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

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***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.***

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## 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%.

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## 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.

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