MIXED MATRIX MEMBRANE MICROEXTRACTION FOR THE ANALYSIS OF POLYCYCLIC AROMATIC HYDROCARBONS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND TOBRAMYCIN IN SOLUTIONS

NURUL HAZIRAH BINTI MUKHTAR

A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy (Chemistry)

Faculty of Science
Universiti Teknologi Malaysia

MARCH 2018

In the name of Allah, the Most Merciful and the Most Beneficent. This thesis is dedicated to my beloved husband (Mohd Nor Firdaus Adnan), parents (Fatimah Mohd Amin &Mukhtar Yusof), son (Abdurrahman Harraz) and family members.

ACKNOWLEDGEMENT

First of all, I am deeply grateful to Allah, the Almighty for blessing and mercy that had been given to me especially during this PhD journey. I also would like to express my deepest gratitude to my supervisor, Dr. See Hong Heng, for his sage advice, patient, encouragement and unconditional helps which enabled me to approach and complete my works positively. Special thanks to my fellow labmates especially Akma, Leeyien, Meiqi, KC and Ain for giving me constructive comments and warm encouragement, especially at times when I almost gave up. My deepest appreciation also goes to science officers and lab assistants in Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia (UTM) for their great helps.

I would like to thank to Ministry of Higher Education (MOHE) for the financial sponsorship given to me for three years. Last but not least, my great appreciation is dedicated to my beloved family and husband for supporting me spiritually throughout my life and study. There is no such meaningful word than "Thank You So Much." I would like to thank my parents and family for constant support, emotional understanding, encouragement that involved indirectly or directly throughout my study.

ABSTRACT

New approaches in miniaturised sample preparation have been investigated. In this study, novel microextraction methods based on the use of a mixed matrix membrane (MMM) were developed in various designs and applications. The potential for carbonaceous nanomaterials to be used as adsorbents for the MMM microextraction and preconcentration of organic pollutants was demonstrated. In this method, multiwall carbon nanotubes (MWCNT) and single layer graphene (SLG) nanoparticles were individually incorporated through dispersion in a cellulose triacetate (CTA) polymer matrix to form MWCNT-MMM and SLG-MMM, respectively. The prepared membranes were evaluated for the extraction of selected polycyclic aromatic hydrocarbons (PAHs) from sewage pond water samples. The extraction was performed by dipping a small piece of membrane (7 mm × 7 mm) in a stirred 7.5 mL sample solution to initiate the analyte adsorption. Enrichment factors of 54 to 100 were achieved with relative recoveries of 99% to 101%. The developed method proved a simple, feasible, and cost-effective microextraction technique. A new sample pre-treatment technique termed mixed matrix membrane tip extraction (MMMTE) has been developed and combined with high performance liquid chromatography (HPLC) for the determination of selected non-steroidal anti-inflammatory drugs, namely sulindac, indoprofen, naproxen, diclofenac and ibuprofen in environmental water samples. The extraction was carried out by preparing a thin film mixed matrix membrane with immobilised C_{18} adsorbents on a 100 µL tip wall. The microextraction was conducted by continuously flowing the sample solution through the membrane tip device for the effective analyte adsorption process. This step was followed by desorption of the analyte into a small amount of organic solvent prior to HPLC analysis. The detection limits of the method for the selected drugs were in the range of 10-50 pg/mL. Enrichment factors of up to 249 fold were achieved with relative recoveries of > 90%. A novel mixed matrix membrane tip extraction using hydrophilic lipophilic balance particles was developed for the preconcentration of the aminoglycoside antibiotic from the human plasma prior to the capillary electrophoresis with a contactless conductivity detection (CE-C^4D). The parameters affecting the extraction efficiency such as the dynamic rinse time and desorption solvent were investigated in detail. Under the optimised conditions, the limit of detection and the limit of quantification of the method for tobramycin are 0.01 and 0.03 µg/mL, respectively. Relative recoveries in spiked human plasma were in the range of 99.6-99.9% with relative standard deviations between 3.6% and 8.7%.

ABSTRAK

Pendekatan baharu dalam penyediaan sampel skala kecil telah dikaji. Dalam kajian ini, kaedah baru pengekstrakan mikro berdasarkan penggunaan membran matriks bercampur (MMM) telah dibangunkan dalam pelbagai reka bentuk dan penggunaan. Potensi bahan nano berkarbon untuk digunakan sebagai penjerap dalam pengekstrakan mikro MMM dan pra-pemekatan bahan pencemar organik telah ditunjukkan. Dalam kaedah ini, nanotiub karbon berbilang dinding (MWCNT) dan nanopartikel grafin lapisan tunggal (SLG) telah digabungkan secara berasingan melalui penyebaran di dalam matrik polimer selulosa triasitat (CTA) masing-masing untuk membentuk MWCNT-MMM dan SLG-MMM. Membran-membran ini dinilai bagi pengekstrakan hidrokarbon aromatik polisiklik (PAH) terpilih daripada sampel air kolam kumbahan. Pengekstrakan dilakukan dengan mencelup sekeping membran bersaiz kecil (7 mm × 7 mm) di dalam sampel air 7.5 mL yang dikacau untuk memulakan penjerapan analit. Faktor pengayaan 54 hingga 100 telah dicapai dengan perolehan semula relatif 99% hingga 101%. Kaedah yang dibangunkan terbukti merupakan suatu teknik pengekstrakan mikro yang mudah, boleh dilaksanakan dan kos efektif. Teknik sampel pra-rawatan baharu dipanggil pengekstrakan muncung membran matrik bercampur (MMMTE) telah dibangunkan dan digabungkan dengan kromatografi cecair prestasi tinggi (HPLC) untuk penentuan dadah anti-radang bukan steroid terpilih iaitu sulindac, indoprofen, naproxen, diclofenac dan ibuprofen di dalam sampel air alam sekitar. Pengekstrakan dijalankan dengan menyediakan filem nipis membran matrik bercampur dengan penjerap C_{18} tak bergerak pada diding muncung 100 µL. Pengekstrakan mikro dijalankan dengan mengalirkan larutan sampel secara berterusan melalui peranti muncung membran untuk proses penjerapan analit yang berkesan. Langkah ini diikuti dengan penyahjerapan analit ke dalam pelarut organik dalam amaun yang kecil sebelum analisis HPLC. Had pengesanan kaedah untuk dadah terpilih adalah dalam julat 10-50 pg/mL. Faktor pengayaan sehingga 249 kali ganda telah dicapai dengan perolehan semula relatif > 90%. Pengekstrakan muncung membran matrik bercampur menggunakan zarah imbangan lipofilik hidrofilik telah dibangunkan untuk pra-pemekatan antibiotik aminoglikosid daripada plasma manusia sebelum elektroforesis kapilari dengan pengesan konduktiviti tanpa-sentuhan (CE-C^4D). Parameter yang mempengaruhi kecekapan pengekstrakan seperti masa bilasan dinamik dan pelarut penyahjerap telah dikaji secara terperinci. Dalam keadaan optimum, had pengesanan dan had kuantifikasi kaedah bagi tobramacin adalah masing-masing 0.01 and 0.03 µg/mL. Perolehan semula relatif di dalam plasma manusia terpaku adalah dalam julat 99.6-99.9% dengan sisihan piawai relatif antara 3.6% dan 8.7%.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ace	-	Acenaphthene
ACN	-	Acetonitrile
Ant	-	Anthracene
AL0136	-	Octa (3-hydroxy-3-methylbutyldimethylsiloxy
BaA	-	Benz (a) anthracene
BDC	-	Benzenedicarboxylate
C_{18}	-	Polymeric octadecylsilane
Ca^{2+}	-	Calcium ion
CAR/PDMS	-	Carboxen/polydimethylsiloxane
CBZ	-	Carbamazepine
CE	-	Capillary electrophoresis
CEP	-	Cellulose acetate phthalate
CH_4	-	Methane
CNT	-	Carbon nanotube
CO_2	-	Carbon dioxide
CTA	-	Cellulose triacetate
Cu^{2+}	-	Copper ion
CVD	-	Chemical vapor deposition
DCE	-	1,2-dichloroethane
DCM	-	Dicloromethane
DI	-	Ultrapure deionized water
DLLME	-	Dispersive liquid-liquidmicroextraction
DNA	-	Deoxyribonucleic acid
DS	-	Diclofenac sodium
DVB	-	Divenylbenzene
EVAL	-	Ethylene vinyl alcohol
FESEM	-	Field emission scanning electron microscopy
Flu	-	Fluorene
Flt	-	Fluranthene
GC	-	Gas chromatography
GNs	-	Graphene nanosheets
HCl	-	Hydrocloric acid
HF-LPME	-	Hollow fiber-liquid phase microextraction
HLB	-	Hydrophilic lipophilic balance
HPLC	-	High performance liquid chromatography
I.D	-	Internal diameter

ISR	-	Isradipine
KH_2PO_4	-	Potassium dihydrogen phosphate
LC	-	Liquid chromatography
LLE	-	Liquid-liquid extraction
LOD	-	Limit of detection
LOQ	-	Limit of quantification
LPME	-	Liquid phase microextraction
MCM	-	Mobil crystalline materials
MeOH	-	Methanol
MIP	-	Molecular imprinted polyemer
MMMs	-	Mixed matrix membrane
MMMTE	-	Mixed matrix membrane tip extraction
MOFs	-	Metal organic frameworks
MS	-	Mass spectrometry
MSD	-	Mass selective detection
MWCNT	-	Multiwall carbon nanotube
N_2	-	Nitrogen
NaAlg	-	Sodium alginate
NaCl	-	Sodium chloride
NaOH	-	Sodium hydroxide
Nap	-	Naphthalene
NSAIDs	-	Non-steroidal anti-inflammatory drugs
O_2	-	Oxygen
O.D	-	Outer diameter
PAH	-	Polycyclic aromatic hydrocarbon
PAN	-	Polyacrylonitrile
Pb	-	Plumbum
PDI	-	Pyridine derivative of isradipine
PDMS	-	Polydimethylsiloxane
PDMS/DVB	-	Polydimethylsiloxane/dimethylbenzene
PEBA	-	Polyether blodck amide
PEBAX/POSS	-	Polyether block amide/polyhedral oligosilsesquioxane
PES	-	Polyether sulfone
PES/HMO	-	Polyethersulfone/hydrous manganese dioxide
Phe	-	Phenanthrene
PrOH	-	Propanol
PTFE	-	Polytetrafluoroethylene
PVDF	-	Polyvinylidenefluoride
Pyr	-	Pyrene
RSD	-	Relative standard deviation
S01440	-	Disilanolisobutyl
SBSE	-	Stib bar sortpive extraction
SDME	-	Single drop microextraction
SEM	-	Scanning electron microscopy

SLG	-	Single layer graphene
SLM	-	Supported liquid membrane
SPE	-	Solid phase extraction
SPME	-	Solid phase microextraction
SPMTE	-	Solid phase membrane tip microextraction
SWCNT	-	Single wall carbon nanotube
TCM	-	Trichloromethane
TE	-	Thermal extraction
TeCE	-	1,1,2,2-tetrachloroethane
TED	-	Triethylenediamine
TEOS	-	Tetraethylorthosilicate
TFME	-	Thin film microextraction
UF	-	Ultrafiltration
UV	-	Ultraviolet
VOCs	-	Volatile organic contaminants
ZIFs	-	Zeolitic imidazole frameworks
ZSM	-	Zeolite of sieve molecular
6FDA	-	Hexafluoroisopropylidene diphthalic anhydride
µ-SPE	-	Micro-solid phase extraction

LIST OF SYMBOLS

Cm	-	Centimeter
G	-	Gram
g/mol	-	Gram per mol
I.D	-	Internal diametr
L	-	-Liter
m	-	-meter
mg	-	-Miligram
m^2/g	-	Meter square per gram
min	-	-Minutes
mL	-	-Mililiter
mL/min	-	-Mililiter per minute
mm	-	Milimeter
mmol	-	Milimole
n	-	Amount of analyte
ng	-	Nanogram
nm	-	Nanometer
nmol/L	-	Nanomole per liter
ng/L	-	Nanogram per liter
ng/mL	-	Nanogram per mililiter
nL	-	Nanoliter
pKa	-	Acid dissociation constant
R	-	Correlation coefficient
rpm	-	Rotation per minute
s	-	Second
v/v	-	Volume per volume
w/v	-	Weight per volume
%	-	Percent
°C	-	Degree celcius
µg	-	Microgram
µm	-	Micrometer
µg/L	-	Microgram per liter
µg/mL	-	Microgram per mililiter

CHAPTER 1

INTRODUCTION

1.1 Research Background

The development of new, simple and effective sample pretreatment techniques is crucial for the aspects of matrix elimination and/or analyte preconcentration in order to achieve the desired detection limits. The oldest pre-concentration and matrix isolation technique in analytical chemistry is the liquid-liquid extraction (LLE) [1]. However, this technique is a time consuming, multistage operation technique and requires a large amount of organic solvents that are potentially toxic and expensive. The solid phase extraction (SPE) has advantages over the LLE, which involve a reduced analysis time and total organic consumption and waste disposal, but can be relatively expensive [2].

Recently, several microscale membrane based methods have been introduced to speed up and simplify the sample preparation procedure as well as minimise organic solvent usage. The best known among them are the hollow fibre liquid phase microextraction (HF-LPME) [3], solid phase membrane tip extraction (SPMTE) [4] and micro–solid phase extraction (μ-SPE) [5] and thin film

microextraction (TFME) [6]. In these reported approaches, the membrane being used can act as a solid matrix support in the form of a supported liquid membrane, a porous solid protected sheet for an adsorbent/organic solvent, or a homogenous thin film.

Over the past decade, membrane technologies are growing rapidly by developing materials that allow greater flux and selectivity. Among these established methods, mixed matrix membrane (MMM) has been rapidly researched. MMM is a heterogeneous membrane consisting of addictive filler embedded in a polymer matrix and can be made into flat sheets and hollow fiber. MMM combine the superior permeability and selectivity of inorganic membranes with the processability of polymeric membranes. The combination in MMM has resulted in a synergistic effect in which the rigid adsorptive porous type inorganic phase provides superior separation properties, meanwhile the presence of flexible polymer enables the ideal membrane forming hence solving the problem of fragility inherent found in the inorganic membranes [7]. The difficulties in controlling the adhesion between the polymer phase and the external surface in MMMs especially when have resulted in the use of new materials to produce MMM. To date, various polymers have been modified with inorganic fillers such as zeolites [8], mesoporous silicas [9], activated carbons [10], carbon nanotubes [11] and even non-porous solids [12] for the preparation of MMM. The use of MMM have been reported in gas separation applications [9, 13-21] and also for the liquid phase separation [8, 22-31].

In this study, new and simple microextraction techniques based on the use of a mixed matrix membrane in various types and designs were developed. Comprehensive studies were conducted on the applicability of new microextraction techniques in various applications. The applicability of the developed method was studied by determining the selected polycyclic aromatic hydrocarbon and drugs in solutions.

1.2 Problem Statement

The increasing amounts of organic pollutants entering the environment have become critical issues. Their presence in the environment, especially in water, is hazardous because they cause human beings to become more susceptible to disease. Furthermore, the contamination of pharmaceuticals in the aquatic environment has also been identified as one of the emerging issues in environmental chemistry. Nevertheless, the contamination level of these drugs in the environmental ecosystem has now reached alarming stages due to their continuous release into the environment through various routes including excreta and the improper disposal of unused drugs [32]. The analysis of samples for these pollutants is problematic, because they are usually present in the environment in low concentrations, in addition to the laborious and time-consuming operations involved in preparing the samples for the analysis, which themselves may be a source of additional contaminations and errors. For these reasons, it is crucial to develop analytical methods for the detection and removal of these pollutants.

Many extraction techniques have evolved from the classical LLE and SPE. Nevertheless, these extraction techniques are time-consuming and require large amounts of toxic and expensive solvents. Therefore, many sample preparation techniques have been developed in order to improve the selectivity in extraction, to minimise the initial sample size, to facilitate the automation and to reduce the volume of organic solvent consumption. Nowadays, several microscale membrane based methods, such as HF-LPME, μ-SPE, SPMTE and TFME, have been developed in order to reduce the amount of solvents and facilitate low costs, the simplicity of the sample preparation procedure and an excellent clean-up. Although these established techniques have proven to be efficient in treating different complex matrices, however, these methods have several disadvantages in terms of the cost of the analysis, tedious experimental setup and possible analyte carryover effects.

Membrane technology has receiving a great attention in the last few decades. Membranes were synthesized with various materials which depended on the applications. The fabrication of polymeric membrane was one of the fastest growing fields of membrane technology. However, polymeric membranes could not meet the separation performances required especially in high operating pressure due to deficiencies problem [33]. The chemistry and structure of support materials like inorganic membranes were also one of the focus areas when inorganic membranes showed some positive results towards gas and liquid separation. However, the materials are somewhat lacking to meet the separation performance requirement because generally they have low permeability of the highly selective (dense) membranes at medium temperatures and difficulty in achieving high selectivities in large scale microporous membranes. Mixed matrix membrane (MMM) which is comprising polymeric and inorganic membranes presents an interesting approach for enhancing the separation performance. Nevertheless, MMM is yet to be commercialized as the material combinations are still in the research stage.

Material selection and method of preparation are the most important part in fabricating a membrane. An alternative nanoparticles adsorbent with greater selectivity and adsorption affinity should be explored for a wider range of potential chemical and biological applications. Although MMM has proven an enhancement of selectivity, it was noticed that most MMMs were endured with poor adhesion between the organic matrix and addictive particles [7]. Even MMM fabrication does have its disadvantages, but exploratory study of MMM should be conducted with different materials is worth to work since it has proven its ability to have high separation performance. Besides, the membrane must be easily manipulated to develop different sizes and shapes that could accommodate the needs of different experimental designs and sample size requirements.

Therefore, in this study, new and simple microextraction techniques based on the use of MMM in various design and sizes were developed. In addition, different materials were studied as adsorbent fillers in the preparation of MMM. Carbonaceous nanomaterials namely multiwall carbon nanotubes (MWCNTs) and

graphene are classified as inorganic fillers [34]. Several atomic simulation studies have suggested that CNTs can serve as an ideal candidate for adsorption and separation purposes as a result of their superior selectivity and permeability [7]. In the case where the CNTs are vertically aligned to the membrane surface, they would behave like pinholes that facilitate the rapid transport of the molecules passing through the channel of the nanotubes, leading to high permeability without selectivity [35]. The adsorption selectivity is strongly driven by the interaction potentials of the molecules with the graphitic CNT walls. Recent studies showed that graphene could be used as a viable and inexpensive filler substitute for CNTs in nanocomposites owing to the excellent in-plane mechanical, structural, thermal and electrical properties of graphite [36]. Graphite can be a good candidate as filler in MMMs due to its high aspect ratio [37]. The permeation rate of molecules diffusing through membranes can be decreased by embedding a high aspect ratio, impermeable particles that provide tortuous paths and reduce the cross sectional area available for permeation [38].

We also studied organic fillers such as C_{18} and hydrophilic lipophilic balance (HLB) particles. The C_{18} particles have been widely used as sorbents in SPE cartridges because the cartridge features a highly retentive alkyl-bonded phase for nonpolar to moderately polar compounds. The hydrophobic reversed phase material is retentive for most nonpolar compounds, and retains most organic analytes from aqueous matrices. The interaction of C_{18} particles with non-polar groups on the analytes of interest are via the Van der Waals force. The HLB is a hydrophilic modified styrene-based polymer developed for the solid phase extraction of a highly broad range of compounds from aqueous samples. The retention mechanism is based primarily on a reversed phase; however, because the polymer is hydrophilically modified, it is also appropriate for more polar compounds. This dual selectivity creates a Hydrophobic Lipophilic Balance (HLB). Moreover, because the HLB polymer phases contain polar functionalities, they are very resistant to over-drying, often rendering the associated extraction methods more reproducible/robust.

1.3 Research Objectives

The aim of this study is to develop miniaturised sample preparation techniques using the mixed matrix membrane microextraction for the analysis of organic pollutants and drugs in different types of sample matrices. The objectives of this research are as follows:

(a) To develop carbonaceous nanomaterials immobilised the mixed matrix membrane microextraction combined with high performance liquid chromatography ultraviolet detection (HPLC-UV) for the determination of polycyclic aromatic hydrocarbons (PAHs) in sewage pond water samples.

(b) To develop the dynamic mixed matrix membrane tip microextraction coupled with high performance liquid chromatography-ultraviolet detection (HPLC-UV) for the determination of non-steroidal anti-inflammatory drugs (NSAIDs) in effluent water samples.

(c) To develop the dynamic mixed matrix membrane tip extraction using capillary electrophoresis with contactless conductivity detection (CE-C^4D) for the determination of tobramycin in human plasma.

1.4 Scopes of Research

In this study, an innovative development of the mixed matrix membrane microextraction was developed for the analysis of organic pollutants and drugs in solutions. The potential to employ carbonaceous nanomaterials namely multiwall

carbon nanotubes (MWCNTs) and single layer graphene (SLG) as alternative nanofillers in flat sheet MMM were investigated for the analysis of polycyclic aromatic hydrocarbon (PAHs) in sewage pond water. Carbonaceous nanomaterials, also known as inorganic fillers have been selected due to their excellent ability to remove various inorganic and organic pollutants from large volumes of aqueous solution.

The study was expanded by fabricating the flat sheet MMM in a commercially available pipette tip. This new sample pre-treatment method denoted as mixed matrix membrane tip extraction (MMMTE) was developed for the analysis of non-steroidal anti-inflammatory drugs (NSAIDs) in effluent water samples using C_{18} particles. The performance of the C_{18} filler immobilised CTA membrane prepared in the pipette tip was compared with the flat sheet of the C_{18}-MMM in our previous study (Kamaruzaman et al., 2013). Furthermore, the new membrane tip device which is a miniaturised version of the previously introduced MMMTE approach was developed for the analysis of tobramycin in human plasma using the hydrophilic lipophilic balance (HLB).

The entire procedure was greatly simplified with automation and was able to accommodate a small solution volume. The HLB particles had been used due to their ability to extract aminoglycoside from the biological samples. The synthesised materials were characterised using field emission scanning electron microscopy (FESEM). Several organic pollutants (PAHs) and drugs (NSAIDs and tobramycin) were selected as model analytes. The separation and quantification of the target analytes were conducted by the HPLC-UV and CE-C^4D system. Several parameters affecting the microextraction techniques were comprehensively optimised and the analytical performances of the developed methods were evaluated, validated and applied to the quantification of the target analytes in solutions.

1.5 Significance of Research

This study is of significance to the development of the mixed matrix membrane microextraction technique in the sample preparation. This technique has been proposed to improve the speed and reduce the cost of the methods, eliminate or reduce the organic solvent consumptions and provide better sensitivity and selectivity for the quantitation of target analytes. In this study, mixed matrix membranes with different types of adsorbent particles were synthesised, demonstrated superior mechanical robustness and were proven to be suitable for the solid-liquid phase microextraction. The study also demonstrates that adsorbents with particles sizes in the nanometre range are capable of being dispersed and immobilised within a membrane for the effective adsorption analytes in an aqueous solution. Hence, this work will provide a great interest to further investigate the applicability of the mixed matrix membrane microextraction method since a wider range of nanomaterial adsorbents is expected to be used especially for the analysis of organic pollutants and drugs in solutions. Furthermore, this study has expanded the fabrication based on the concept of the mixed matrix membrane since the membrane could be developed in different sizes and shapes that could accommodate the needs of different experimental designs and sample size requirements. Through this work, various alternative microextraction methods can be implemented effectively with environmental benignity due to the small amounts of organic solvents used, simplicity of the microextraction setup and cost effectiveness. Moreover, this research will be useful for the establishment of more rapid and efficient methods for wider applications.

1.6 Outline of the Thesis

This thesis is divided into six chapters. The first chapter presents a detailed account of the research background, problem statement, objective, scope and

significance of the study. The second chapter provides the literature review on conventional extraction and microextraction techniques, mixed matrix membrane and model analytes in this study.

Chapter three describes the experimental methodology of the preparation and application of carbonaceous nanomaterials immobilised mixed matrix membrane microextraction for the analysis of the selected PAHs namely naphthalene, acenaphthene, fluorine, anthracene, phenanthrene, fluoranthene, pyrene and benz[a] anthracene in sewage pond water. Several important extraction parameters, such as the sample pH, ionic strength, sample volume, extraction time, desorption solvents and desorption time were optimised.

In chapter four, the experimental methodology of the preparation, characterisation and application of the C_{18}-mixed matrix membrane tip extraction for the determination of five selected NSAIDs in effluent water samples will be elaborated in further detail. The experimental parameters which influence microextraction efficiency, such as the pH value, salting out effect, dynamic extraction cycle, desorption solvent, and desorption time, were comprehensively optimised.

Chapter 5 reports the development of the hydrophilic lipophilic balance-mixed matrix membrane tip extraction (HLB-MMMTE) for the analysis of tobramycin in human plasma using capillary electrophoresis with contactless conductivity detection (CE-C^4D). The parameters affecting the extraction efficiency, such as the dynamic rinse time and desorption solvent were investigated in detail.

Finally, in Chapter 6, the overall conclusions and future directions for further studies were covered. This chapter summarises the overall results acquired, such as the optimised conditions and the analytical performance of the development

methods. Moreover, future directions are presented and discussed for a further improvement of the study.

REFERENCES

1. Augusto, F. and Valente, A. L. P. Applications of solid-phase microextraction to chemical analysis of live biological samples. *Trac-Trends in Analytical Chemistry*. 2002. 21:428-438.

2. Rezaee, M., Assadi, Y., Hosseinia, M. R. M., Aghaee, E., Ahmadi, F. and Berijani, S. Determination of organic compounds in water using dispersive liquid-liquid microextraction. *Journal of Chromatography A.* 2006. 1116: 1-9.

3. Pedersen-Bjergaard, S. and Rasmussen, K. E. Liquid-liquid-liquid microextraction for sample preparation of biological fluids prior to capillary electrophoresis. *Analytical Chemistry*. 1999. 71: 2650-2656.

4. See, H. H., Sanagi, M. M., Ibrahim, W. A. W. and Naim, A. A. Determination of triazine herbicides using membrane-protected carbon nanotubes solid phase membrane tip extraction prior to micro-liquid chromatography. *Journal of Chromatography A.* 2010. 1217: 1767-1772.

5. Basheer, C., Ainedhary, A. A., Rao, B. S. M., Valliyaveettil, S. and Lee, H. K. Development and application of porous membrane-protected carbon nanotube micro-solid-phase extraction combined with gas chromatography/mass spectrometry. *Analytical Chemistry*. 2006. 78: 2853-2858.

6. Bruheim, I., Liu, X. C. and Pawliszyn, J. 2003. Thin-film microextraction. *Analytical Chemistry.* 2003. 75: 1002-1010.

7. Goh, P. S., Ismail, A. F., Sanip, S. M., Ng, B. C. and Aziz, M. Recent advances of inorganic fillers in mixed matrix membrane for gas separation. *Separation and Purification Technology*. 2011. 81: 243-264.

8. Zhan, X., Lu, J., Tan, T. T. & Li, J. D. Mixed matrix membranes with HF acid etched ZSM-5 for ethanol/water separation: Preparation and

pervaporation performance. *Applied Surface Science.* 2012. 259**:** 547-556.

9. Anjum, M. W., De Clippel, F., Didden, J., Khan, A. L., Couck, S., Baron, G. V., Denayer, J. F. M., Sels, B. F. & Vankelecom, I. F. J. Polyimide mixed matrix membranes for CO2 separations using carbon-silica nanocomposite fillers. *Journal of Membrane Science*. 2015. 495: 121-129.

10. Azimi, H., Tezel, F. H. & Thibault, J. Effect of embedded activated carbon nanoparticles on the performance of polydimethylsiloxane (PDMS) membrane for pervaporation separation of butanol. *Journal of Chemical Technology and Biotechnology.* 2017. 92**,** 2901-2911.

11. Nejad, M. N., Asghari, M. & Afsari, M. Investigation of Carbon Nanotubes in Mixed Matrix Membranes for Gas Separation: A Review. ChemBioEng Reviews. 2016. 3: 276-298.

12. Sekizkardes, A. K., Zhou, X., Nulwala, H. B., Hopkinson, D. & Venna, S. R. Ionic cross-linked polyether and silica gel mixed matrix membranes for CO2 separation from flue gas. *Separation and Purification Technology*. 2018. 191: 301-306.

13. Zhao, D., et al., Gas separation properties of poly(amide-6-b-ethylene oxide)/amino modified multi-walled carbon nanotubes mixed matrix membranes. *Journal of Membrane Science*. 2014. 467: p. 41-47.

14. Zulhairun, A. K. and Ismail, A. F. The role of layered silicate loadings and their dispersion states on the gas separation performance of mixed matrix membrane. *Journal of Membrane Science.* 2014. 468: 20-30.

15. Dashtarzhandi, M. R., Ismail, A. F., Matsuura, T., Ng, B. C. and Abdullah, M. S. Fabrication and characterization of porous polyetherimide/montmorillonite hollow fiber mixed matrix membranes for CO_2 absorption via membrane contactor. *Chemical Engineering Journal*, 2015. 269: 51-59.

16. Lin, R. J., Ge, L., Liu, S. M., Rudolph, V. and Zhu, Z. H. Mixed-Matrix Membranes with Metal-Organic Framework-Decorated CNT Fillers for Efficient CO_2 Separation. *Acs Applied Materials and Interfaces.* 2015. 7: 14750-14757.

17. Gh, A.S. and A.H. Navarchian, Matrimid–polyaniline/clay mixed-matrix membranes with plasticization resistance for separation of CO2 from natural gas. *Polymers for Advanced Technologies*. 2016. 27(9): 1228-1236.

18. Zarshenas, K., Raisi, A. and Aroujalian, A. Mixed matrix membrane of nano-zeolite NaX/poly (ether-block-amide) for gas separation applications. *Journal of Membrane Science*. 2016. 510: 270-283.

19. Jamil, A., Ching, O. P. and Shariff, A. M. Mixed matrix hollow fibre membrane comprising polyetherimide and modified montmorillonite with improved filler dispersion and CO_2/CH_4 separation performance. *Applied Clay Science*. 2017. 143: 115-124.

20. Boroglu, M. S., Ugur, M. and Boz, I. Enhanced gas transport properties of mixed matrix membranes consisting of Matrimid and RHO type ZIF-12 particles. *Chemical Engineering Research and Design*. 2017. 123: 201-213.

21. Eltahir Mustafa, S. G. E., Mannan, H. A., Nasir, R., Mohshim, D. F. and Mukhtar, H. Synthesis, characterization, and performance evaluation of PES/EDA-functionalized TiO_2 mixed matrix membranes for CO_2/CH_4 separation. *Journal of Applied Polymer Science*. 2017. 134: 45346-n/a.

22. Le, N. L., Wang, Y. and Chung, T. S. Pebax/POSS mixed matrix membranes for ethanol recovery from aqueous solutions via pervaporation. *Journal of Membrane Science.* 2011. 379: 174-183.

23. Jamshidi Gohari, R., Lau, W. J., Matsuura, T. and Ismail, A. F. Fabrication and characterization of novel PES/Fe–Mn binary oxide UF mixed matrix membrane for adsorptive removal of As(III) from contaminated water solution. *Separation and Purification Technology*. 2013. 118: 64-72.

24. Kamaruzaman, S., Hauser, P. C., Sanagi, M. M., Ibrahim, W. A. W., Endud, S. and See, H. H. A simple microextraction and preconcentration approach based on a mixed matrix membrane. *Analytica Chimica Acta*. 2013a. 783: 24-30.

25. Mukherjee, R. and De, S. Adsorptive removal of phenolic compounds using cellulose acetate phthalate–alumina nanoparticle mixed matrix membrane. Journal of Hazardous *Materials*. 2014. 265: 8-19.

26. Siddique, H., Rundquist, E., Bhole, Y., Peeva, L. G. and Livingston, A. G. Mixed matrix membranes for organic solvent nanofiltration. *Journal of Membrane Science*. 2014. 452: 354-366.
27. Han, Y. J., Wang, K. H., Lai, J. Y. and Liu, Y. L. Hydrophilic chitosan-modified polybenzoimidazole membranes for pervaporation dehydration of isopropanol aqueous solutions. *Journal of Membrane Science*. 2014b. 463: 17-23.

28. Chatterjee, S. and De, S. Adsorptive removal of fluoride by activated alumina doped cellulose acetate phthalate (CAP) mixed matrix membrane. *Separation and Purification Technology*. 2014. 125: 223-238.

29. Ghaemi, N., Madaeni, S. S., Daraei, P., Rajabi, H., Shojaeimehr, T., Rahimpour, F. and Shirvani, B. PES mixed matrix nanofiltration membrane embedded with polymer wrapped MWCNT: Fabrication and performance optimization in dye removal by RSM. *Journal of Hazardous Materials.* 2015. 298: 111-121.

30. Mukhtar, N. H. and See, H. H. Carbonaceous nanomaterials immobilised mixed matrix membrane microextraction for the determination of polycyclic aromatic hydrocarbons in sewage pond water samples. *Analytica Chimica Acta*. 2016. 931: 57-63.

31. Farahani, M., Hua, D. and Chung, T. S. Cross-linked mixed matrix membranes consisting of carboxyl-functionalized multi-walled carbon nanotubes and P84 polyimide for organic solvent nanofiltration (OSN). *Separation and Purification Technology*. 2017. 186: 243-254.

32. Stahl-Timmins, W., White, M., Depledge, M., Fleming, L. & Redshaw, C. The Pharma Transport Town: Understanding the Routes to Sustainable Pharmaceutical Use. *Science*. 2013. 339: 515-515.

33. Mohshim, D. F., Mukhtar, H. B., Man, Z. & Nasir, R. Latest Development on Membrane Fabrication for Natural Gas Purification: A Review. *Journal of Engineering,* 2013**,** 7.

34. Jusoh, N., Yeong, Y. F., Chew, T. L., Lau, K. K. & Shariff, A. M. Current Development and Challenges of Mixed Matrix Membranes for CO2/CH4 Separation. *Separation & Purification Reviews. 2016.* 45**:** 321-344.

35. Ge, L., Du, A., Hou, M., Rudolph, V. & Zhu, Z. Enhanced hydrogen separation by vertically-aligned carbon nanotube membranes with zeolite imidazolate frameworks as a selective layer. 2012. *RSC Advances*. 2012. 2: 11793-11800.

36. Singh, V., Joung, D., Zhai, L., Das, S., Khondaker, S. I. & Seal, S. Graphene based materials: Past, present and future. *Progress in Materials Science*. 2011. 56: 1178-1271.

37. Kim, H. & Macosko, C. W. Morphology and Properties of Polyester/Exfoliated Graphite Nanocomposites. *Macromolecules.* 2008. 41: 3317-3327.

38. Cussler, E. L., Hughes, S.E., Ward Iii, W.J. And Aris, R. Barrier Membranes. *Journal of Membrane Science*. 1988. 161-174.

39. Dai, X. P., Jia, X. N., Zhao, P., Wang, T., Wang, J., Huang, P. T., He, L. and Hou, X. H. A combined experimental/computational study on metal - organic framework MIL-101(Cr) as a SPE sorbent for the determination of sulphonamides in environmental water samples coupling with UPLC-MS/MS. *Talanta*. 2016. 154: 581-588.

40. Tran, N. H., Chen, H. J., Do, T. V., Reinhard, M., Ngo, H. H., He, Y. L. and Gin, K. Y. H. Simultaneous analysis of multiple classes of antimicrobials in environmental water samples using SPE coupled with UHPLC-ESI-MS/MS and isotope dilution. *Talanta*. 2016. 159: 163-173.

41. Gurke, R., Rossmann, J., Schubert, S., Sandmann, T., Rossler, M., Oertel, R. and Fauler, J. Development of a SPE-HPLC-MS/MS method for the determination of most prescribed pharmaceuticals and related metabolites in urban sewage samples. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences*. 2015. 990: 23-30.

42. Paiga, P., Lolic, A., Hellebuyck, F., Santos, L., Correia, M. and Delerue-Matos, C. Development of a SPE-UHPLC-MS/MS methodology for the determination of non-steroidal anti-inflammatory and analgesic pharmaceuticals in seawater. *Journal of Pharmaceutical and Biomedical Analysis.* 2015. 106: 61-70.

43. Islam, A., Kumar, S., Zaidi, N. and Ahmad, H. SPE coupled to AAS trace determination of Cd(II) and Zn(II) in food samples using amine functionalized GMA-MMA-EGDMA terpolymer: Isotherm and kinetic studies. *Food Chemistry*. 2016. 213: 775-783.

44. Tuzimski, T. and Rejczak, T. Application of HPLC-DAD after SPE/QuEChERS with ZrO_2-based sorbent in d-SPE clean-up step for pesticide analysis in edible oils. *Food Chemistry*. 2016. 190: 71-79.

45. Arthur, C. L. and Pawliszyn, J. Solid-Phase Microextraction With Thermal-Desorption Using Fused-Silica Optical Fibers. *Analytical Chemistry*. 1990. 62: 2145-2148.

46. Arthur, C. L., Potter, D. W., Buchholz, K. D., Motlagh, S. and Pawliszyn, J. Solid-Phase Microextraction For The Direct Analysis Of Water - Theory And Practice. Lc Gc-*Magazine of Separation Science*. 1992. 10: 656.

47. Saraji, M. and Bidgoli, A. A. H. Dispersive liquid-liquid microextraction using a surfactant as disperser agent. *Analytical and Bioanalytical Chemistry*. 2010. 397: 3107-3115.

48. Pawliszyn, J. *Solid phase microextraction: theory and practice*. Ontario. Wiley-VCH, Inc. 1997.

49. Zhao, L. and Lee, H. K.. Application of static liquid-phase microextraction to the analysis of organochlorine pesticides in water. *Journal of Chromatography A*. 2001. 919: 381-388.
50. Huang, S. P. and Huang, S. D. Determination of organochlorine pesticides in water using solvent cooling assisted dynamic hollow-fiber-supported headspace liquid-phase microextraction. *Journal of Chromatography A.* 2007. 1176: 19-25.

51. He, Y. and Lee, H. K. Liquid phase microextraction in a single drop of organic solvent by using a conventional microsyringe. *Analytical Chemistry*. 1997. 69: 4634-4640.

52. Zhang, J., Su, T. and Lee, H. K. Development and application of microporous hollow fiber protected liquid-phase microextraction via gaseous diffusion to the determination of phenols in water. Journal of Chromatography A. 2006a. 1121: 10-15.

53. Sarafraz-Yazdi, A. and Amiri, A. Liquid-phase microextraction. *TrAC Trends in Analytical Chemistry*. 2010. 29(1): 1-14.

54. Vergel, C., Montoya, R., Mendiguchia, C., Garcia-Vargas, M. and Moreno, C. HF-LPME as a green alternative for the preconcentration of nickel in natural waters. *Analytical and Bioanalytical Chemistry.* 2012. 404: 665-670.

55. Meng, L., Zhang, W. W., Meng, P. J., Zhu, B. L. and Zheng, K. F. Comparison of hollow fiber liquid-phase microextraction and ultrasound-assisted low-density solvent dispersive liquid-liquid microextraction for the determination of drugs of abuse in biological samples by gas chromatography-mass spectrometry. *Journal of Chromatography B.* 2015. 989: 46-53.

56. Jiang, H. M., Hu, B., Chen, B. B. and Zu, W. Q. Hollow fiber liquid phase microextraction combined with graphite furnace atomic absorption spectrometry for the determination of methylmercury in human hair and sludge samples. *Spectrochimica Acta Part B-Atomic Spectroscopy.* 2008. 63: 770-776.

57. Lee, J., Lee, H. K., Rasmussen, K. E. and Pedersen-Bjergaard, S. Environmental and bioanalytical applications of hollow fiber membrane liquid-phase microextraction: A review. *Analytica Chimica Acta*. 2008. 624: 253-268.

58. Tian, H., Hühmer, A. F. R. and Landers, J. P. Evaluation of Silica Resins for Direct and Efficient Extraction of DNA from Complex Biological Matrices in a Miniaturized Format. *Analytical Biochemistry.* 2000. 283: 175-191.

59. Basheer, C., Chong, H. G., Hii, T. M. and Lee, H. K. Application of porous membrane-protected micro-solid-phase extraction combined with HPLC for the analysis of acidic drugs in wastewater. *Analytical Chemistry*. 2007. 79: 6845-6850.

60. Ridgway, K., Lalljie, S. P. D. and Smith, R. M. Sample preparation techniques for the determination of trace residues and contaminants in foods. *Journal of Chromatography A.* 2007. 1153: 36-53.

61. Pedersen-Bjergaard, S. and Rasmussen, K. E. Electrokinetic migration across artificial liquid membranes - New concept for rapid sample preparation of biological fluids. *Journal of Chromatography A.* 2006. 1109: 183-190.

62. Berduque, A. and Arrigan, D. W. M. Selectivity in the coextraction of cation and anion by electrochemically modulated liquid-liquid extraction. *Analytical Chemistry*. 2006. 78: 2717-2725.

63. Middelthon-Bruer, T. M., Gjelstad, A., Rasmussen, K. E. and Pedersen-Bjergaard, S. Parameters affecting electro membrane extraction of basic drugs. *Journal of Separation Science*. 2008. 31: 753-759.

64. Gjelstad, A. and Pedersen-Bjergaard, S. 2013. Recent developments in electromembrane extraction. *Analytical Methods*. 2013. 5: 4549-4557.

65. Kermani, F. R. and Pawliszyn, J. Sorbent Coated Glass Wool Fabric as a Thin Film Microextraction Device. *Analytical Chemistry*. 2012. 84: 8990-8995.

66. Jiang, R. F. and Pawliszyn, J. Preparation of a Particle-Loaded Membrane for Trace Gas Sampling. *Analytical Chemistry*. 2014. 86: 403-410.

67. Togunde, O. P., Cudjoe, E., Oakes, K. D., Mirnaghi, F. S., Servos, M. R. and Pawliszyn, J. Determination of selected pharmaceutical residues in wastewater using an automated open bed solid phase microextraction system. *Journal of Chromatography A*. 2012. 1262: 34-42.

68. Mirnaghi, F. S. and Pawliszyn, J. Development of coatings for automated 96-blade solid phase microextraction-liquid chromatography-tandem mass spectrometry system, capable of extracting a wide polarity range of analytes from biological fluids. *Journal of Chromatography A*. 2012. 1261: 91-98.

69. Mirnaghi, F. S., Mousavi, F., Rocha, S. M. and Pawliszyn, J. Automated determination of phenolic compounds in wine, berry, and grape samples using 96-blade solid phase microextraction system coupled with liquid chromatography-tandem mass spectrometry. *Journal of Chromatography A*. 2013. 1276: 12-19.

70. Jiang, R. F. and Pawliszyn, J. Thin-film microextraction offers another geometry for solid-phase microextraction. *Trac-Trends in Analytical Chemistry*. 2012. 39: 245-253.

71. Chung, T. S., Jiang, L. Y., Li, Y. and Kulprathipanja, S. Mixed matrix membranes (MMMs) comprising organic polymers with dispersed inorganic fillers for gas separation. *Progress in Polymer Science*. 2007. 32: 483-507.

72. Mahajan, R. and Koros, W. J. Factors controlling successful formation of mixed-matrix gas separation materials. *Industrial and Engineering Chemistry Research*. 2000. 39: 2692-2696.

73. Zimmerman, C. M., Singh, A. and Koros, W. J. Tailoring mixed matrix composite membranes for gas separations. *Journal of Membrane Science*. 1997. 137: 145-154.

74. Tetala, K. K. R. and Stamatialis, D. F. Mixed matrix membranes for efficient adsorption of copper ions from aqueous solutions. *Separation and Purification Technology*. 2013. 104: 214-220.

75. Aroon, M. A., Ismail, A. F., Matsuura, T. and Montazer-Rahmati, M. M. Performance studies of mixed matrix membranes for gas separation: A review. *Separation and Purification Technology*. 2010. 75: 229-242.

76. Jiang, L. Y., Chung, T. S., Cao, C., Huang, Z. and Kulprathipanja, S. Fundamental understanding of nano-sized zeolite distribution in the formation of the mixed matrix single- and dual-layer asymmetric hollow fiber membranes. *Journal of Membrane Science*. 2005. 252: 89-100.

77. Jiang, L. Y., Chung, T. S. and Kulprathipanja, S. An investigation to revitalize the separation performance of hollow fibers with a thin mixed matrix composite skin for gas separation. *Journal of Membrane Science*. 20006. 276: 113-125.

78. Li, Y., Chung, T.-S., Huang, Z. and Kulprathipanja, S. Dual-layer polyethersulfone (PES)/BTDA-TDI/MDI co-polyimide (P84) hollow fiber membranes with a submicron PES–zeolite beta mixed matrix dense-selective layer for gas separation. *Journal of Membrane Science*. 2006. 277: 28-37.

79. Cong, H., Radosz, M., Towler, B. F. and Shen, Y. Polymer–inorganic nanocomposite membranes for gas separation. *Separation and Purification Technology*. 2007. 55: 281-291.

80. Kim, S., Pechar, T. W. and Marand, E. Poly(imide siloxane) and carbon nanotube mixed matrix membranes for gas separation. *Desalination*. 2006. 192: 330-339.

81. Zhang, Y., Li, H., Lin, J., Li, R. and Liang, X. Preparation and characterization of zirconium oxide particles filled acrylonitrile-methyl acrylate-sodium sulfonate acrylate copolymer hybrid membranes. *Desalination*. 2006b. 192: 198-206.

82. Husain, S. and Koros, W. J. Mixed matrix hollow fiber membranes made with modified HSSZ-13 zeolite in polyetherimide polymer matrix for gas separation. *Journal of Membrane Science.* 2007. 288: 195-207.

83. Kim, S. and Marand, E. High permeability nano-composite membranes based on mesoporous MCM-41 nanoparticles in a polysulfone matrix. *Microporous and Mesoporous Materia*ls. 2008. 114: 129-136.

84. Rafizah, W. A. W. and Ismail, A. F. Effect of carbon molecular sieve sizing with poly(vinyl pyrrolidone) K-15 on carbon molecular sieve–polysulfone mixed matrix membrane. *Journal of Membrane Science.* 2008. 307: 53-61.

85. Kesting, R. E., Fritzsche, A. K., Murphy, M. K., Cruse, C. A., Handermann, A. C., Malon, R. F. and Moore, M. D. The second-generation polysulfone gas-separation membrane. I. The use of lewis acid: Base complexes as transient templates to increase free volume. *Journal of Applied Polymer Science.* 1990. 40: 1557-1574.

86. Mukherjee, R. and De, S. Adsorptive removal of phenolic compounds using cellulose acetate phthalate–alumina nanoparticle mixed matrix membrane. Journal of Hazardous *Materials*. 2014. 265: 8-19.

87. He, J., Cui, A., Deng, S. & Chen, J. P. Treatment of methylene blue containing wastewater by a cost-effective micro-scale biochar/polysulfone mixed matrix hollow fiber membrane: Performance and mechanism studies. *Journal of Colloid and Interface Science.* 2018. 512**:** 190-197.

88. Amedi, H.R. and M. Aghajani. Aminosilane-functionalized ZIF-8/PEBA mixed matrix membrane for gas separation application. *Microporous and Mesoporous Materials*. 2017. 247: 124-135.

89. Mukherjee, R. and S. De. Adsorptive removal of nitrate from aqueous solution by polyacrylonitrile–alumina nanoparticle mixed matrix hollow-fiber membrane. *Journal of Membrane Science*. 2014. 466: 281-292.

90. Zinadini, S., Zinatizadeh, A. A., Rahimi, M., Vatanpour, V. & Zangeneh, H. Preparation of a novel antifouling mixed matrix PES membrane by embedding graphene oxide nanoplates. *Journal of Membrane Science*. 2014. 453: 292-301.

91. Iijima, S. Helical microtubules of graphitic carbon. *Nature*. 1991. 354(6348): 56-58.

92. Girao, E. C., Fagan, S. B., Zanella, I. and Souza, A. G. Nicotine adsorption on single wall carbon nanotubes. *Journal of Hazardous Materials*. 2010. 184: 678-683.

93. Yang, C. G., Ji, X. J. and Lan, X. Z. Preparation of PDMS-coated microspheres by sol-gel method for sorptive extraction of PAHs. *Chinese Chemical Letters*. 2008. 19: 996-999.

94. Wang, X. L., Tao, S. and Xing, B. S. Sorption and Competition of Aromatic Compounds and Humic Acid on Multiwalled Carbon Nanotubes. *Environmental Science and Technology*. 2009. 43: 6214-6219.

95. Chen, W., Duan, L., Wang, L. and Zhu, D. Adsorption of Hydroxyl- and Amino-Substituted Aromatics to Carbon Nanotubes. *Environmental Science and Technology*. 2008. 42: 6862-6868.

96. Chen, W., Duan, L. and Zhu, D. Q. Adsorption of polar and nonpolar organic chemicals to carbon nanotubes. *Environmental Science and Technology*. 2007. 41: 8295-8300.

97. Wang, Z. Y., Yu, X. D., Pan, B. and Xing, B. S. Norfloxacin Sorption and Its Thermodynamics on Surface-Modified Carbon Nanotubes. *Environmental Science and Technology*. 2010. 44: 978-984.

98. Zhang, S. X., Niu, H. Y., Zhang, Y. Y., Liu, J. S., Shi, Y. L., Zhang, X. L. and Cai, Y. Q. Biocompatible phosphatidylcholine bilayer coated on magnetic nanoparticles and their application in the extraction of several polycyclic aromatic hydrocarbons from environmental water and milk samples. *Journal of Chromatography A*. 2012. 1238: 38-45.

99. Pan, B. and Xing, B. S. Adsorption Mechanisms of Organic Chemicals on Carbon Nanotubes. *Environmental Science and Technology*. 2008. 42: 9005-9013.

100. Allen, M. J., Tung, V. C. and Kaner, R. B. Honeycomb Carbon: A Review of Graphene. *Chemical Reviews*. 2010. 110: 132-145.

101. Geim, A. K. and Novoselov, K. S. The rise of graphene. *Natural Material*. 2007. 6: 183-191.

102. Novoselov, K. S., Geim, A. K., Morozov, S. V., Jiang, D., Zhang, Y., Dubonos, S. V., Grigorieva, I. V. and Firsov, A. A. Electric field effect in atomically thin carbon films. *Science*. 2014. 306: 666-669.

103. Mehrali, M., Latibari, S. T., Mahlia, T. M. I. and Metselaar, H. S. C. Preparation and properties of highly conductive palmitic acid/graphene oxide composites as thermal energy storage materials. *Energy*. 2013. 58: 628-634.

104. Yang, X., Li, J. X., Wen, T., Ren, X. M., Huang, Y. S. and Wang, X. K. Adsorption of naphthalene and its derivatives on magnetic graphene composites and the mechanism investigation. *Colloids and Surfaces a-Physicochemical and Engineering Aspects*. 2013: 422: 118-125.

105. Wang, J. G., Wang, Y. S., He, D. W., Liu, Z. Y., Wu, H. P., Wang, H. T., Zhao, Y., Zhang, H., Yang, B. Y., Xu, H. T. and Fu, M. Direct Synthesis of Hydrophobic Graphene-Based Nanosheets via Chemical Modification of Exfoliated Graphene Oxide. *Journal of Nanoscience and Nanotechnology*. 2012. 12: 6460-6466.

106. Wang, Y. X., Wang, S. H., Niu, H. Y., Ma, Y. R., Zeng, T., Cai, Y. Q. and Meng, Z. F. Preparation of polydopamine coated Fe_3O_4 nanoparticles and their application for enrichment of polycyclic aromatic hydrocarbons from environmental water samples. *Journal of Chromatography A*. 2013. 1283: 20-26.

107. Shen, T., Shen, Y., Ma, X. T., Gao, W. T., Cao, M., Gu, F. and Wang, L. J. *Preparation of Graphene Films and their Applications in dye-sensitized solar cells*. In: HUANG. Y. M. (ed.) Progress in Functional Materials. 2013.

108. Park, S., Vosguerichian, M. and Bao, Z. A. A review of fabrication and applications of carbon nanotube film-based flexible electronics. *Nanoscale*. 2013. 5: 1727-1752.

109. Pumera, M., Scipioni, R., Iwai, H., Ohno, T., Miyahara, Y. and Boero, M. A Mechanism of Adsorption of β-Nicotinamide Adenine Dinucleotide on Graphene Sheets: Experiment and Theory. *Chemistry – A European Journal*. 2009. 15: 10851-10856.

110. Tang, Q. and Zhou, Z. Graphene-analogous low-dimensional materials. *Progress in Materials Science*. 2013. 58: 1244-1315.

111. Cheng, C., Li, S., Zhao, J., Li, X. X., Liu, Z. Y., Ma, L., Zhang, X., Sun, S. D. and Zhao, C. S. Biomimetic assembly of polydopamine-layer on graphene: Mechanisms, versatile 2D and 3D architectures and pollutant disposal. *Chemical Engineering Journal*. 2013. 228: 468-481.

112. Zhang, W. X., Yan, H., Li, H. J., Jiang, Z. W., Dong, L., Kan, X. W., Yang, H., Li, A. M. and Cheng, R. S. Removal of dyes from aqueous solutions by straw based adsorbents: Batch and column studies. *Chemical Engineering Journal*. 2011. 168: 1120-1127.

113. Cabrera-Sanfelix, P. Adsorption and Reactivity of CO2 on Defective Graphene Sheets. *Journal of Physical Chemistry A*. 2009. 113: 493-498.

114. Plenis, A., Frolow, A., Rekowska, N., Oledzka, I., Kowalski, P., Bien, E., Krawczyk, M. A., Adamkiewicz-Drozynska, E. and Baczek, T. Determination of Bendamustine in Human Plasma and Urine by LC-FL Methods: Application in a Drug Monitoring. *Chromatographia*. 2016. 79: 861-873.

115. Gullick, D. R., Bruckner, J. V., White, C. A., Chen, C., Cummings, B. S. and Bartlett, M. G. Quantitation of Deltamethrin in Rat Liver and Muscle Homogenates Using Dispersive Solid-Phase Extraction with GC-NCI-MS. *Journal of Aoac International*.2016. 99: 813-820.

116. Moosavi, S. M., Shekar, K., Fraser, J., Smith, M. T. and Ghassabian, S. High-throughput assay for quantification of the plasma concentrations of thiopental using automated solid phase extraction (SPE) directly coupled to LC-MS/MS instrumentation. *Journal of Chromatography B*. 2016. 1038: 80-87.

117. Archana, G., Dhodapkar, R. and Kumar, A. Offline solid-phase extraction for preconcentration of pharmaceuticals and personal care products in environmental water and their simultaneous determination using the reversed phase high-performance liquid chromatography method. *Environmental Monitoring and Assessment*. 2016. 188.

118. Valente, N. I. P., Tarelho, S., Castro, A. L., Silvestre, A. and Teixeira, H. M. Analysis of organophosphorus pesticides in whole blood by GC-MS-mu ECD with forensic purposes. *Journal of Forensic and Legal Medicine*. 2015. 33: 28-34.

119. Rao, T. N., Reddy, A. M., Murthy, S., Revathi, P. and Kumar, K. S. Pre-concentration of Pesticide Residues in Environmental Water Samples Using Silica Nanoparticles and Identification of Residues By GC-MS Method. *Oriental Journal of Chemistry*. 2016. 32: 2221-2230.

120. Sousa, A. S., Duavi, W. C., Cavalcante, R. M., Milhome, M. A. L. and Do Nascimento, R. F. Estimated Levels of Environmental Contamination and Health Risk Assessment for Herbicides and Insecticides in Surface Water of Ceara, Brazil. *Bulletin of Environmental Contamination and Toxicology*. 2016. 96: 90-95.

121. Rahman, M. M., Abd El-Aty, A. M., Kim, S. W., Na, T. W., Shin, H. C., Hong, S. M. and Shim, J. H. A simple extraction method for the detection and quantification of polyoxin D, a nucleoside antibiotic, in butterbur using UPLC-MS/MS. *Food Chemistry*. 2017. 221: 683-688.

122. Zhu, W.-X., Yang, J.-Z., Wei, W., Liu, Y.-F. and Zhang, S.-S. Simultaneous determination of 13 aminoglycoside residues in foods of animal origin by liquid chromatography–electrospray ionization tandem mass spectrometry with two consecutive solid-phase extraction steps. *Journal of Chromatography A*. 2008a. 1207: 29-37.

123. Rajput, N. and Lakhani, A. Measurements of polycyclic aromatic hydrocarbons in an urban atmosphere of Agra, India. *Atmosfera*. 2010. 23: 165-183.

124. Pelletier, M. C., Burgess, R. M., Ho, K. T., Kuhn, A., Mckinney, R. A. and Ryba, S. A. Phototoxicity of individual polycyclic aromatic hydrocarbons and petroleum to marine invertebrate larvae and juveniles. *Environmental Toxicology and Chemistry*. 1997. 16: 2190-2199.

125. Staal, Y. C. M., Hebels, D., Van Herwijnen, M. H. M., Gottschalk, R. W. H., Van Schooten, F. J. and Van Delft, J. H. M. Binary PAH mixtures cause additive or antagonistic effects on gene expression but synergistic effects on DNA adduct formation. *Carcinogenesis.* 2007. 28: 2632-2640.

126. Zeledon-Toruno, Z. C., Lao-Luque, C., De Las Heras, F. X. C. and Sole-Sardans, M. Removal of PAHs from water using an immature coal (leonardite). *Chemosphere*. 2007. 67: 505-512.

127. Menzie, C. A., Potocki, B. B. and Santodonato, J. Exposure to carcinogenic PAHs in the environment. *Environmental Science and Technology*. 1992. 26: 1278-1284.

128. Shahbazi, A., Zakaria, M. P., Yap, C. K., Surif, S., Bakhtiari, A. R., Chandru, K., Bahry, P. S. & Sakari, M. Spatial distribution and sources of polycyclic aromatic hydrocarbons (PAHs) in green mussels (Perna viridis) from coastal areas of Peninsular Malaysia: implications for source identification of perylene. *International Journal of Environmental Analytical Chemistry,* 2010. 90**:** 14-30. *Chromatography A,* 1153**,** 36-53.

129. Saha, M., Togo, A., Mizukawa, K., Murakami, M., Takada, H., Zakaria, M. P., Chiem, N. H., Tuyen, B. C., Prudente, M., Boonyatumanond, R., Sarkar, S. K., Bhattacharya, B., Mishra, P. & Tana, T. S. Sources of sedimentary PAHs in tropical Asian waters: Differentiation between pyrogenic and petrogenic sources by alkyl homolog abundance. *Marine Pollution Bulletin.* 2009. 58**:** 189-200.

130. Organization, W. H. 2003. Bakgroud Document for Preparation of WHO Guidelines for Drinking-water Quality.

131. Portet-Koltalo, F., Oukebdane, K., Robin, L., Dionnet, F. and Desbene, P. L. Quantification of volatile PAHs present at trace levels in air flow by aqueous trapping - SPE and HPLC analysis with fluorimetric detection. *Talanta.* 2007. 71: 1825-1833.

132. Hawthorne, S. B., Grabanski, C. B., Miller, D. J. and Kreitinger, J. P. Solid-Phase Microextraction Measurement of Parent and Alkyl Polycyclic Aromatic Hydrocarbons in Milliliter Sediment Pore Water Samples and Determination of KDOC Values. *Environmental Science and Technology*. 2005. 39: 2795-2803.

133. Kavran, G. and Erim, F. B. Separation of polycyclic aromatic hydrocarbons with sodium dodecylbenzenesulfonate in electrokinetic chromatography. *Journal of Chromatography A.* 2002. 949: 301-305.

134. Fan, R. F., Ramage, R., Wang, D. L., Zhou, J. Q. and She, J. W. Determination of ten monohydroxylated polycyclic aromatic hydrocarbons by liquid-liquid extraction and liquid chromatography/tandem mass spectrometry. *Talanta,* 2012. 93: 383-391.

135. Busetti, F., Heitz, A., Cuomo, M., Badoer, S. and Traverso, P. Determination of sixteen polycyclic aromatic hydrocarbons in aqueous and solid samples from an Italian wastewater treatment plant. *Journal of Chromatography A*. 2006. 1102: 104-115.

136. Talley, N. J., Evans, J. M., Fleming, K. C., Harmsen, W. S., Zinsmeister, A. R. and Melton, L. J. 1995. Nonsteroidal Antiinflammatory Drugs And Dyspepsia In The Elderly. *Digestive Diseases and Sciences.* 1995. 40: 1345-1350.

137. Petruzzelli, M., Vacca, M., Moschetta, A., Sasso, R. C., Palasciano, G., Van Erpecum, K. J. and Portincasa, P. Intestinal mucosal damage caused by non-steroidal anti-inflammatory drugs: Role of bile salts. *Clinical Biochemistry*. 2007. 40: 503-510.

138. Dwivedi, A. D., Gopal, K. and Jain, R. Strengthening adsorption characteristics of non-steroidal anti-inflammatory drug onto microwave-assisted mesoporous material: Process design, mechanism and characterization. *Chemical Engineering Journal*. 2011. 168: 1279-1288.

139. Khetan, S. K. and Collins, T. J. Human pharmaceuticals in the aquatic environment: A challenge to green chemistry. *Chemical Reviews*. 2007. 107: 2319-2364.

140. Payan, M. R., Lopez, M. A. B., Fernandez-Torres, R., Mochon, M. C. and Ariza, J. L. G. Application of hollow fiber-based liquid-phase microextraction (HF-LPME) for the determination of acidic pharmaceuticals in wastewaters. *Talanta.* 2010. 82: 854-858.

141. Payan, M. R., Lopez, M. A. B., Torres, R. F., Navarro, M. V. and Mochon, M. C. Electromembrane extraction (EME) and HPLC determination of non-steroidal anti-inflammatory drugs (NSAIDs) in wastewater samples. *Talanta*. 2011. 85: 394-399.

142. Kamaruzaman, S., Sanagi, M. M., Endud, S., Ibrahim, W. A. W. and Yahaya, N. MCM-41 solid phase membrane tip extraction combined with liquid chromatography for the determination of non-steroidal anti-inflammatory drugs in human urine. *Journal of Chromatography B.* 2013b. 940: 59-65.

143. Wang, M. H., Hu, B., Yang, C., Zhang, Z. H., He, L. H., Fang, S. M., Qu, X. W. & Zhang, Q. X. Electrochemical biosensing based on protein-directed carbon nanospheres embedded with SnOx and TiO2 nanocrystals for sensitive detection of tobramycin. *Biosensors & Bioelectronics.* 2018. 99**:** 176-185.

144. Bernardi, P. M., Barreto, F. & Costa, T. D. Application of a LC-MS/MS method for evaluating lung penetration of tobramycin in rats by microdialysis. *Journal of Pharmaceutical and Biomedical Analysis.2017.* 134**:** 340-345.

145. He, S., Chen, Q., Sun, Y., Zhu, Y., Luo, L., Li, J. & Cao, Y. Determination of tobramycin in soil by HPLC with ultrasonic-assisted extraction and solid-phase extraction. *Journal of Chromatography B. 2011*. 879**:** 901-907.

146. Aronson, J. K. and Reynolds, D. J. ABC of monitoring drug therapy. Aminoglycoside antibiotics. *British Medical Journal*. 1992. 305: 1421-1424.

147. Scida, K., Stege, P. W., Haby, G., Messina, G. A. and Garcia, C. D. Recent applications of carbon-based nanomaterials in analytical chemistry: Critical review. *Analytica Chimica Acta*. 2011. 691: 6-17.

148. Zhang, B. T., Zheng, X. X., Li, H. F. and Lin, J. M. Application of carbon-based nanomaterials in sample preparation: A review. *Analytica Chimica Acta*. 2013. 784: 1-17.

149. Geim, A. K. Graphene: Status and Prospects. *Science*. 2009. 324: 1530-1534.

150. Guo, S. J. and Dong, S. J. Graphene nanosheet: synthesis, molecular engineering, thin film, hybrids, and energy and analytical applications. *Chemical Society Reviews*. 2011. 40: 2644-2672.

151. Han, Q., Wang, Z. H., Zhang, X. Q. and Ding, M. Y. Graphene and Its Composites in Sample Preparation. *Progress in Chemistry*. 2014a. 26: 820-833.

152. Ye, N. S. and Shi, P. Z. Applications of Graphene-Based Materials in Solid-Phase Extraction and Solid-Phase Microextraction. *Separation and Purification Reviews*. 2015. 44: 183-198.

153. Sun, F.S., D. Littlejohn, and M.D. Gibson, Ultrasonication extraction and solid phase extraction clean-up for determination of US EPA 16 priority pollutant polycyclic aromatic hydrocarbons in soils by reversed-phase liquid chromatography with ultraviolet absorption detection. *Analytica Chimica Acta*. 1998. 364(1-3):1-11.

154. Zawisza, B., Baranik, A., Malicka, E., Talik, E. & Sitko, R. Preconcentration of Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and Pb(II) with ethylenediamine-modified graphene oxide. *Mikrochimica Acta. 2016.* 183**,** 231-240.

155. Kuo, C. Y., Wu, C. H. and Wu, J. Y. Adsorption of direct dyes from aqueous solutions by carbon nanotubes: Determination of equilibrium, kinetics and thermodynamics parameters. *Journal of Colloid and Interface Science*. 2008. 327: 308-315.

156. Pichon, V. Solid-phase extraction for multiresidue analysis of organic contaminants in water. *Journal of Chromatography A*. 2000. 885: 195-215.

157. Shamsipur, M. and B. Hashemi. Extraction and determination of polycyclic aromatic hydrocarbons in water samples using stir bar sorptive extraction (SBSE) combined with dispersive liquid-liquid microextraction based on the solidification of floating organic drop (DLLME-SFO) followed by HPLC-UV. *RSC Advances*. 2015. 5(26): 20339-20345.

158. Fernández, M., Clavijo, S., Forteza, R. & Cerdà, V. Determination of polycyclic aromatic hydrocarbons using lab on valve dispersive liquid–liquid microextraction coupled to high performance chromatography. *Talanta*. 2015. 138: 190-195.

159. Der Beek, T. A., Weber, F. A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A. and Kuster, A. Pharmaceuticals in the environment-gloal occurences and perspectives. *Environ Toxicol Chem*. 2016. 35: 823-835.

160. Caro, E., Marcé, R. M., Cormack, P. A. G., Sherrington, D. C. and Borrull, F. A new molecularly imprinted polymer for the selective extraction of naproxen from urine samples by solid-phase extraction. *J. Chromatogr. B*. 2004. 813: 137-143.

161. Macià, A., et al., Capillary electrophoresis for the analysis of non-steroidal anti-inflammatory drugs. TrAC-Trend. *Anal. Chem*. 2007. 26(2): 133-153.

162. Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy (1), 2013, Off. J. Eur. Union. p. L226.

163. Arous, O., Kerdjoudj, H. and Seta, P. Comparison of carrier-facilitated silver (i) and copper (ii) ions transport mechanisms in a supported liquid membrane and in a plasticized cellulose triacetate membrane. *Journal of Membrane Science*. 2004.

164. Gardner, J. S., Walker, J. O. and Lamb, J. D. Permeability and durability effects of cellulose polymer variation in polymer inclusion membranes. *Journal of Membrane Science*. 2004. 229: 87-93.

165. Ascar, L., Ahumada, I., López, A., Quintanilla, F. & Leiva, K. Nonsteroidal anti-inflammatory drug determination in water samples by HPLC-DAD under isocratic conditions. *Journal of the Brazilian Chemical Society*. 2013. 24: 1160-1166.

166. El-Kommos, M.E., N.A. Mohamed, and A.F. Abdel Hakiem, Selective micellar electrokinetic chromatographic method for simultaneous determination of some pharmaceutical binary mixtures containing non-steroidal anti-inflammatory drugs. *Journal of Pharmaceutical Analysis*. 2013. 3(1): 53-60.

167. Isaacs, D., Elliott, E., Gilbert, R., Moyer, V. and Pichichero, M. Aminoglycosides: Dosing and Monitoring Blood Levels. *Evidence-based Pediatric Infectious Diseases*, Appendix 2. 2008. 301-305.

168. Zhu, W. X., Yang, J. Z., Wei, W., Liu, Y. F. and Zhang, S. S. Simultaneous determination of 13 aminoglycoside residues in foods of animal origin by liquid chromatography-electrospray ionization tandem mass spectrometry with two consecutive solid-phase extraction steps. *Journal of Chromatography A*. 2008b. 1207: 29-37.

169. Brandl, M. & Gu, L. Degradation of tobramycin in aqueous solution. *Drug Development and Industrial Pharmacy. 1992.* 18**:** 1423-1436.

170. Fonge, H., Kaale, E., Govaerts, C., Desmet, K., Schepdael, A. V. & HoogmartenS, J. Bioanalysis of tobramycin for therapeutic drug monitoring by solid-phase extraction and capillary zone electrophoresis. *Journal of Chromatography B. 2004.* 810**,** 313-318.

171. Megoulas, N. C. & Koupparis, M. A. Development and validation of a novel HPLC/ELSD method for the direct determination of tobramycin in pharmaceuticals, plasma, and urine. *Analytical and Bioanalytical Chemistry. 2005.* 382**:** 290-296.

172. Attema-De Jonge, M. E., Bekkers, J. M., Oudemans-Van Straaten, H. M., Sparidans, R. W. & Franssen, E. J. F. Simple and sensitive method for quantification of low tobramycin concentrations in human plasma using HPLC–MS/MS. *Journal of Chromatography B. 2008.* 862**,** 257-262.