UNIVERSITI PUTRA MALAYSIA

MOLECULAR DYNAMICS SIMULATION OF PALM KERNEL OIL ESTERS-BASED NANO-EMULSION WITH IBUPROFEN AND DIPALMITOYLPHOSPHATIDYL-CHOLINE LIPID BILAYER

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FS 2016 51

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By

NUR HANA BINTI FAUJAN

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

June 2016

DEDICATED

This thesis is lovingly dedicated to

My great parents,
Prof. Dr. Faujan B. H. Ahmad @ Amat and Mrs. Samilah binti Kutim.

My beloved husband,
Khairul Syahmi bin Kamso.

My dearest kids,
Muhammad Ahnaf and Khairunnajah.

My kindness siblings,
Nur Huda, Nur Hadi, Nur Hani, Nur Hafizah, Nur Hidayah, Nur Hakim, Nur Hariz and Nur Haziqah.

Who lead me with the light of their endless love, support and encourage me throughout my life.

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

MOLECULAR DYNAMICS SIMULATION OF PALM KERNEL OIL ESTERS-BASED NANO-EMULSIONS WITH IBUPROFEN AND DIPALMITOYLPHOSPHATIDYL-CHOLINE LIPID BILAYER

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NUR HANA BINTI FAUJAN

June 2016

Chairman : **Roghayeh Abedi Karjiban, PhD**
Faculty : **Science**

Transdermal drug delivery shows a great potential to enhance the permeation process of drugs with poor solubility and low degree of bioavailability. Nevertheless, the penetration of drug through the skin is a big challenge to overcome. Nano-emulsion system can offer the solution to this problem by acting as chemical penetration enhancers (CPEs). Therefore, palm kernel oil esters (PKOEs)-based and oleyl laurate (OLA)-based nano-emulsion systems were used as drug carrier model. PKOEs-based nano-emulsions with ibuprofen (PKOEs:IBU/T80) and without ibuprofen (PKOEs/T80) were simulated followed by the simulation with dipalmitoylphosphatidylcholine (DPPC) in water (PKOEs/DPPC).

The PKOEs/T80, PKOEs:IBU/T80 and PKOEs/DPPC were simulated to determine the effect of surfactant and drug in the model systems. All simulations were performed using all-atom level molecular dynamics (MD) technique for 50 ns. The aggregation process was observed rapidly in the PKOEs-based nano-emulsion systems. These simulations provided better understanding and insight onto the properties of esters, surfactants, drug and water as well as the diffusion of IBU in PKOEs-based nano-emulsion system. A prolate ellipsoidal shape was obtained in both PKOEs/T80 and PKOEs:IBU/T80 models whereas a doughnut-like toroidal shape was gained in PKOEs/DPPC system. The average radius of gyration (R_g) values of 4.43 (±0.01), 4.50 (±0.00) and 4.09 (±0.01) nm were reported for the PKOEs/T80, PKOEs:IBU/T80 and PKOEs/DPPC aggregates, respectively. The radial distribution function (RDF) analysis detected higher interaction between the PKOEs molecules compared to surfactant molecules in all models which could

be due to the hydrophobic interaction in the aggregated structures. In addition, oleyl oleate (OLE) produced the strongest interaction between IBU molecules with the RDF value of 1.26 (±0.41) in the PKOEs:IBU/T80 aggregate.

Oleyl laurate was used as the main composition of PKOEs for coarse-grained molecular dynamics (CG-MD) simulation study. CG-MD simulation was applied to investigate the aggregation process of OLA-based nano-emulsion with IBU (OLA:IBU/T80) and without IBU (OLA/T80) for 500 ns. The structure of the OLA/T80 and OLA:IBU/T80 aggregates were not completely spherical. The R_g values obtained were 4.36 (±0.04) and 4.34 (±0.04) nm, respectively. The distribution of IBU molecules between the OLA was higher compared to T80 molecules in OLA:IBU/T80 model with the RDF values of 1.77 (±1.16) and 1.12 (±0.40), respectively. The OLA:IBU/T80 was then simulated with DPPC as a lipid bilayer model. The new model created provided a detailed understanding of the diffusion process of drug through the skin. The OLA:IBU/T80 aggregate was able to move freely inside DPPC molecules. The diffusion of OLA:IBU/T80 also affected the DPPC lipid bilayer structure by disturbing the structure of DPPC and losing the bilayer compactness during 500 ns. The RDF value of DPPC as a lipid bilayer model was decreased from g(r)=2.92 to g(r)=1.22 in the presence of OLA:IBU/T80 aggregate.

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

SIMULASI DINAMIK MOLEKUL BAGI NANO-EMULSI BERASASKAN ESTER MINYAK ISIRONG KELAPA SAWIT DENGAN IBUPROFEN DAN LIPID DWILAPISAN DIPALMITOILFOSFATIDIL-KOLIN

Oleh

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Penghantaran transdermal ubatan mempunyai potensi yang sangat hebat bagi meningkatkan proses penelapan ubat yang kurang larut dan rendah tahap bioketersediaan. Namun begitu, penembusan ubat melalui kulit merupakan satu cabaran yang besar. Sistem nano-emulsi dapat menyelesaikan masalah ini dengan bertindak sebagai bahan kimia peningkat penembusan. Oleh yang demikian, nano-emulsi berasaskan ester minyak isirong kelapa sawit (PKOEs) dan oleil laurat (OLA) telah digunakan sebagai model pembawa ubatan. Nano-emulsi berasaskan PKOEs dengan ibuprofen (PKOEs:IBU/T80) dan tanpa ibuprofen (PKOEs/T80) telah disimulasi dan diikuti oleh simulasi dengan dipalmitoilfosfatidilkolin (DPPC) dalam air (PKOEs/DPPC).

PKOEs/T80, PKOEs:IBU/T80 dan PKOEs/DPPC telah disimulasi untuk menentukan kesan surfaktan dan ubat pada model sistem. Kesemua simulasi telah dijalankan menggunakan teknik dinamik molekul (MD) seluruh-atom selama 50 ns. Proses penggumpalan telah dilihat berlaku sangat pantas pada sistem nano-emulsi berasaskan PKOEs. Simulasi ini memberikan pemahaman yang baik dan pengertian yang mendalam tentang sifat ester, surfaktan, ubat dan air serta penyebaran IBU pada sistem nano-emulsi berasaskan PKOEs. Bentuk elipsoidal lonjong telah terbentuk pada kedua-dua model PKOEs/T80 and PKOEs:IBU/T80 sementara bentuk toroid seakan donat telah terbentuk pada sistem PKOEs/DPPC. Nilai jejari putaran (R_g) yang telah dilaporkan bagi agregat PKOEs/T80, PKOEs:IBU/T80 dan PKOEs/DPPC, masing-masing adalah sebanyak 4.43 (±0.01), 4.50 (±0.00) dan 4.09 (±0.01) nm. Analisis fungsi pengagihan radial (RDF) telah mengesan interaksi yang lebih tinggi di antara molekul PKOEs berbanding molekul surfaktan pada semua model yang

mungkin disebabkan oleh interaksi hidrofobik pada struktur agregat yang diperolehi. Di samping itu, oleil oleat (OLE) telah menghasilkan interaksi yang kuat terhadap molekul IBU dengan nilai RDF sebanyak 1.26 (±0.41) nm pada agregat PKOEs:IBU/T80.

Oleil laurat telah digunakan untuk pengajian simulasi berbutir kasar-dinamik molekul (CG-MD) kerana ia merupakan komposisi yang utama bagi PKOEs. CG-MD telah digunakan untuk menyiasat proses pengagregatan bagi nano-emulsi berasaskan OLA dengan IBU (OLA:IBU/T80) dan tanpa IBU (OLA/T80) selama 500 ns. Struktur bagi OLA/T80 dan OLA:IBU/T80 agregat merupakan sfera yang tidak sempurna. Nilai R_g yang diperolehi masing-masing adalah 4.36 (±0.04) dan 4.34 (±0.04) nm. Pengagihan di antara molekul IBU terhadap OLA adalah lebih tinggi berbanding dengan molekul T80 pada model OLA:IBU/T80 dengan nilai RDF masing-masing 1.77 (±1.16) dan 1.12 (±0.40). OLA:IBU/T80 kemudiannya disimulasi terhadap DPPC sebagai model lipid dwilapisan. Model yang baharu dibina dapat memberikan pemahaman yang lebih mendalam bagi penyebaran ubat melalui kulit. Agregat OLA:IBU/T80 mempunyai kebolehan untuk bergerak dengan bebas di dalam molekul DPPC. Penyerapan agregat OLA:IBU/T80 juga mempengaruhi struktur lipid dwilapisan DPPC dengan menggangu struktur DPPC and kehilangan kepadatan dwilapisan sepanjang 500 ns. Nilai RDF bagi membran DPPC sebagai model lipid dwilapisan telah berkurangan daripada g(r)=2.92 ke g(r)=1.22 dengan kehadiran struktur agregat OLA:IBU/T80.

ACKNOWLEDGEMENTS

ALHAMDULILLAH, most of thank to ALLAH through these blessings to complete this thesis. First and foremost, I would like to sincerely thank my supervisor Dr Roghayeh Abedi Karjiban. Performing the projects described herein and writing this dissertation would not have been possible without her continuing support and guidance. I am also very grateful for the rest of my committee members, Professor Dr. Mohd Basyaruddin Abdul Rahman and Professor Dr. Mahiran Basri for their closer guidance and suggestions. Through meaningful discussions, they helped me to refine and expand upon my projects, resulting in better work, better publications, and greater scientific impact. I thank each of them for their patience and their belief in my abilities. Their knowledge in a broad range of disciplines helped me gain a new perspective and direction on this research project.

I am deeply grateful to my colleagues for providing me the opportunity to pursue graduate research and creating an environment in which I was able to grow and excel as a researcher. Many thanks to Nurul Syahidah Shaari, Rozana Yahya, Fong Pik Mun, Lim Wu Zhuan and Muhammad Alif Muhammad Latif have been incredibly helpful, especially in doing any computational works. Shafiqah Abdul Ghani, Zalikha Ibrahim, and several other fellow lab mates have been fantastic friends and have made my research work both interesting and valuable. I also thank Dr Rozana Othman for encouraging me an interest in molecular modeling. They have each been exceptionally constructive towards the improvement of my work through lab meetings, informal discussions, e-mail exchanges and general advice in the list goes on.

Many other members of the Universiti Putra Malaysia have been instrumental to my growth and success as a graduate student. Universiti Putra Malaysia and Ministry of Education have each supported part of my work financially and through the intellectual contributions during the attachment at Lancaster University, United Kingdom under Professor Dr Jamshed Anwar. The rest of the staff of Faculty of Science, Department of Chemistry and Centre of Foundation Studies for Agricultural Science, which have created a friendly and inviting atmosphere in which it was a pleasure to work. For each of these things, I am exceedingly grateful.

A special deeply thank to my parents and my family members have been a great support to me through their mutual encouragement. My husband has been incredibly patient and supportive throughout my graduate career. These works are dedicated to him because he is both my motivation and my reason to work hard and to try my best in everything I do. Thank you so much.

I certify that a Thesis Examination Committee has met on 16 June 2016 to conduct the final examination of Nur Hana binti Faujan on her thesis entitled "Molecular Dynamics Simulation of Palm Kernel Oil Esters-Based Nano-Emulsion with Ibuprofen and Dipalmitoylphosphatidyl-Choline Lipid Bilayer" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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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. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AA	all-atom
ACAT	advanced compartment absorption and transit
AO	Atomic Orbitals
AOT	aerosol OT
BBB	blood brain barrier
CERs	ceramides
CG	coarse-grained
CG-MD	coarse-grained molecular dynamics
CHOL	cholesterol
CMC	critical micelle concentration
CML	Chemical Markup Language
COX	cyclo-oxygenase
COX-1	cyclo-oxygenase-1
COX-2	cyclo-oxygenase-2
CPEs	chemical penetration enhancers
DeTAB	*n*-decyltrimetylammonium bromide
DMPC	dimyristoylphosphatidylcholine
DMSO	dimethyl sulfoxide
DOPC	dioleylphosphatidylcholine
DPD	dissipative particle dynamics
DPPC	Dipalmitoylphosphatidylcholine
ER	enhancement ratio
FFAs	free fatty acids
FFT	Fast Fourier Transform
GAMESS	General Atomic and Molecular Electronic Structure System
GI	Gastrointestinal
GROMACS	Groningen Machine for Chemistry Simulation
GTO	Gaussian Type Orbitals
HF	Hartree-Fock
HLB	hydrophilic-lipophilic balance
IBU	Ibuprofen
IV	intravenous
L_α	lamellar phase
LCAO	linearly combining atomic orbitals
LJ	Lennard-Jones
MC	Monte Carlo
MD	Molecular dynamics
MM	molecular mechanical
MM/QM	molecular mechanics/quantum mechanics
NPT	number of atoms, pressure, temperature
NSAIDs	Non-steroidal anti-inflammatory drugs
NVE	number of atoms, volume and energy
NVT	number of atoms, volume, temperature
O/W	oil-in-water
OCL	Oleyl caprylate

OCP	Oleyl caprate
OCR	Oleyl caproate
OLA	Oleyl laurate
OLE	Oleyl oleate
OLI	Oleyl linoleate
OMY	Oleyl myristate
OPA	Oleyl palmitate
OPLS	optimized potentials for liquid
OPLS	Optimized Potential for Liquid
OST	Oleyl stearate
PBC	Periodic boundary condition
PBC	Periodic Boundary Condition
PC	posphatidylcholine
PE	phosphatidylethanolamine
PEG400	polyethylene glycol 400
PFOB	perfluorooctylbromide
PFOB-based	perflurooctylbromide-based
PFOB-NEP	PFOB nano-emulsion interface
PGs	prostaglandins
PGTOs	Primitive Gaussian Type Orbital
PKO	Palm kernel oil
PKOEs	palm kernel oil esters
PME	Particle-mesh Ewald
PMFs	potentials of mean force
POPC	1-palmitoyl-2-oleyl-phosphatidylcholine
PPEs	physical penetration enhancers
PVA	polyvinyl alcohol
QM	quantum mechanical
RESP	restrained electrostatic potential
RMs	reverse micelles
SANS	small-angle neutron scattering
SC	*Stratum corneum*
SDS	sodium dodecyl sulphate
SLM	solid lipid micro-particles
STO	Slater Type Orbitals
T80	Tween 80
UA	united atom
VMD	Visual Molecular Dynamics
W/O	water-in-oil

CHAPTER 1

INTRODUCTION

1.1 Background of Research

Ibuprofen (IBU) is one of the non-steroidal anti-inflammatory drugs (NSAIDs) used for pain relief, anti-stiffness and anti-inflammatory effect in rheumatoid arthritis, osteoarthritis, fever and gout treatments. It has a short plasma half-life, low degree of bioavailability and low solubility in water (Winstanley and Walley, 2002). Drug based nano-emulsions with nano droplet size have the ability to enhance the absorption of drugs with poor solubility and low bioavailability like IBU. Drugs can diffuse effectively by using the nano-emulsion formulation. Nano-emulsion systems can solubilize the hydrophobic substances within water-based phase (Delmas *et al.,* 2010) and improve the permeation of many drugs for transdermal delivery application (Shakeel *et al.,* 2009).

Nano-emulsion systems can act as chemical penetration enhancers (CPE) and drug carrier (*Shakeel et al.,* 2007; Kong *et al.,* 2011). Palm kernel oil esters (PKOEs)-based nano-emulsions have been produced to be applied for drug delivery system (Salim *et al.,* 2011; Musa *et al.,* 2013; De Costa *et al.,* 2014; Razaee *et al.,* 2014). PKOEs with relatively short chain length hydrocarbon can be considered as a good carrier to deliver drugs into the body (Keng *et al.,* 2009).

Transdermal drug delivery system has been developed to control the release of drugs. Transdermal delivery is the administration of drug molecules directly to the targeting area through the *stratum corneum (SC)* of skin. The mobility of drugs, ions and water molecule is controlled by the *SC* skin barrier arranged in multiple bilayers called lamellae structure (Marrow *et al.,* 2007; Subedi *et al.,* 2010; Iwai *et al.,* 2012).

The skin barrier consists of lipid structure in the extracellular space between the *SC* cells. Lipid consists of free fatty acids (FFAs), long-chain ceramides (CERs) and cholesterol (CHOL) (Wertz and Noelen, 2003). The *SC* is a dead keratinocytes layer of epidermal cells embedded in a lipid matrix (Morrow *et al.,* 2007). The lipid matrix is formed by a parallel orientation of the lipid head groups in a bilayer structure.

Molecular dynamics (MD) simulation is one of the computational approaches which have been used to model the nano-emulsion (Abdul Rahman *et al.,* 2008; Abdul Rahman *et al.,* 2009; Lee *et al.,* 2010) and lipid systems (Eriksson and

Eriksson, 2011; Mihailescu *et al.,* 2011) for several years. Many interesting properties of the systems are possible to be understood and estimated in both atomic and molecular levels. MD technique also has the abilities to simulate the interactions of nano-materials with biological membranes (Shi *et al.,* 2008; Wallace and Sansom, 2008).

1.2 Problem Statements

Oral intakes of IBU may cause gastrointestinal (GI) ulcers or perforations, stomach bleeding and kidney toxicity in long term treatment (Beetge *et al.,* 2000). Transdermal drug delivery system could be the alternative to transfer IBU drug through the skin. Transdermal delivery has many advantages as compared to other routes by avoiding first-pass hepatic metabolism and providing patient compliance (Prausnitz and Langer, 2008). Nevertheless, there is a big challenge in transdermal application, considering the physicochemical properties of IBU. The transportation of IBU molecules has to overcome the skin barrier. Nano-emulsion systems could improve the properties of IBU in order to enhance the permeability of drug passing through the skin.

Many experimental works tried to produce nano-emulsion systems to achieve the optimal level of drug permeation through the *SC* (Shakeel *et al.,* 2009). They focused mostly on the formulation and preparation process. However, the self-assembly or self-aggregation of nano-emulsions and the formation of droplet are difficult to be observed using laboratory tools. The laboratory experiments hardly detect the distribution of drug molecules in nano-emulsion droplet and the fundamental mechanism on how the system can penetrate the *SC*.

Computer simulations could be applied to describe the behaviour of the simulated nano-emulsion model by determining their structural and dynamical properties (Abedi Karjiban *et al.,* 2015). An all-atomic MD technique is still limited due to a practical upper simulation time limit of ~100 ns for complex systems if computer clusters are not used. The main problem for all-atom (AA) MD techniques is to reach the real equilibration state. This problem can be solved by using coarse-grained molecular dynamics (CG-MD). CG-MD represents the system by reducing the numbers of atoms as compared with an all-atom description. Coarse-graining approach can be very helpful to extend the simulation time and bridge the gap between the simulation and experimental techniques.

1.3 Scope of Research

By using the experimental findings reported, detailed understanding and insight into the interaction of nano-emulsion system with lipid bilayer can be

further explained by applying computer simulation approaches. In this project, MD simulation was applied to obtain the molecular structure, the stability and the dynamical information of PKOEs-based nano-emulsion system. The simulations were utilized to investigate the mechanism of self-assembly process of PKOEs-based nano-emulsion model with and without IBU. Later on, the CG-MD study was performed to simulate the self-assembly process of oleyl laurate (OLA)-based nano-emulsion system with and without IBU. Oleyl laurate (OLA) is the main component of PKOEs. This CG model was then used to study the distribution of OLA-based nano-emulsion containing IBU through dipalmitoylphosphatidyl-choline (DPPC) lipid bilayer. DPPC lipid bilayer was simulated as the uppermost *SC* layer of skin. Overall, this study could explain the application of PKOEs-based nano-emulsion system as a carrier of IBU drug for transdermal delivery.

1.4 Objectives

The main objective of this research was to apply MD simulation techniques to model the self-assembly process of PKOEs-based and OLA-based nano-emulsions with and without IBU followed by exploring the distribution of OLA-based nano-emulsion with IBU through DPPC lipid bilayer. Therefore, the following specific objectives were pursued:

1. To examine the mechanism of self-assembly process in both PKOEs-based and OLA-based nano-emulsion systems.

2. To determine the physicochemical and dynamical properties of PKOEs-based and OLA-based nano-emulsions models.

3. To investigate the diffusion process of IBU in both PKOEs-based and OLA-based nano-emulsions model systems.

4. To identify the distribution OLA:IBU/T80 aggregate in DPPC.

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