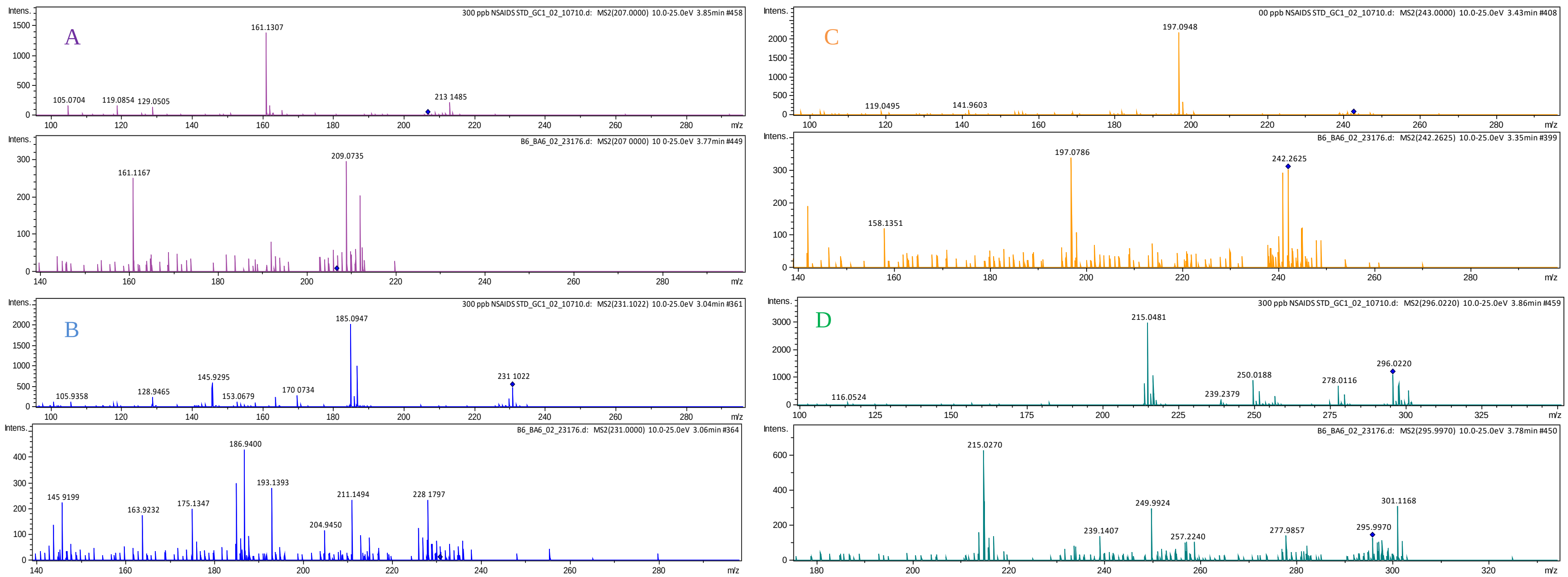


Figure 3.3.5. Fragmentation patterns of NSAIDs in standard solutions and in plant samples. A – naproxen, B – naproxen, C – fenoprofen, D – diclofenac.

Table 3.3.7. Performance of analytical method in aqueous samples and water hyacinth (n = 3).

NSAID	Linearity (r^2)	Wastewater			Water hyacinth		
		LOD (μg L^{-1})	LOQ (μg L^{-1})	Recovery (%) ± RSD	LOD (μg kg^{-1})	LOQ (μg kg^{-1})	Recovery (%) ± RSD
Naproxen	0.995	0.10	0.47	98 ± 0.5	0.41	0.59	86 ± 2.3
Fenoprofen	0.997	0.05	0.09	96 ± 0.1	0.16	0.21	99 ± 3.6
Diclofenac	0.995	0.35	0.59	99 ± 0.6	0.12	0.13	116 ± 0.9
Ibuprofen	0.998	0.24	0.49	96 ± 1.9	0.10	0.11	108 ± 3.7

3.3.4 Monitoring of non-steroidal anti-inflammatory drugs in environmental samples

3.3.4.1 Environmental monitoring of NSAIDs in wastewater samples

The developed analytical method HF-LPME-UHPLC-MS was applied in the monitoring of selected NSAIDs in the influents and effluents of Durban based WWTPs. The results presented in **Table 3.3.8** show naproxen and diclofenac as the most prominent drugs in the wastewater samples. These two NSAIDs were detected in all the samples. In some cases, the concentrations of NSAIDs were found to be higher in the effluent rather than the influent. This could be due to the collection of samples in WWTPs using grab sampling protocol which did not consider the wastewater retention times. In a different view, matrix effects could significantly affect the results of the environmental monitoring where they are expected to be higher in the influents than in the effluents of WWTPs which precede to higher quantitation limits in influents (Gracia-Lor et al., 2012). Although the removal efficiencies of these NSAIDs were not computed in the studied WWTPs due to unquantifiable concentrations in most cases, the results (**Table 3.3.8)** show the evidence of their poor removal during the sewage treatment process.

The results of the current study differ significantly from the concentrations of the same compounds previously reported in the studied WWTPs (Madikizela et al., 2014; Madikizela and Chimuka, 2017; Madikizela and Chimuka, 2017c; Madikizela and Chimuka, 2016a). As an example, the concentration of fenoprofen detected in Amanzimtoti WWTP effluent was 2.03 µg L^{-1} (Table 8), whereas Mbhele et al., 2018 (Mbhele et al., 2018) detected fenoprofen at 6 and 47 µg L^{-1} over a period of two consecutive weeks. This might be an indication that the concentration of NSAIDs entering the WWTPs vary over time due to deviations in consumption patterns. Also, climate can influence the concentrations of pharmaceuticals in the environment. This is caused by variations in the rainfalls over years which dilute the pharmaceutical levels in the environment. It is speculated that the heavy rainfalls that occurred in October 2018 during the time of sampling could have diluted the NSAID levels in the studied WWTPs. Another notable difference between previous studies and the current study is that there was no detectable concentration of ibuprofen in the influent wastewater. However, in the previous work, the concentrations of ibuprofen reported in the influents of Amanzimtoti, Northern, Shallcross and Marrianridge WWTPs were 28, 72, 34, 30 µg L^{-1}, respectively (Madikizela and Chimuka, 2017a). Ibuprofen concentration in the influent of Umbilo WWTP previously reported by Madikizela and Chimuka (2017) was 55 µg L^{-1} (Madikizela and Chimuka, 2017). These observations are supported in literature as the concentrations of NSAIDs have been shown to widely deviate in other South African WWTPs with Kanama et al., 2018 reporting diclofenac and ibuprofen concentrations variations from 0.12 - 10.34 µg L^{-1} and 0.33 - 53.40 µg L^{-1} respectively in a single WWTP (Kanama et al., 2018). The concentrations of diclofenac and ibuprofen in the effluent of the same WWTP were again found to be 0.07 - 0.75 µg L^{-1} and <LOQ - 13.66 µg L^{-1}, respectively (Kanama et al., 2018). In this regard, it is obvious that the concentrations of NSAIDs in WWTPs also follow the general trend in which pollutant concentration have been found to depend on the time of the day (Amdany et al., 2015), seasonal changes (Sun et al., 2016), population dynamics (Sun et al., 2016) and availability of proper sanitation systems in the study area (Bean and Rattner, 2018).

Table 3.3.8. Average concentrations of target non-steroidal anti-inflammatory drugs found in aqueous samples (n = 3).

Sampling site	Average concentration (μg L^{-1}) ± %RSD			
	Naproxen	Fenoprofen	Diclofenac	Ibuprofen
Amanzimtoti WWTP influent	2.84 ± 0.5	nd	0.70 ± 0.3	nq
Amanzimtoti WWTP effluent	1.15 ± 3.2	2.03 ± 1.4	0.97 ± 1.8	nq
Northern WWTP influent	2.52 ± 0.8	<LOQ	0.49 ± 0.4	nd
Northern WWTP effluent	2.97 ± 2.3	nd	0.36 ± 2.4	nd
Umbilo WWTP influent	2.85 ± 1.6	nq	1.97 ± 2.8	nq
Umbilo WWTP effluent	2.90 ± 0.9	nd	3.13 ± 1.7	0.92 ± 1.8
Shallcross influent	3.07 ± 2.1	nq	1.64 ± 2.2	nq
Marrianridge influent	3.23 ± 0.4	nd	0.67 ± 3.5	nq
Umhlathuzana effluent	3.30 ± 0.1	nd	0.90 ± 4.7	nq

nd - not detected

nq - detected but cannot be quantified

<LOQ - the compound was detected but its concentration was below the quantitation limit

3.3.4.2 Environmental monitoring of NSAIDs in *Eichhornia crassipes*

The results in **Table 3.3.9** show that all the NSAIDs were detected and quantified in plant samples from Springfield whereas only naproxen and ibuprofen could be quantified in plant samples collected in Mbokodweni. This was expected as the plants in Springfield were collected near the outfall of the Northern WWTP whereas the plant samples from Mbokodweni were only found far away from where WWTP effluent enters the river. In this context, the concentration of the NSAIDs was generally higher in plants collected in Springfield than those sampled in Mbokodweni. With the NSAIDs detected in various segments of the plants, naproxen was more prominent with concentrations reaching 4.47 µg kg^{-1} in the roots of the plants collected from Springfield. Consequently, the total bioaccumulation of naproxen was the highest with 10.97 µg kg^{-1} recorded in samples from Springfield. In a previous study conducted in Mbokodweni River, Sibeko et al., 2019 also observed that the concentrations of naproxen in different segments of water hyacinth were higher than any other NSAID (Sibeko et al., 2019). In terms of translocation, it was observed that ibuprofen and fenoprofen displayed high tendencies to accumulate in aerial parts of the plant with translocation percentages of 80 – 100% recorded in plant samples where they were quantified. Ibuprofen concentrations reached up to 3.35 µg kg^{-1} in the leaves of the plants. Naproxen seemed to fairly accumulate equally in the plants with translocation percentages of 57 – 59%. Diclofenac was the least translocated with maximum 34% in plant samples from Springfield while it was only detected in roots in samples from Mbokodweni. The translocation results observed in this study might be related to the pKa values of the study NSAIDs **(Table 3.3.1)**. The results of the current study are supported by other studies available in literature, that have reported the uptake of pharmaceuticals from contaminated water by plant roots and get translocated into stem and leaves (Dodgen et al., 2013; Herklotz et al., 2010; Matamoros et al., 2012; Miller et al., 2016; Petrie et al., 2017; Pi et al., 2017; Sibeko et al., 2019; Zhang et al., 2013, 2012).

Generally, the results of this study demonstrate the potential of using water hyacinth for the removal of NSAIDs from contaminated surface water. The information available elsewhere indicated that the concentration of ibuprofen can reach up to 800 µg kg^{-1} in roots of the water hyacinth within 8 days of analyte exposure to the plant in the controlled environment (Pi et al., 2017). Furthermore, Lin and Li (2016) observed that the water hyacinth can stimulate the removal of pharmaceuticals which included ibuprofen after 13 days of incubation (Lin and Li, 2016). Poor detection of diclofenac in this study could be linked to its rapid metabolism within the plant species. A study by Huber et al., 2012 has reported that once diclofenac is taken up by plants (*Hordeum vulgare*) it easily transforms into some metabolites within 3 h (Huber et al., 2012).

Table 3.3.9. Concentrations of the NSAIDs found in different segments of water hyacinth (n = 3).

		Concentration in plant samples (µg kg^{-1})					
Sampling point	Target compound	Roots	Stem	Leaves	Total	Stem + leaves only	Translocation (%)
Mbokodweni	Naproxen	2.76 ± 0.33	1.94 ± 0.81	1.70 ± 0.65	6.4	3.64	57
	Fenoprofen	nd	nd	nd	-	-	-
	Diclofenac	1.18 ± 0.63	<LOQ	<LOQ	-	-	-
	Ibuprofen	1.18 ± 0.63	1.67 ± 0.42	3.10 ± 0.88	5.95	4.77	80
Springfield	Naproxen	4.47 ± 0.36	3.22 ± 0.27	3.35 ± 0.54	10.97	6.5	59
	Fenoprofen	0.21 ± 0.40	1.18 ± 0.82	<LOQ	1.39	1.18	85
	Diclofenac	0.65 ± 0.22	0.21 ± 0.19	0.13 ± 0.16	0.99	0.34	34
	Ibuprofen	<LOQ	0.60 ± 0.11	0.11 ± 0.37	0.71	0.71	100

nd - not detected

<LOQ - detected but below the quantitation limit

Conclusion

A multivariate optimization of HF-LPME for the pre-concentration of naproxen, fenoprofen, diclofenac and ibuprofen in wastewater and *Eichhornia crassipes* was developed and accomplished by means of a half fractional factorial and a central composite design. This was followed by their isolation, identification and quantitation using UHPLC-MS. The HF-LPME-UHPLC-MS exhibited good analytical performance and pre-concentration of the analytes with high enrichment factors, minimal solvent consumption and sensitivity. The optimized method afforded detection of NSAIDs in wastewater effluents an indication that pharmaceuticals continue to be discharged from WWTPs into surface water sources. Their detection in hyacinth plants means that NSAIDs in polluted areas get taken-up by aquatic plants through roots followed by their translocation into various segments. In this regard, the hyacinth plants generally viewed as problematic because of their invasive nature might in fact be a solution in the search for cheap, readily available and environmentally friendly phytoremediation tools for pharmaceuticals especially in WWTP effluents.

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4 CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

4. CHAPTER FOUR: GENERAL CONCLUSION

4.1 CONCLUSION

This research presented the analysis of ARVDs and NSAIDs in wastewater influents and effluents, as well as in different plant segments of *Eichhornia crassipes*. A convenient extraction process based on microwave assisted extraction and hollow fiber liquid phase microextraction of three ARVDs (emtricitabine, tenofovir disoproxil and efavirenz) and four NSAIDs (naproxen, fenoprofen, diclofenac and ibuprofen) from water and aquatic plants followed by their quantitative analysis using LC-QTOF/MS was developed. The analytical technique was optimized using a multivariate approach. This allowed for identification of essential factors using half-fractional design followed by identification of optimum conditions based on paired interactive effects of the essential factors in HF-LPME using central composite designs. The optimized technique allowed for trace quantification of the target compounds in surface water, wastewater and various plant tissues of *Eichhornia crassipes*. The optimum conditions for the HF-LPME technique that allowed for the simultaneous isolation and enrichment of the selected ARVDs and NSAIDs in both aqueous and plant samples were found to be effective with recoveries ranging from 86% to 111% and 86% to 116%, with detection limits as low as 0.03 µg L^{-1} and 0.09 µg L^{-1}, respectively. These method validation parameters are an indication that the developed HF-LPME-LC-MS method can be a viable alternative in the extraction and quantification of ARVDs and NSAIDs in aqueous samples. The ARVDs and NSAIDs under investigation were detected in most water sample matrices which indicates that they are discharged into surface water from WWTPs. Results further showed that these ARVDs and NSIADs are taken by plant roots and get translocated to aerial tissues of *Eichhornia crassipes*. EFV was the most abundant compound in all studied matrices. Whereas NAP was the most detected compound in water samples with ibuprofen being accumulated at 100% in stems and leaves of the water hyacinth. Overall, ARVDs had a higher uptake or accumulation rate in the tissues of the water hyacinth than NSAIDs.

4.2 RECOMMENDATIONS

The occurrence of pharmaceuticals namely ARVDs and NSAIDs in various water samples analyzed in this study is a cause for concern hence the need to conduct more investigation on their presence in water resources as there are still individuals that depend on untreated surface water for their day-to-day needs. Also, since the number of HIV-1 infected people increases daily, extensive monitoring of the least monitored drugs (ARVDs) need more attention in order to understand their occurrence and removal efficiency patterns in various South African and world-wide water resources. It is now evident that ARVDs monitoring in different environmental samples might provide awareness about the occurrence and distribution of these drugs by different scientists. The detection of these ARVDs and NSAIDs in WWTP effluents is an indication that these pharmaceuticals are discharged into surface water. Therefore, there is a need to investigate the new designs for WWTPs that could lead to a complete removal of ARVDs and NSAIDs from wastewater. Furthermore, the pharmaceutical contamination of surface water across South Africa should be investigated in order to understand the extent of water pollution caused by the introduction of these compounds into rivers from WWTPs. More studies can be done to evaluate the bioaccumulation of ARVDs and NSAIDs in other aquatic plants as well as to evaluate their mechanism of uptake. The ability of other plant species to take-up pharmaceuticals from contaminated water should be investigated.

Environmental monitoring studies should be a norm especially in the rural areas as most residents still use pit toilets and consume river water which might be infested with various pollutants. Also, they use surface water for irrigation purposes as they rely on crop farming in order to sustain their families. As is well known that long term exposure to these pollutants in the human system may have detrimental effects.