DEVELOPMENT AND APPLICATIONS OF ELECTROMEMBRANE EXTRACTION (EME) METHODS ACROSS HOLLOW POLYMER INCLUSION MEMBRANE (HPIM) FOR ANALYSIS OF DRUGS AND HERBICIDES

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Specially dedicated to my beloved parents and families for all support and encouragement in completing this study

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ABSTRACT

Electromembrane extraction (EME) has become an effective method in the development of sample preparation technique. In this study, a novel microextraction method based on the EME and employed with hollow polymer inclusion membrane (HPIM) was developed in order to get better stability and reproducibility compared to the conventional EME. HPIM was prepared by dipping the glass capillary tubes into a solution of the desired proportions of cellulose triacetate (CTA), tris(2-ethylhexyl)phosphate (TEHP) and di-(2-ethylhexyl)phosphoric acid (D2EHPA) or Aliquat 336 in dichloromethane. Three basic drugs, namely amphethamine, methamphetamine and 3,4-methylenedioxy-*N*-methylamphethamine (MDMA) were selected as the target analytes to evaluate the extraction efficiency of the new approach. Parameters affecting the extraction efficiency, including the composition of HPIM, pH of sample, extraction voltage and extraction time were investigated in detail. Under the optimized conditions, enrichment factors in the range of 97-103 fold were obtained from 3 mL sample solution with a 10 min extraction time and an applied voltage of 300 V across the HPIM. A comparison was also made between the newly developed approach and the conventional EME as well as standard sample preparation methods (liquid-liquid extraction) used by the Toxicology Unit, Department of Chemistry, Malaysia. The applied voltage in EME is an important parameter for efficient extraction of the analyte, however, when dealing with extremely high voltage, instability occurs due to the formation of bubbles. This limitation has stimulated the development of the exhaustive simultaneous EME across HPIM with the aim of employing a bubbleless electrode for the determination of selected cationic and anionic pesticides present in the environmental water samples. Bubbleless electrode was prepared to solve the bubble formation problem during the extraction process. Cationic herbicides namely paraquat (PQ) and diquat (DQ) as well as anionic herbicides namely (4-chlorophenoxy)acetic acid (4-CPA) and 2-(2, 4-dichlorophenoxy)acetic acid (2,4-D) were selected as the model analytes to evaluate the extraction performance of this new approach. Under the optimized conditions, the enrichment factors in the range of 152–185-fold were obtained from 4 mL of river water sample with a 20 min extraction time and an applied voltage of 3000 V. The proposed method provided good linearity with the correlation coefficients ranging from 0.9982 to 0.9997 over a concentration range of 1–1000 ng/mL. The detection limits of the method for the herbicides were in the range of 0.3–0.4 ng/mL, with the relative standard deviations ranged between 4.8% and 8.5%. A comparison was also made between the newly developed method with that of conventional EME setup using normal electrode.

ABSTRAK

Kaedah pengekstrakan elektromembran (EME) telah menjadi satu kaedah yang berkesan dalam perkembangan teknik penyediaan sampel. Dalam kajian ini, satu kaedah pengekstrakan mikro baru yang berlandaskan kepada EME dan menggunakan membran terkandung polimer berongga (HPIM) telah dibangunkan untuk memperoleh kestabilan dan kebolehulangan yang lebih baik berbanding dengan EME konvensional. HPIM telah disediakan dengan mencelup tiub kaca kapilari ke dalam larutan selulosa asetat (CTA), tris(2-etilheksil)fosfat (TEHP) dan asid di-(2-etilheksil)fosforik (D2EHPA) atau Aliquat 336 di dalam diklorometana pada perkadaran yang diinginkan. Tiga dadah berbes iaitu amfetamin, metamfetamin dan 3,4-metilenadioksi-*N*-metilamfetamin (MDMA) telah dipilih sebagai analit sasaran untuk menilai kecekapan pengekstrakan bagi pendekatan baharu. Parameter yang mempengaruhi kecekapan pengekstrakan, termasuk komposisi HPIM, pH sampel, voltan pengekstrakan dan masa pengekstrakan telah dikaji dengan mendalam. Di bawah keadaan optimum, faktor pengayaan dalam julat 97-103 kali telah diperoleh daripada 3 mL sampel larutan dengan 10 min masa pengekstrakan dan voltan 300 V dikenakan merentasi HPIM. Satu perbandingan telah dibuat antara pendekatan baharu yang dibangunkan dengan EME konvensional serta kaedah penyediaan sampel piawai (pengekstrakan cecair-cecair) yang digunakan oleh Unit Toksikologi, Jabatan Kimia, Malaysia. Penggunaan voltan dalam EME adalah satu parameter yang penting untuk pengekstrakan analit yang cekap, namun, apabila berurusan dengan voltan yang sangat tinggi, ketidakstabilan berlaku disebabkan oleh pembentukan buih. Pembatasan ini telah merangsang pembangunan EME selari merentasi HPIM yang lengkap dengan tujuan untuk menggunakan elektrod tanpa buih untuk penentuan pestisid kationik dan anionik terpilih yang hadir dalam sampel air persekitaran. Elektrod tanpa buih telah disediakan untuk menyelesaikan masalah pembentukan buih semasa proses pengekstrakan. Herbisid kationik iaitu parakuat (PQ) dan dikuat (DQ) serta herbisid anionik iaitu asid (4-klorofenoksi)asetik (4-CPA) dan asid 2-(2,4-diklorofenoksi)asetik (2,4-D) telah dipilih sebagai model analit untuk menilai prestasi pengekstrakan bagi pendekatan baharu ini. Di bawah keadaan optimum, faktor pengayaan dalam julat 152-185 kali telah diperoleh daripada 4 mL sampel air sungai dengan 20 min masa pengekstrakan dan menggunakan 3000 V. Kaedah yang dicadangkan telah memberikan kelinearan yang baik dengan pekali korelasi antara 0.9982 hingga 0.9997 dalam julat kepekatan 1-1000 ng/mL. Had pengesanan kaedah ini untuk herbisid adalah dalam julat 0.3-0.4 ng/mL, dengan sisihan piawai antara 4.8% dan 8.5%. Satu perbandingan telah dibuat antara kaedah baharu yang telah dibangunkan dengan EME konvensional yang menggunakan elektrod biasa.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

$Ag(CN)_2$	-	Silver cyanide
AP	-	Amphetamine
Cd	-	Cadmium
CE	-	Capillary electrophoresis
CNT	-	Carbon nanotube
CPA	-	Chlorinated phenoxyacetic acids
Cr	-	Chromium
CTA	-	Cellulose triacetate
CZE	-	Capillary Zone Electrophoresis
C^4D	-	Capacitively coupled contactless conductivity detector
DLME	-	Dispersive liquid microextraction
D2EHPA	-	Di-(2-ethylhexyl) phosphoric acid
DQ	-	Diquat
EOF	-	Electroosmotic flow
EME	-	Electromembrane Extraction
FESEM	-	Field emission scanning electron microscopy
GC	-	Gas chromatography
HPIM	-	Hollow polymer inclusion membrane
HF-LPME	-	Hollow Fiber- Liquid Phase Microextraction
KCl	-	Potassium chloride
KOH	-	Potassium hydroxide
LC	-	Liquid chromatography
LLE	-	Liquid-Liquid Extraction
LPME	-	Liquid Phase Microextraction
MA	-	Methamphetamine
MDA	-	3,4-methylenedioxy amphetamine
MDMA	-	3,4-methylenedioxy methamphetamine

MEKC	-	Micellar electrokinetic chromatography
NaCl	-	Sodium chloride
NaOH	-	Sodium hydroxide
NPOE	-	2-nitrophenyl octyl ether
PA	-	Polyacrylate
Pb	-	Lead
PDMS	-	Polydimethylsiloxane
PIM	-	Polymer inclusion membrane
PVC	-	Poly(vinyl chloride)
PQ	-	Paraquat
RSD	-	Relative standard deviation
SBSE	-	Stir bar sorptive extraction
SDME	-	Single drop microextraction
SDS	-	Sodium dodecyl sulphate
SLM	-	Supported Liquid Membrane
SPE	-	Solid Phase Extraction
SPME	-	Solid Phase Microextraction
TEHP	-	Tris-(2-ethylhexyl) phosphate
UV	-	Ultra violet
Zn	-	Zinc
2,4- D	-	(4-chlorophenoxy) acetic acid
4-CPA	-	2-(4-dichlorophenoxy) acetic acid

LIST OF SYMBOLS

A	-	Ampere
C_{ih}	-	Analyte concentration
cm	-	Centimeter
$gmol^{-1}$	-	Gram per mol
g	-	Gram
h	-	Hour
H	-	Height
I	-	Current
I.D	-	Internal diameter
L		Liter
mbar	-	Millibar
mg	-	Milligram
MHz	-	Megahertz
min	-	Minute
mL	-	Milliliter
mM	-	Millimolar
ng mL^{-1}	-	Nanogram per milliliter
nm	-	Nanometer
rpm	-	Revolutions per minute
µA	-	Microampere
µL	-	Microliter
µg/mL	-	Microgram per milliliter
µm	-	Micrometer

LIST APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background

The target analytes (e.g. drugs, pesticides and herbicides) in environmental or biological samples usually occur in complex matrices, which are able to disturb the separation and analysis steps. Therefore, a series of procedures called sample preparation is needed to remove the interference substances, pre-concentrate the target analyte and increase the sensitivity. In addition, the sample preparation method can help to solve the limitations of the sensitivity of the analytical instrument detector.

As a consequence, many sample preparation methods have been developed for various applications in analytical methods. Most of the developed methods are aimed at searching for more cost effective analyses, higher sample preparation throughput, faster procedures and low consumption of solvents (1). These innovative techniques are derived from traditional sample preparation methods, namely liquid-liquid extraction (LLE) and solid phase extraction (SPE). The major drawbacks of the LLE method are that it is time consuming and not environmentally friendly (2). SPE is relatively easy and it consumes low amounts of organic solvent. Nevertheless, the SPE cartridges are costly and evaporation of the eluent and reconstituents is normally required prior to analysis (3).

To address the problems such as large solvent needs and cost, new research committed towards the development of convenient, efficient, economical and

miniaturized sample preparation methods is required. A miniaturized version of solid-phase extraction (SPE), termed solid-phase microextraction (SPME) (4) and liquid phase microextraction (LPME) (1, 2, 5) were introduced.

Hollow fibre liquid phase microextraction (HF-LPME) is one of the most promising techniques among LPME. In this method, a transport mechanism based on passive diffusion is applied, by adjusting a pH gradient established across the supported liquid membrane (SLM). In this technique, the target analytes are extracted from the sample solution through SLM which is held by capillary forces in the pores of a hollow fibre membrane (support) into the acceptor solution. The SLM is in direct contact with both the aqueous sample and the acceptor solution. Although this method can give good clean-up and also good selectivity by the proper organic solvents (SLM), the extraction time of 20-60 min was considered a major drawback (6).

For this reason, electro-assisted extraction was investigated based on the hypothesis that charged molecules can be transferred faster across SLM by an electric force than passive diffusion. Hence, in 2006, a new extraction principle termed electromembrane extraction (EME) was introduced (7). The equipment for EME was exactly the same as HF-LPME, except for the addition of two electrodes and a D/C power supply. The application of an electrical potential difference as the driving force successfully shortened the extraction time to within the range of 5-20 min (8). In the early development stages of the EME, most of the research focused on the screening and selection of differently composed SLMs. Significant efforts have been made over the course of the past year to expand the EME to a new application area and to improve its performance. The simultaneous electromembrane extraction of cationic and anionic analytes was reported by Safari *et al.* (2013) (9) along with the correlation between the EME and other extraction methods (10). EME has been widely employed in the analysis of drugs (11-14), the extraction of metals (15, 16) and the extraction of ions (17). This technique offered faster extraction time, lower consumption of organic solvent and also high pre-concentrations.

Most EMEs reported the use of water immiscible organic solvents such as 2-nitrophenyl octyl ether (NPOE), 1-octanol, tris (2-ethylhexyl) phosphate (TEHP), and di-hexyl ether (18) immobilized in the pores in the wall of hollow fibre membranes such as SLMs. Unfortunately, SLM was reported to have low mechanical stability, leading to membrane breakdown and leaching of the membrane liquid phase (19, 20). Kim *et al.* (2000) (21) have investigated the stability of polymer inclusion membrane (PIM) and SLM under similar conditions. They reported no flux decline or evidence of material losses within 15 days of continuous transport experiment in PIM. In contrast, leakage of the organic material in SLM after 48 h agitation in aqueous solution was clearly observed.

Consequently, the use of PIM as an alternative for electromembrane extraction has recently been investigated and was reported to be successful for the extraction of inorganic ions and pesticides (19, 22-25). PIM are self-supporting membranes, where a base polymer, plasticizer and carrier are incorporated into homogenous membrane. Therefore, for the first time, in this study, a new variation of the EME approach was created in which a hollow polymer inclusion membrane (HPIM) was developed for the extraction of selected drugs in human plasma. In addition, for the first time, the direct comparison of PIM and SLM for EME was undertaken in this study. The performance of the proposed method was also compared with the standard method (liquid-liquid extraction) used by the Toxicology Unit, Department of Chemistry, Malaysia (26).

The basis of EME is the electromigration of a targeted charged analyte under an electric field. Therefore, electric strength plays a crucial role in EME and depends on the applied voltage. Although it is anticipated that the extraction efficiency will increase as the applied voltage increases, there are some limitations to increasing the voltage; for example, instability of the system due to the formation of bubbles. In addition, the EME also suffered from an increase in the current level when high voltage was applied, especially in the analysis of real samples containing large amounts of ionic components. Therefore, there are several recent publications seeking to overcome the instability problem in the EME, including the application of

a stabiliser circuit in order to prevent the occurrence of an increasing current (27) and pulsed voltage (28). It was shown that the pulsed voltage increased the system stability by decreasing the thickness of the double layer at the interface (29).

For this reason, in this study, a stable EME was achieved by employing bubbleless electrodes to solve the problem of bubble formation during the extraction process. The bubbleless electrode was introduced by Gu *et al.* (2012) (30) and was employed in the electroosmotic pump for the purpose of solution delivery within a microfluidic device. The bubbleless setup facilitated the use of high voltage on the pump without the formation of the bubble in the pump channel.

A new way of thinking about the bubbleless electode in order for it to be employed in the EME so as to eliminate the bubble formation when high voltage is applied during the extraction process was carried out in this study. A conventional EME approach using platinum electrodes was performed as a comparison.

1.2 Problem statement

Various sample preparation methods have been used in the analysis of drugs and pesticides/herbicides. A conventional extraction method like LLE and SPE was used for the analysis of drugs and pesticides. However, these methods are more time-consuming and use large volumes of organic solvents. On the other hand, HF-LPME was introduced to overcome the large consumption of organic solvents. This method offers several advantages, like good enrichment and sample clean-up, thereby reducing potential problems from matrix components (31). However, this method suffered a major drawback of long extraction times

By taking advantage of the electric field to enhance the extraction efficiency, a new extraction, namely EME, was introduced in 2006. In this method, a potential

difference is applied across the SLM which acts as the driving force. This method promises to be fast, simple, selective and rapid. Nevertheless, EME has problems with the mechanical instability of SLM, which can lead to a loss of the SLM under agitation and an electric field (19). Moreover, EME also suffers instability of the system due to the formation of bubbles when high voltages are applied (32). To address these issues, a PIM was introduced as it exhibits excellent stability and versatility compared to SLM.

In this study, a new variation of EME employing a hollow polymer inclusion membrane (HPIM) was developed. In order to get a better understanding, the comparison EME based on SLM was performed. Furthermore, this is the first time that a direct comparison between PIM and SLM was done. The developed methods were applied for the determination of amphetamine, methamphetamine and MDMA abuse in human plasma. In addition, the simultaneous EME of cationic and anionic herbicides was investigated by employing bubbleless electrodes to overcome a bubble formation problem when high voltages are applied during the extraction process. There have been no reports on the use of bubbleless electrodes as an alternative for stable EME.

1.3 Research Aim and Objectives

The aim of this research is to develop simple, miniaturised sample preparation method based on EME for the analysis of drugs and herbicides. The objectives of the study are as follows:

1. To evaluate conventional EME across SLM for the analysis of amphetamine, methamphetamine and MDMA in human plasma

2. To design and characterize new membrane materials, namely HPIM, for the purpose of a highly stable EME approach

3. To develop and evaluate new methods based on EME across the HPIM for the analysis of amphetamine, methamphetamine and MDMA in human plasma

4. To prepare a bubbleless electrode for the simultaneous ultra-high voltage EME of cationic and anionic herbicides across the HPIM

1.4 Scopes of the Research

In this study, an innovative development of EME with capillary electrophoresis (CE) was developed for the analysis of drugs and herbicides in human plasma and river water samples. The potential to employ HPIM as an alternative to SLM was investigated for the analysis of amphetamine, methamphetamine and MDMA in human plasma in order to achieve greater membrane stability. In this work, the HPIMs were prepared, characterized and applied in EME. The HPIMs were characterized using field emission scanning electron microscopy (FESEM) and contact angle analysis. In order to get a good extraction efficiency, a series of optimizations was done, including optimization of the amount of plasticizer, the amount of carrier, sample pH, extraction voltage and extraction time. Analytical performances of the developed methods were evaluated, validated and applied to the analysis of drug of abuse in human plasma. The study was expanded by introducing a bubbleless electrode to overcome bubble formation during extraction when using a high voltage. The preparation of bubbleless electrodes was characterized in detail. The simultaneous electromembrane extraction of cationic and anionic herbicides employing the bubbleless electrode was developed. Parameters affecting EME were optimized comprehensively and applied to determine cationic and anionic herbicides in river water samples. A conventional EME using normal electrodes was performed as a comparison.

1.5 Significance of Research

In this study, EME across HPIM was developed for the first time. HPIMs were prepared as alternatives to SLM. It is expected that HPIM can give better stability compared to SLM due to its physical and chemical features. This proposed method was subsequently employed for the analysis of amphetamine, methamphetamine and MDMA in human plasma. This particular application is important to demonstrate the sample clean-up capability of the new proposed membrane materials against complex matrices present in human biological fluid.

Meanwhile, the introduction of bubbleless electrodes in EME could improve the stability of EME systems when a high voltage was applied. In addition, a simultaneous EME approach was introduced and this unique setup enabled the extraction of positively and negatively charged analytes at the same time. Therefore, it is expected that the extraction process could be achieved in a simple setup without any tedious procedures. In addition, the developed methods are expected to be simple, fast, efficient, sensitive and environmentally friendly, potentially being adopted as established methods for the monitoring of other drugs and organic pollutants such as pesticides.

1.6 Outline of the Thesis

This thesis consists of seven chapters. Chapter 1 describes in detail the research background, problem statement, objective, scope and significance of the study. Chapter 2 compiles the literature review on the details of conventional sample preparation method and microextraction of derivative sample preparation methods and focusses on EME and the development of PIM.

Chapter 3 discusses the microextraction of EME across SLM combined with capillary electrophoresis with a C^4D detector for the analysis of three selected drugs in human plasma. The parameter affecting the extraction efficiency was investigated

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