UNIVERSITI PUTRA MALAYSIA

ELECTROCHEMICAL CHARACTERISATION AND SENSING OF DICLOFENAC ANION AND DIBUCAINE CATION BY ION TRANSFER ACROSS WATER AND DICHLOROHEXANE INTERFACE

EISSA MOHAMED ALMBROK ABDULLA

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By

EISSA MOHAMED ALMBROK ABDULLA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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November 2021

Chair : Ruzniza Mohd Zawawi, PhD
Faculty : Science

Ion sensing is a significant challenge in both clinical diagnosis and environmental monitoring. Ion transfer reactions at liquid | liquid interfaces allow detection of substances that are not easy to oxidise/reduce or that undergo significant interference in these reactions. In addition, it offers the advantages of simplicity of instrumentation, easily of miniaturisation and portability. However, very few sensing applications have been reported for the quantitative analysis of organic molecules, including drugs. This study discussed the characterisation, and application of ion transfer at the interface between two immiscible electrolyte solutions (ITIES) using cyclic voltammetry (CV) and differential pulse voltammetry (DPV). Early studies have relied on the exploration of the electrochemical behaviour of diclofenac anion (DCF^-) and dibucaine cation (DIC^+) via water|1,6-dichlorohexane (1,6-DCH) at such regular ITIES and in particular examination of the pH of the aqueous phase. Both ions were found to undergo ion-transfer voltammetry at the liquid | liquid interface. Some of the analytical parameters, such as standard transfer potential, the Gibbs energy of transfer and the partition coefficient, for DCF^- and DIC^+ were determined. Subsequently, essential modifications to the ITIES by micropores silicon nitride membrane were brought to enhance the analytical performance and lower the detection limits. The micro-ITIES array formed with 2500 micropores arranged in a cubic close-packed (CCP) arrangement, with a diameter of 2.5±0.09 µm, a pore centre-to-centre separation of 12.65±0.13 µm and 100 nm membrane thickness, was electrochemically characterised by ion transfer of the model analyte, tetramethylammonium cation (TMA^+), across the water | 1,6-DCH interface. The resulting voltammogram has showed the linear diffusion dominance within the arrays, suppressing the radial diffusion at the edge of the arrays, due to overlapping diffusion profiles at adjacent micro-ITIES resulted in lower experimental current. The analytical performance of micro-ITIES to drug molecules (DCF^- and DIC^+) detection in the aqueous phase was investigated, with the limits of detection (LODs) in the ranges of 8–56 µM and

4–24 μM were calculated to be 1.5±0.05 μM and 0.9±0.06 μM for DCF^- and DIC^+, respectively. In addition, the influence of possible interfering substances (ascorbic acid, sugar, amino acid, urea, and metal ions) on the detection of DCF^- and DIC^+ was investigated. Finally, the ability to use electrochemistry at liquid | liquid micro-interface for direct determination of the targeted drugs in bio-mimic fluids (serum and saliva) and in a realistic mixture (human urine) were assessed. Both drugs could be detected in biological matrices, despite of deproteinisation of samples is required for detecting DCF in artificial serum. The LODs were 12.9±.5 μM and 1.4±0.02 μM in artificial serum, 1.8±0.2 μM and 1.5±0.14 μM in artificial saliva and 2.6±0.2 μM and 1.2±0.12 μM in human urine sample for DCF^- and DIC^+, respectively.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENCIRIAN ELEKTROKIMIA DAN PENDERIAAN ANION DIKLOFENAK DAN KATION DIBUKAIN MELALUI PENGANGKUTAN ION MERENTASI ANTARA MUKA AIR DAN DIKLOROHEXANA

Oleh

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Penderiaan ion adalah cabaran penting dalam diagnosis klinikal dan pemantauan alam sekitar. Tindak balas pemindahan ion pada antara muka cecair | cecair membolehkan pengesanan bahan yang tidak mudah teroksida / terturun atau yang mengalami gangguan yang ketara dalam tindak balas ini. Di samping itu, ia menawarkan kelebihan instrumentasi yang ringkas, mudah dikecilkan dan dialih. Walau bagaimanapun, sangat sedikit aplikasi penderiaan telah dilaporkan untuk analisis kuantitatif molekul organik, termasuk ubat-ubatan. Kajian ini membincangkan pencirian dan aplikasi pemindahan ion pada antara muka di antara dua larutan elektrolit tak terlarut (ITIES) menggunakan voltametri berkitar (CV) dan voltametri pembezaan denyutan (DPV). Kajian awal telah bergantung kepada penerokaan tingkah laku elektrokimia bagi anion diklofenak (DCF^-) dan kation dibukain (DIC^+) melalui air|1,6-diklorohexana (1,6-DCH) pada ITIES biasa tersebut dan khususnya pemeriksaan pH bagi fasa akueus. Kedua-dua ion itu didapati menjalani voltametri pemindahan ion pada antara muka cecair | cecair. Beberapa parameter analisis, seperti keupayaan pemindahan piawai, tenaga pemindahan Gibbs dan pekali pembahagian untuk DCF^- dan DIC^+ telah ditentukan. Seterusnya, pengubahsuaian penting pada ITIES oleh membran silikon nitrid mikroliang telah dilakukan untuk meningkatkan prestasi analisis dan menurunkan had pengesanan. Tatasusunan mikro-ITIES yang terbentuk dengan 2500 mikroliang yang diatur dalam susunan kiub tertutup padat (CCP), dengan diameter 2.5±0.09 µm, pemisahan pusat ke pusat liang 12.65±0.13 µm dan ketebalan membran 100 nm telah dicirikan secara elektrokimia oleh pemindahan ion bagi analit model, kation tetramethylammonium (TMA^+), pada antara muka air | 6-DCH. Voltamogram

yang terhasil menunjukkan penyebaran linear yang dominan, mengurangkan penyebaran jejaripada hujung jajaran disebabkan oleh pertindihanprofil penyebaran bersebelahan dengan mikro-ITIES yang menghasilkan arus eksperimen yang rendah. Prestasi analisis mikro-ITIES kepada pengesanan molekul ubat (DCF^- dan DIC^+) dalam fasa akueus telah disiasat, dengan had pengesanan (LOD) dalam julat 8–56 μM dan 4–24 μM dikira sebagai 1.5±0.05 μM dan 0.9±0.06 μM untuk DCF^- dan DIC^+, masing-masing. Sebagai tambahan, pengaruh bahan gangguan yang mungkin (asid askorbik, gula, asid amino, urea, dan ion logam) pada pengesanan DCF^- dan DIC^+ telah disiasat. Akhirnya, keupayaan untuk menggunakan elektrokimia pada antara muka mikro cecair | cecair untuk penentuan langsung ubat yang disasarkan dalam cecair bio-mimik (serum dan air liur) dan dalam campuran realistik (air kencing manusia) telah dinilai. Kedua-dua ubat boleh dikesan dalam matriks biologi, walaupun penyahproteinan sampel diperlukan untuk mengesan DCF dalam serum tiruan. Nilai LOD adalah 12.9±1.5 μM dan 1.4±0.02 μM dalam serum tiruan, 1.8±0.2 μM dan 1.5±0.14 μM dalam air liur tiruan dan 2.6 ±0.2 μM dan 1.2±0.12 μM dalam sampel air kencing manusia untuk DCF^- dan DIC^+, masing-masing.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

Standard abbreviations

aq	Aqueous
CA	Chronoamperometry
C.A.	contact angle
ca.	Circa
CCP	cubic close-packed
CE	counter (or auxiliary) electrode
CV	cyclic voltammetry
DPV	differential pulse voltammetry
DRIE	deep reactive ion etching
ITIES	interface between two immiscible electrolyte solutions
LOD	limit of detection
LSV	linear sweep voltammetry
LSSV	linear sweep stripping voltammetry
org	Organic
pI	isoelectric point
pKa	logarithmic of the acid dissociation constant
R	linear correlation coefficient
RE	reference electrode

redox	reduction-oxidation
RSD.	relative standard deviation
SEM	scanning electron microscope/microscopy
SECM	scanning electrochemical microscopy
SWV	square wave voltammetry
TEM	transmission electron microscope/microscopy
WE	working electrode
MVN	the 'modified Verwey-Niessen'
SHE	standard hydrogen electrode

Chemical abbreviations

Ag | AgCl	silver | silver chloride
BSA	bovine serum albumin
$BTPPA^+$	bis(triphenylphosphoranylidene)ammonium cation
$BTPPACl^-$	bis(triphenylphosphoranylidene)ammonium chloride
$BTPPA^+TPBCl^-$	bis(triphenylphosphoranylidene)ammonium tetrakis(4-chlorophenyl)borate
1,2-DCE	1,2-dichloroethane
1,6-DCH	1,6-dichlorohexane
K^+TPBCl^-	potassium tetrakis(4-chlorophenyl)borate
NB	Nitrobenzene

NPOE	2-nitrophenyl octyl ether
PET	polyethylene terephthalate
Pt	Platinum
PBS	phosphate buffered saline
PVC	poly(vinylchloride)
Si_3N_4	silicon nitride
TEA^+	tetraethylammonium cation
TEACl	tetraethylammonium chloride
$TPBCl^-$	tetrakis(4-chlorophenyl)borate anion
$TPrA^+$	tetrapropylammonium cation
TPrACl	tetrapropylammonium chloride
TMA^+	tetramethylammonium cation
DCF, DCF^-	the neutral and ionic forms of diclofenac
DIC, DIC^+	the neutral and ionic forms of dibucaine
DNA	deoxyribonucleic acid

LIST OF SYMBOLS

Symbol	Meaning	Usual unit
A	a) electrode area b) cross Sectional area of pores	a) cm^2, m^2 b) cm^2, m^2
a	activity of the species	None
C_{dl}	experimental capacitance	F
$C_{dl}°$	specific capacitance per unit area	F cm^{-2}
C_i	bulk concentration of the transferring ions or electroactive species	M, mol cm^{-3}, mol m^{-3}
D	diffusion coefficient	cm^2 s^{-1}
$D_i{}^w$	diffusion coefficients of the transferring ions in the aqueous phase	cm^2 s^{-1}
$D_i{}^o$	diffusion coefficients of the transferring ions in the organic phase	cm^2 s^{-1}
d	diameter	m, cm
dE/dt	potential variation with time	V s^{-1}
E	potential of an electrode	V
$\bar{\mu}_i^w$	electrochemical potential of water	V
$\bar{\mu}_i^O$	electrochemical potential of organic	V
E_p	peak potential	V
E_p,$W \rightarrow O$	forward peak potential	V
E_p,$O \rightarrow W$	reverse peak potential	V
E_1	initial (or starting) potential	V

E_2	final (or switching) potential	V
$E_{1/2}$	half-wave potential in voltammetry	V
ΔE	a) potential interval b) peak-to-peak separation	a) V b) V
F	Faraday constant	C mol^{-1}
$\Delta G_{transfer,}^{i0,w\rightarrow O}$	standard Gibbs transfer energy of species i from phase w into phase o	kJ mol^{-1}
I_c	charging current	A
I_p	peak current	A
$I_{p,W\rightarrow O}$	forward peak current	A
$I_{p,O\rightarrow W}$	reverse peak current	A
I_{ss}	steady-state (or limiting) current	A
I_{calc}	calculated current	A
$I_{calc,total}$	calculated total current	A
I_{exp}	measured experimental current from cyclic voltammetry experiment	A
IR	potential drop	V
l	a) recess depth, b) membrane thickness	m
N_p	number of pores in the array	None
P_{DCH}°	(ionised) partition coefficient of the ionised form in DCH	None
P_{n-oct}	partition coefficient of the neutral form in n- octanol	None
R	molar gas constant	J K^{-1} mol^{-1}
$R_{a,b}$	total bulk array resistance	Ω

R_b	bulk solution resistance	Ω
$R_{a,p}$	total pore array resistance	Ω
R_p	pore resistance	Ω
R_u	uncompensated resistance	Ω
RuC_{dl}	cell time constant	S
r_a	pore radius	m, cm, nm
r_c	pore centre-to-centre separation	m, cm, nm
T	absolute temperature	K
t	time	S
v	scan (or sweep) rate	V s^{-1}
$v^{1/2}$	square root of the scan rate	$V^{1/2}$ $s^{-1/2}$
z	charge number of the transferring ion	None
γ	an activity coefficient	None
δ	diffusion zone extension	None
κ	conductivity of a solution	S cm^{-1}
Θ	membrane macroscopic coverage of pores or membrane porosity	None
$\Delta\emptyset^{w}_{inn}$, $\Delta\emptyset^{o}_{inn}$	the potential differences across the diffuse layers the organic phase or aqueous phase	V
$\Delta^{o}_{w}\emptyset$	The Galvani interfacial potential difference	V

CHAPTER 1

INTRODUCTION

1.1. Liquid | Liquid Interface Electrochemistry

1.1.1. Background of the Study

Liquid surfaces and liquid | liquid interfaces have great significance in the real world, especially in the biological system. The interfaces between two immiscible liquid electrolyte solutions (ITIES) are present in cells and tissues of all living organisms. The primary reason for the study of the electrochemical nature of ITIES is the use of aqueous electrolyte solution as one of phase of such interfaces (Koczorowski, 2001).

The ITIES is formed when two liquid solvents of a low (or ideally zero) mutual miscibility, usually less than 1% in weight, are brought into contact, each behaving as an electrolyte. Typically, water is one of these solvents that behave as the aqueous phase, the other phase is a polar organic solvent, such as 1,2-dichloroethane (1,2-DCE), 1,6-dichlorohexane (1,6-DCH) or nitrobenzene (NB), which allows for at least partial dissociation of dissolved electrolyte(s) into ions (Samec, 2004). For an aqueous|organic interface system, the aqueous phase solvent usually contains a hydrophilic electrolyte salt (typically LiCl or Li_2SO_4), while the polar organic phase solvent contains a hydrophobic electrolyte salt (commonly bis(triphenylphosphoranylidene) ammonium tetrakis(4-chlorophenyl) borate, ($BTPPA^+TPBCl^-$). This study employed the $BTPPA^+TPBCl^-$, a hydrophobic cation and anion pair, both of which are difficult to transfer into the aqueous phaseThe presence of electrolytes in both phases to cause the potential difference between them, which is the force that drives the ions to move from one phase to another when the transition energy is available (Molina *et al.* 2012; Arrigan, 2008; Vanýsek & Ramírez, 2008; Samec, 2004).

1.1.2. The Electrical Double Layer of the Liquid | Liquid Interface

The structure of the liquid | liquid interface was proposed for the first time by Verwey and Niessen (1939) based on Gouy-Chapman theory, which described an electric double layer as two back-to-back electric double layers with opposite charges separated by a continuous geometric boundary (Figure 1.1 (a)). However, the first experimental report dealing with the interfacial structure was given by Gavach *et al.* (1977) almost 40 years later, that proved the presence of specific adsorption, which was explained in terms of ion pair

formation at the liquid | liquid interface by measuring the interfacial tension versus the concentration of different tetraalkylammonium ions.

One year later, Gros *et al.* (1978) proposed what is known today as the 'modified Verwey-Niessen' model (MVN) (Figure 1.1 (b)). The experimental approach consisted of control of interfacial Galvani potential difference between a sodium bromide aqueous solution and a tetraalkylammonium tetraphenylborate organic solution tetraalkylammonium bromide to the aqueous phase and subsequent interfacial tension measurement, giving the electrocapillary curve. The electric double layers at the ITIES contain an organic-phase diffusion layer, an aqueous-phase diffusion layer, and an ion-free inner layer between two phases. The distribution of the potential drop across the interface when the latter is electrified can be separated into three major contributions: the potential drop across the aqueous diffuse layer ($\emptyset^w$), the potential drop across the organic diffuse layer ($\emptyset^o$), and the potential drop across the inner layer for aqueous and organic phases ($\emptyset^w_{inn}$ and $\emptyset^o_{inn}$). Furthermore, Girault & Schiffrin (1983 & 1984) demonstrated the formation of a mixed solvent layer at the interface through excess water surface at the interface between organic solvents of different polarity, which in turn has suggested that the surface excess of water at the liquid | liquid interface was not enough to form a monolayer and these ions penetrate the interfacial region (Figure 1.1 c) (Poltorak, 2015).

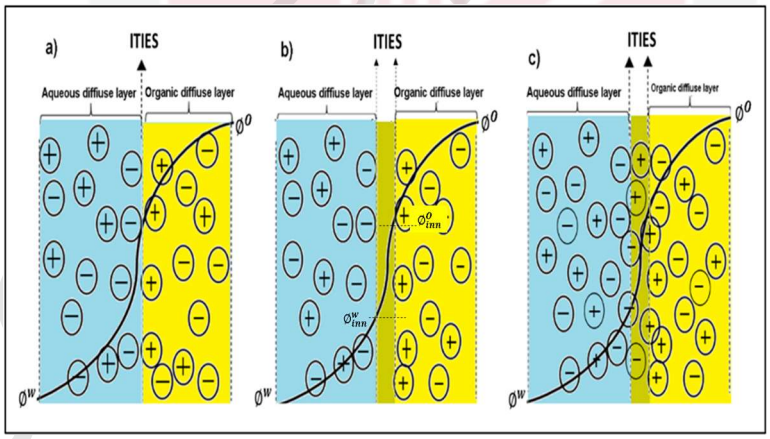

Figure 1.1: Different models for the ITIES structure. a) Verwey-Niessen model, b) modified Verwey-Niessen and c) mixed solvent layer model. Black solid lines correspond to potential distribution across the polarised liquid | liquid interface (Source: Poltorak, 2015)**.**

1.1.3. The Applications and Limitations at Liquid | Liquid Interfaces

The application of ion transfer voltammetry at the ITIES overcomes the drawbacks of the solid | liquid (electrode | electrolyte) interface, where non-redox-active species may not be detected via conventional electroanalytical methods (Arrigan, 2008). Electrochemistry of liquid | liquid interfaces have developed significantly in its applications during the last quarter of the 20th century (Volkov, 2001), where its studies have covered charge transfer (Amemiya *et al.* 2003; Senthilkumar *et al.* 2007), ion-pairing (Kontturi *et al.* 1995), the voltammetric and amperometric detection of ions (Arrigan *et al.* 2004; Wilke *et al.*1992; Lee *et al.* 2000), adsorption-desorption (Amemiya *et al.* 2003; (Alvarez and Arrigan, 2012), extractions and separation (Berduque *et al.* 2005; Berduque & Arrigan, 2006), phase-transfer catalysis (Liu *et al.* 2011; Tan *et al.* 1994) and drug release and delivery in pharmacology (Ortuno *et al.* 2007; Ribeiro *et al.* 2013; Collins & Arrigan, 2009; Collins *et al.*, 2008).

Electrochemical processes at ITIES have aroused the interest of many researchers for two reasons. First, the electrochemical reaction at ITIES represents a significant aspect of diverse practical applications in chemistry. Second, the biomimetic features of these processes have been a concern for over one century. (Samec, 2004). Electrochemistry at the ITIES has developed from the transfer of small ions such as model ions to the detection of biologically important species such as proteins (Alvarez & Arrigan, 2012; Herzog *et al.*, 2009), peptides (Yuan & Amemiya, 2004; Scanlon *et al.*, 2008), amino acids (Chen *et al.*,2004), ionised drugs (Ortuño *et al.*, 2007; Collins *et al.*, 2008 &2009; Ribeiro *et al.*, 2013; Alemu, 2004; Ulmeanu *et al.*, 2003; Ortuño *et al.*, 2007), neurotransmitters (Beni *et al.*, 2005; Berduque *et al.*, 2008; Zhan *et al.*, 2004), food additives (Herzog *et al.*, 2008), carbohydrates (Guo *et al.*, 2005) and deoxyribonucleic acid (DNA) (Osakai *et al.*, 2007). In addition, electrochemical sensing built on ion transfer via the ITIES has examined the detection of a wide range of inorganic species such as alkali, alkaline earth, heavy metals and anions (Lee *et al.*, 1998; Hossain *et al.*, 2012; Samec *et al.*, 1988; Lagger *et al.*, 1998). Thus, it plays a vital role in pharmaceutical chemistry, medicine, pharmacology.

The conventional experimental studies with ITIES have limitations, so several strategies have been developed to overcome these limitations and broaden their scope of application. Firstly, the issue of the volatility of the organic phase was solved by replacing the conventionally used solvents (nitrobenzene and 1,2-dichloroethane) with 2-nitrophenyl octyl ether (NPOE), which encompasses excellent properties such as low vapour pressure, low mutual miscibility with water and medium permittivity (Molina *et al.*, 2012). Recently, ionic liquids are being used as organic phase solvents to demonstrate low vapour pressure and high electrical conductivity (Silvester & Arrigan, 2011). Secondly, the problem of mechanical instability of the liquid | liquid interface is solved by partial solidification of the organic phase (dissolving a polymer such as poly (vinyl chloride) (PVC) in it (Scanlon *et al.*,

2010; Ortuño *et al.*, 2007) and supporting the organic solution within micro- or nanopore arrays (Zazpe *et al.*, 2007; Scanlon *et al.*, 2010). Finally, the issue of the reduced width of the potential window is solved through proper selection of the electrolytes dissolved in both phases (for example, highly hydrophobic organic ions and highly hydrophilic aqueous ions), and an organic phase constituted by mixed solvents (for example 1:1 mixture of 1,2-DCE: cyclohexane), which can lead to a broader potential window of up to 1.3 V (Cousens & Kucernak, 2011).

1.1.4. Miniaturisation of Liquid | Liquid Interface

Similar to conventional electrochemical methods, miniaturisation of the ITIES offers some benefits over their macro counterparts, such as smaller size and portability, increased mass transport rates, reduced ohmic drop and charging currents, ease of data analysis and integration into complementary techniques (Scanlon & Arrigan, 2011; Compton *et al.*, 2008; Davies & Compton, 2005; Arrigan, 2004). The feature lies in the interfacial surface area, which decreases as the system decreases, lowering the capacitance current and improves detection limits (Arrigan *et al.*, 2013; Liu *et al.*, 2011; Shao & Mirkin, 1997). Moreover, reducing the size of the ITIES improves the sensitivity as a reason of increased mass transfer to a solid | liquid or the liquid | liquid interface arising from radial diffusion zone geometry (Henstridge & Compton, 2012; Scanlon & Arrigan, 2011; Scanlon *et al.*, 2010; Shao & Mirkin, 1997). Utilizing a single micro- and nano- ITIES has significantly enabled voltammetric measurements in media without supporting electrolytes or low polarity media (Laforge *et al.*, 2006; Sun *et al.*, 2005 & 2007).

The miniaturisation of the ITIES also offers prospects for measurements in microenvironments (e.g., the study of living cells) and as a probe for scanning electrochemical microscopy (SECM) (Shao & Mirkin, 1997; Solomon & Bard, 1995). In addition, it assists in simplifying the electrochemical measurement instrumentation on the introduction of a two-electrode potentiostat set up to replace the conventional four-electrode setup (Liu *et al.*, 2011). To date, two approaches for establishing micro-ITIES have been reported (Arrigan *et al.*,2013; Strutwolf *et al.*,2008; Zazpe *et al.*, 2007). The first is based on the use of micropipettes in which the liquid | liquid interface is created at the tip of a pulled glass pipette (Tong *et al.,* 2001; Shao & Mirkin, 1998). These micropipettes suffer from a high electric resistance but also from being highly asymmetric, which strongly influences the diffusion of species at the interface. The second is based on placement of the aqueous and organic phases on either side of membranes containing arrays of micron-sized pores or holes (Zazpe *et al.*, 2007). Furthermore, preparing several miniaturised ITIES in parallel as arrays creates micro or nano-ITIES arrays, which are beneficial to amplify the electroanalytical current signal and improve the mechanical stability (Arrigan *et al.*, 2013; Scanlon & Arrigan, 2011; Scanlon *et al.*, 2010).

1.1.5. Fabrication of Solid-State Membranes

Membrane science and technology has evolved from basic applications in the laboratory to high impact industrial utilisation. Membrane processes offer a diverse range of applications in modern society, including in the areas of chemical sensor, biosensor, food and pharmaceutical industries processing, desalination, gas separation and so on (Strathmann, 1981). Currently, various approaches have been investigated in the challenge to fabricate solid-state micro and nano pores with real dimensions. On the other hand, these techniques involve more complex and lengthy procedures, requiring several additives, subtractive, and reactive ion etching (RIE) through a template structure processes to accomplish pore transfer (Desormeaux *et al.,*2014). The fabrication materials generally used in the creation of the solid-state micropore membranes have been well characterised voltammetry at the ITIES such as polymers (polyimide, polyester, polyethylene terephthalate (PET) and cellulose) ((Lee *et al.*, 1997; Kralj & Dryfe, 2001; Wilke *et al.*,1997&1998; Sladkov *et al.*, 2004; Josserand *et al.*,1999; Dryfe, 2006) and silicon ((Scanlon *et al.*, 2008; Zazpe *et al.*, 2007; Lhotsky *et al.*, 1996). Cellulose was observed to be unsuitable as it became swollen when in contact with the aqueous phase, while polyester, which is chemically inert in the aqueous and organic phases, is suitable (Peulon *et al.*, 2001). Although silicon nitride (Si_3N_4) and silicon oxide (SiO) are the most widely used materials of solid-state nanopores structures generated by focused ion beam (FIB) and electron-beam lithography (EBL) (Sairi, 2014). However, no information on these engineered microporous Si_3N_4 membranes that are commercially available for utilising as platforms for micro-ITIES and electrochemical drug sensing, which provide the platform for this study. The advantages of using porous silicon nitride membrane for ITIES-based sensor system include commercially availability in pore sizes appropriate micro and nanoscale and its ready preparation by established methods from micromachining technologies, providing the time for complicated procedures and the cost of fabrication technologies (Desormeaux *et al.,*2014).

1.2. Problem Statement

Based on literature review, the problem statement of this study is defined as following:

The fabrication of solid-state micro and nano pores with the techniques currently established involves more complex, lengthy procedures and high cost of materials, requiring several additives, subtractive, and RIE through a template structure processes to accomplish pore transfer. Furthermore, no information on electrochemical characterisation for microporous Si_3N_4 membranes that are commercially available in pore sizes appropriate for utilising micro-ITIES array. Therefore, the application of an electrochemical sensor at microporous Si_3N_4 membrane provides a new platform for forming liquid | liquid micro-interface arrays as a basis for electrochemical sensing.

In both clinical diagnosis and environmental monitoring, ion sensing is a significant challenge. There are several works reported for studying transfer reactions of various ionisable drugs via the ITIES. However, very few reports demonstrated the design of ITIES as a sensing platform for the quantitative analysis of drugs, in particularly, drug anion sensing compared to drug cations sensing.

Due to clinically common use of diclofenac and dibucaine drugs and the complexity of the biological matrices such as blood and plasma, application to develop simple, sensitive, and economical methods to improve the precision and efficiency of these frequently used procedures in various biological matrices is still a challenging task.

1.3. Scope and Objectives of the Study

The core work is based on utilising liquid | liquid electrochemistry to investigate the behaviour of diclofenac anion (DCF^-) and dibucaine cation (DIC^+) molecules at such regular ITIES, and in particular examination of the pH ranges of the aqueous phase in which the targeted drugs are ionised and thus amenable to study at the interface (Chapter 4). Subsequently, important modifications to the ITIES are brought in in order to enhance the analytical performance and lead to lower detection limits and better sensitivities. This miniaturisation of the interface to micrometer scale (Chapter *5*) will lead to enhanced diffusion rates for molecules in the aqueous phase, yielding better sensitivity and detection limits (Chapter 6). Finally, the ability to use electrochemistry at ITIES for direct determination of the targeted benzodiazepines in bio-mimetic (artificial serum and saliva) and biological fluid (human urine) will be assessed (Chapter 7). This will entail study of the influence of individual components of biological fluids on micro-interfaces as well as the concerted influence of realistic mixtures. Together, all of these studies will lead to new data and knowledge on the analytical chemistry of pharmaceutical substances. The study presented in this thesis aims to explore the electrochemical performance of microporous membranes at the liquid | liquid interface as a basis for sensor technologies.

The specific objectives of this research are:

a) To characterise the fundamental behaviour of ion transfer of diclofenac anion and dibucaine cation at liquid | liquid interfaces.
b) To characterise the microporous membrane supported-ITIES arrays by morphological and electrochemical methods.
c) To evaluate the electrochemical performance of miniaturised liquid | liquid interface towards its sensitivity for drug detection.
d) To assess the direct detection of targeted drugs in bio-mimic fluids and biological samples at micro-interfaces.

1.4. The limitations of the Study

The handling of the electrochemical cell requires special attention, skill, and experience, especially, keeping the interface in a stable position for the two Luggin capillaries approaching the interface from both sides.

The detection of ions across the ITIES is limited by Gibbs energies of their transfer within the available potential window, which is defined by transferring background electrolyte species from one phase to the other at the limits of the potential window. Therefore, hydrophilic anionic species usually require high Gibbs energies of transfer and makes it difficult to implement the ITIES as a sensing tool. The disadvantage of this system is that the chloride ions limiting the potential window interfere with diclofenac transfer and could distort the measured limiting current. For this reason, another drug molecule, dibucaine, was studied using the modified interface to confirm the methodology used here is valid.

Although the Si_3N_4 membrane surface has been proven to be hydrophobic, the organic phase could not permeate the micropore walls, thus no contact with the aqueous phase occurs. Accordingly, the aqueous phase was assumed to fill the pores, resulting in a recessed interface.

The mathematical treatment is complicated in the case recessed interface with the possibility of overlap between the individual diffusion layers established at each pore on the aqueous side and/or the organic side of the membrane. As result, ion transfer at micro-and nano-ITIES are usually treated via numerical simulations and including simplified hypotheses (Molina *et al.*, 2017).

1.5. Novelty and Motivation of Research

For first time, the objective work is to present the kinetic methodology for studying charge transfer reactions at the liquid | liquid interface via experimental facilities at Universiti Putra Malaysia. Initially, this involved applying some of the classical methodologies mentioned above to the simple ion transfer case and later using a microscale interface. Current changes associated with target drug ion transfer processes across a polarized ITIES, also being a linear function of the drug concentration, can be powerfully used for developing drug sensitive or selective sensors. Similarly, the application of an electrochemical sensor using microporous Si_3N_4 membrane provides a new platform for forming liquid | liquid micro-interface arrays as a basis for drugs sensing. Additionally, this electrochemical sensor could be used as an alternative way to the solid | electrolyte interface method to avoid interferences and secondary products from redox reactions.

The quantification of ionisable drugs transfer processes across ITIES can be an important alternative for understanding drug lipophilicity and sensing purposes (Kim *et al.*, 2015; Goh & Lee, 2016). The efforts of using supportive membranes or substrates with micro-interface features, as well as gelating one of the liquid phases, have enabled great advances in transforming ITIES to a field potentially applicable for instrument incorporated sensing devices for determining a wide range of charged inorganic, organic, drug and even protein species. However, there are still many challenges including selectivity and sensitivity to tackle when using ITIES for developing drug ion sensors.

The investigations to be undertaken here will provide new knowledge on the behaviour of the targeted drug molecules at electrified liquid | liquid interfaces, on the behaviour of such drugs at micro-scale interfaces and the direct detection of these drugs in bio-mimetic and biological fluids. These results will pave the path to future sensing technologies, which will be aimed toward monitoring of therapy while bringing on board some of the advantages of electrochemistry at the microscale to achieve desirable detection limits. Therefore, liquid | liquid electrochemistry can play an important role in the areas of pharmaceutical chemistry, medicine, and pharmacology (Collins & Arrigan, 2009).

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