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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By

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

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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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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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Fakulti : **Sains**

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.

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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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TABLE OF CONTENTS

		Page
ABSTRACT		i
ABSTRAK		iii
ACKNOWLEDGEMENT		v
APPROVAL		vi
DECLARATION		viii
LIST OF TABLES		xiv
LIST OF FIGURES		xvi
LIST OF APPENDICES		xxi
LIST OF ABBREVIATIONS		xxii
CHAPTER		
1	**INTRODUCTION**	1
	1.1 Background of Research	1
	1.2 Problem Statements	2
	1.3 Scope of Research	2
	1.4 Objectives	3
2	**LITERATURE RIVIEW**	4
	2.1 Transdermal Drug Delivery	4
	2.1.1 The Skin	5
	2.1.2 Skin Permeation	5
	2.1.3 Stratum Corneum and Its Compositions	7
	2.1.4 Penetration Enhancers	8
	2.1.5 Nano-emulsion and Its Components	8
	2.1.5.1 Palm Kernel Oil	9
	2.1.5.2 Surfactants	11
	2.1.6 Non-steroidal Anti-Inflammatory Drugs	13
	2.1.6.1 Ibuprofen	14
	2.2 Computational Studies of Bilayer Transport	15
	2.2.1 Dipalmitoylphosphatidyl-choline as the Skin Membrane Model	15
	2.2.2 Computational Methods Used in the Bilayer Transport Studies	16
	2.2.2.1 Molecular Dynamics Simulation	16
	2.2.2.2 Coarse-grained Molecular Dynamics Simulation	18
3	**METHODOLOGY**	20
	3.1 Materials	20
	3.1.1 Computer Software	21
	3.1.2 Computer Hardware	22
	3.2 The Model Systems	23
	3.2.1 Palm Kernel Oil Esters-based	23

Nano-emulsions with and without Ibuprofen
3.2.2 Palm Kernel Oil Esters-based Nano-emulsion with Dipalmitoylphosphatidyl-choline 25
3.2.3 Oleyl Laurate-based Nano-emulsions with and without Ibuprofen 26
3.2.4 Oleyl Laurate-based Nano-emulsions with Ibuprofen and Dipalmitoylphosphatidyl-choline 26
3.3 Simulation Technique 26
3.3.1 Force Field 26
3.3.1.1 The Optimized Potentials for Liquid Force Field 27
3.3.1.2 MARTINI Force Field 28
3.3.2 Preparing the Initial Structure 31
3.3.3 Creating the Topology 33
3.3.4 Mapping Coarse-Grained Structure 33
3.3.4.1 Tween 80 35
3.3.4.2 Oleyl Laurate 38
3.3.4.3 Ibuprofen 40
3.3.4.4 Dipalmitoylphosphatidyl-choline 42
3.3.5 Periodic Boundary Condition 44
3.3.6 Thermodynamic Ensembles 45
3.3.6.1 Constant Temperature Dynamics 46
3.3.6.2 Constant Pressure Dynamics 47
3.3.7 Energy Minimization 48
3.3.8 Production of Model Simulations 49
3.3.8.1 Molecular Dynamics Simulations of Palm Kernel Oil Ester-based Nano-emulsion 49
3.3.8.2 Coarse-Grained Molecular Dynamics Simulations of Oleyl Laurate-based Nano-emulsions 50
3.3.8.3 Coarse-Grained Molecular Dynamics Simulation of Oleyl Laurate-based Nano-emulsion with Ibuprofen and Dipalmitoylphosphatidylcholine 51
3.4 Analysis of the System 53
3.4.1 Physical Properties 53
3.4.1.1 Shape of the Aggregate 53
3.4.1.2 Size of the Aggregate 54
3.4.2 Hydration Properties 55
3.4.2.1 Solvent Accessible Surface Area 55
3.4.2.2 Radial Distribution Function 55
3.4.2.3 Diffusion Analysis 56
3.4.2.4 Area per Lipid 57

4 RESULTS AND DISCUSSION 59
4.1 Effect of Ibuprofen in Palm Kernel Oil Esters-based Nano-emulsions with Tween 80 59

4.1.1 Self-assembly Process 59
4.1.2 Physical Properties 62
4.1.2.1 The Shape of the Aggregates 63
4.1.2.2 The Size of the Aggregates 66
4.1.3 Hydration Properties 67
4.1.3.1 Solvent Accessible Surface Area 67
4.1.3.2 Radial Distribution Function 70
4.1.3.3 Diffusion Analysis 75
4.2 Palm Kernel Oil Ester-based Nano-emulsion with Dipalmitoylphosphatidyl-choline 78
4.2.1 Self-assembly Process 78
4.2.2 Physical Properties 81
4.2.2.1 The Shape of the Aggregate 82
4.2.2.2 The Size of the Aggregate 84
4.2.3 Hydration Properties 85
4.2.3.1 Solvent Accessible Surface Area 85
4.2.3.2 Radial Distribution Function 86
4.2.3.3 Self-diffusion Coefficient 88
4.3 Effect of Ibuprofen in Oleyl Laurate-based Nano-emulsion Model 90
4.3.1 Self-assembly Process 90
4.3.2 Physical Properties 93
4.3.2.1 The Shape of the Aggregates 94
4.3.2.2 The Size of the Aggregates 99
4.3.3 Hydration Properties 100
4.3.3.1 Solvent Accessible Surface Area 100
4.3.3.2 Radial Distribution Function 102
4.3.3.3 Diffusion Analysis 106
4.4 Oleyl Laurate-based Nano-emulsion with Ibuprofen and Dipalmitoylphosphatidyl-choline 108
4.4.1 Physical Properties 108
4.4.1.1 DPPC Bilayer Structure 109
4.4.1.2 Bilayer Thickness 111
4.4.1.3 Area per Lipid 113
4.4.2 The transport of Oleyl Laurate-based Nano-emulsion with Ibuprofen into Dipalmitoylphosphatidyl-choline Bilayer 115
4.4.2.1 Hydration Properties 116
4.4.2.2 Distribution of Oleyl Laurate-based Nano-emulsion with Ibuprofen within the Dipalmitoylphosphatidyl-choline Bilayer 117
4.4.3 Diffusion Analysis 121

5 CONCLUSIONS AND RECOMMENDATION 124
5.1 Conclusions 124
5.2 Recommendations for Future Studies 125

REFERENCES 127
APPENDICES 146
BIODATA OF STUDENT 181
LIST OF PUBLICATIONS 182

LIST OF TABLES

Table		Page
1	The composition of fatty acid in palm kernel oil	10
2	List of Computer Hardware and Software	22
3	The number of molecules used in the PKOEs-based nano-emulsions with and without ibuprofen	24
4	The number of molecules used in the PKOEs-based nano-emulsion with DPPC	25
5	The number of molecules used in the OLA-based nano-emulsions with and without ibuprofen	26
6	The level of interactions between the different CG sites	30
7	Masses assigned to CG particles of T80	35
8	LJ interaction parameters for coarse-grained T80	37
9	Bond parameters for coarse-grained T80	37
10	Angle bending parameters used for coarse-grained T80	38
11	Masses assigned to CG particles of OLA	39
12	LJ interaction parameters for coarse-grained OLA	39
13	Bond parameters for coarse-grained OLA	40
14	Angle bending parameters used for coarse-grained OLA	40
15	Masses assigned to CG particles of IBU	41
16	LJ interaction parameters for coarse-grained IBU	41
17	Bond parameters for coarse-grained IBU	42
18	Angle bending parameters used for coarse-grained IBU	42
19	Masses assigned to CG particles of DPPC	43
20	LJ interaction parameters for coarse-grained DPPC	44
21	Bond parameters for coarse-grained DPPC	44
22	Angle bending parameters used for coarse-grained DPPC	44
23	The radius of gyration (R_g) of PKOEs-based nano-emulsion with and without ibuprofen during the last 2 ns for both simulations	67
24	Total solvent-accessible surface areas (SASA) of PKOEs-based nano-emulsion with and without ibuprofen during the last 2 ns	68
25	Total solvent-accessible surface areas (SASA) of PKOEs, T80 and IBU molecules in both simulations of PKOEs-based nano-emulsions during the last 2 ns	70
26	A summary of the radial distribution function (RDF) values between each oleyl ester, T80 and IBU molecules in the PKOEs-based nano-emulsion model with and without drug	76
27	A summary of the diffusion rate of the PKOEs, T80 and IBU molecules in the PKOEs-based nano-emulsions models	77

28	The principal moments of inertia and the eccentricity (e) values of the OLA/T80 and OLA:IBU/T80 aggregate at 500 ns	98
29	The radial distribution function (RDF) average values between OLA, T80 and IBU in oleyl laurate nano-emulsion system during the last 100 ns of both simulation	106
30	The diffusion rate of OLA, T80 and IBU molecules in OLA/T80 and OLA:IBU/T80 models for 500 ns	108

LIST OF FIGURES

Figure		Page
1	The physiology of human skin	5
2	Transepidermal permeation route in transdermal drug delivery system	6
3	Transappendegeal pathway involves the sweat ducts (1) and the hair follicles (3) whereas the transcellular route through the continuous SC (2) in transdermal drug delivery system	7
4	A Flowchart of the summary of all simulations carried out in this study	21
5	Phase diagram of PKOEs/T80/H_2O system at 25±1.0 ^oC. The isotropic, multiphase, and liquid crystal regions represented in blue, green and yellow, respectively	23
6	Phase diagram of PKOEs with ibuprofen/T80/H_2O system at 25±1.0 ^oC. The isotropic, multiphase, and liquid crystal regions represented in blue, green and yellow, respectively	24
7	Phase diagram of PKOEs/DPPC/H_2O system at 25±1.0 ^oC. The homogenous region represented in white and the multiphase region in green	25
8	Molecular structure of oleyl esters, surfactants and IBU	32
9	CG model for T80 molecule	36
10	CG model of OLA molecule	39
11	CG model of IBU molecule	41
12	CG model of DPPC molecule	43
13	Periodic boundary conditions in two dimensions represented by atom *i* and j with their images of *i'* and *j'*	45
14	Snapshot pictures of the aggregation process for PKOEs/T80 model show a spontaneous self-assembly of PKOEs together with T80 molecules at 4 ns. A prolate ellipsoidal shape was obtained from PKOEs-based nano-emulsion system at 50 ns. The PKOEs molecules are shown in magenta and T80 molecules are lime. Water molecules have been removed for clarity	60
15	Snapshot pictures of the aggregation process for PKOEs:IBU/T80 model show a spontaneous self-assembly of PKOEs together with T80 molecules at 2 ns. A prolate ellipsoidal shape was obtained from PKOEs-based nano-emulsion system at 50 ns. The PKOEs molecules are shown in magenta, T80 molecules are lime and IBU molecules are orange. Water molecules have been removed for clarity	61
16	Root mean square deviations (RMSD) during the self-assembly process of the PKOEs/T80 and PKOEs:IBU/T80 aggregates over 50 ns	62
17	The principal moments of inertia fluctuation of PKOEs/T80 for 50 ns	63

18	The principal moments of inertia fluctuation of PKOEs:IBU/T80 for 50 ns simulation	63
19	The average ratios of the principal moments of inertia (I_1/I_2, I_1/I_3 and I_2/I_3) of PKOEs/T80 aggregate as a function of time	64
20	The average ratios of the principal moments of inertia (I_1/I_2, I_1/I_3 and I_2/I_3) of PKOEs:IBU/T80 aggregate as a function of time	65
21	The time evolution profile of the eccentricity (e) fluctuation for PKOEs/T80 and PKOEs:IBU/T80 models	65
22	Radius of gyration (R_g) fluctuation versus time for PKOEs/T80 and PKOEs:IBU/T80 nano-emulsion during 50 ns	66
23	Total solvent-accessible surface areas (SASA) is shown in purple, hydrophobic (green) and hydrophilic (black) contacted with the PKOEs/T80 aggregate in PKOEs-based nano-emulsion system as a function of time	69
24	Total solvent-accessible surface areas (SASA) is shown in purple, hydrophobic (green) and hydrophilic (black) contacted with the PKOEs:IBU/T80 aggregate in PKOEs-based nano-emulsion system as a function of time	69
25	Radial distribution function (RDF) changes in both PKOEs/T80 and PKOEs:IBU/T80 aggregates	71
26	Radial distribution functions (RDF) changes between the PKOEs and the T80 molecules in the PKOEs/T80 aggregated structure	72
27	Radial distribution functions (RDF) changes between the PKOEs, T80 and IBU molecules in the PKOEs:IBU/T80 aggregated structure	72
28	Radial distribution function (RDF) of the water molecules that were near to the T80 molecules and PKOEs molecules in the PKOEs/T80 nano-emulsion system during the last 2 ns of the simulation times	73
29	Radial distribution function (RDF) of the water molecules that were near to the T80 molecules and PKOEs molecules in the PKOEs:IBU/T80 nano-emulsion system during the last 2 ns of the simulation times	74
30	Mean square displacements (MSD) changes of the PKOEs/T80 and PKOEs:IBU/T80 aggregates for 50 ns	77
31	Snapshot pictures of PKOEs/DPPC system during molecular dynamics (MD) simulations. These snapshots show the spontaneous self-assembly of PKOEs together with the DPPC into the doughnut-like toroidal shape. The PKOEs are shown in orange and DPPC molecules are in blue. Water molecules have been removed for clarity	80

32	The number of cluster changes during the self-assembly process	81
33	Root mean square deviations (RMSD) of the PKOEs/DPPC model system as a function of simulation time	82
34	The principal moments of inertia fluctuations of PKOEs/DPPC model system for 50 ns	83
35	The changes of the ratio of the principal moments of inertia of PKOEs/DPPC aggregate during 50 ns	83
36	Eccentricity fluctuations of the formation PKOEs/DPPC aggregate during 50 ns	84
37	The radius of gyration (R_g) fluctuations of PKOEs/DPPC model system for 50 ns	85
38	Solvent accessible surface areas (SASA) of PKOEs/DPPC model system during 50 ns simulation	86
39	Radial distribution functions (RDF) of PKOEs and DPPC molecules in the PKOEs/DPPC model during 50 ns	87
40	Radial distribution functions (RDF) analysis between the PKOEs molecules and the DPPC molecules in the aggregated structure formed during the self-assembly of PKOEs/DPPC system	88
41	Mean Square Displacement (MSD) of PKOEs/DPPC self-assembled structure as a function of time	89
42	Mean Square Displacement (MSD) changes of PKOEs and DPPC molecules in the PKOEs/DPPC model during 50 ns	89
43	Potential energy of OLA/T80 and OLA:IBU/T80 models for 500 ns	90
44	The snapshots of OLA/T80 aggregate for 500 ns; oleyl laurate (orange) and Tween 80 (purple). Water was omitted for clarity	91
45	The snapshots of OLA:IBU/T80 aggregate for 500 ns; oleyl laurate (orange), Tween 80 (purple) and ibuprofen (blue). Water was omitted for clarity	92
46	The Root Mean Squre Deviations (RMSD) of OLA/T80 and OLA:IBU/T80 aggregates for 500 ns	94
47	The principal moments of inertia fluctuations of OLA/T80 aggregate for 500 ns	95
48	The principal moments of inertia fluctuations of OLA:IBU/T80 aggregate for 500 ns	96
49	The principle moment of inertia ratios plot for OLA/T80 model as a function of time	97
50	The principle moment of inertia ratios changes for OLA:IBU/T80 model as a function of time	97
51	The eccentricity (e) fluctuation for OLA/T80 and OLA:IBU/T80 aggregates through 500 ns simulation times	99
52	Radius of gyration fluctuations of OLA/T80 and OLA:IBU/T80 aggregates during 500 ns simulation	100

53	The hydrophobic SASA of OLA/T80 and OLA:IBU/T80 models during the simulation	101
54	Radial Distribution Function (RDF) change of the hydrophobic regions for OLA/T80 and OLA:IBU/T80 models during the last 100 ns of both simulation	103
55	Radial Distribution Function (RDF) between OLA/T80 and OLA:IBU/T80 aggregates with water during the last 100 ns	104
56	Radial Distribution Function (RDF) between OLA and T80 molecules with water in the OLA/T80 system during the last 100 ns of simulation	104
57	Radial Distribution Function (RDF) between OLA, T80 and IBU molecules with water in OLA:IBU/T80 system during the last 100 ns of simulation	105
58	The Mean Square Displacement (MSD) changes of OLA/T80 and OLA:IBU/T80 aggregates during 500 ns simulation	107
59	The snapshot pictures of DPPC aggregation for 500 ns simulation time; the polar head groups of choline (blue); phosphate (grey); glycerol (pink); the hydrocarbon tail (cyan) and water (yellow)	110
60	Density distribution profile of DPPC in water during the last 100 ns	112
61	Density distribution profile of DPPC lipid bilayer with OLA:IBU/T80 system during 500 ns	113
62	The area per lipid changes of DPPC lipid bilayer in the presence of OLA:IBU/T80 aggregate for 500 ns simulation time	114
63	The snapshots picture of the starting simulation. The OLA:IBU/T80 aggregate was placed outside of the DPPC bilayer.	115
64	The snapshot pictures of OLA:IBU/T80 and DPPC bilayer during 500 ns simulation time	116
65	Radial distribution function changes of DPPC in the bilayer system at the last 100 ns	117
66	Radial distribution function of DPPC in the presence of OLA:IBU/T80 at the last 100 ns	118
67	Radial distribution function of *sn*-1 tail relative to the other *sn*-1 tails	118
68	Radial distribution function of the center of mass of *sn*-1 tail relative to the other *sn*-1 tails in the presence of OLA:IBU/T80	119
69	The radial distribution function (RDF) of DPPC lipid bilayer at interface	120
70	The distribution of OLA:IBU/T80 calculated according to the distance between the OLA:IBU/T80 center of mass and the membrane center of mass during 500 ns simulation time	121
71	The Mean Square Displacement (MSD) change of DPPC lipid bilayer system	122

72 The Mean Square Displacement (MSD) changes of DPPC in the presence of OLA:IBU/T80 aggregate 123

LIST OF APPENDICES

Appendix		Page
A	Supplementary data for the Model System	146
A1	Calculation for number of molecule used in the model	146
B	Topology of the molecules used for MD Simulation	147
B1	Oleyl caproate	147
B2	Oleyl laurate	148
B3	Oleyl stearate	150
B4	Oleyl caprate	152
B5	Oleyl myristate	153
B6	Oleyl oleate	155
B7	Oleyl caprylate	157
B8	Oleyl palmitate	159
B9	Oleyl linoleate	160
B10	Tween 80	162
B11	Ibuprofen	166
C	Supplementary data for Mapping Coarse-Grained Structure	168
C1	Mapping of Tween 80 Structure	168
D	Simulation Parameters for MD Simulation	170
D1	Parameter file for Energy Minimization	170
D2	Parameter file for Position Restrained Heating	170
D3	Parameter file for Equilibration	171
D4	Parameter file for Production runs	173
D5	Simulation Parameters for CG-MD Simulation	174
	Parameter file for Energy Minimization	174
D6	Parameter file for Position Restrained Heating	175
D7	Parameter file for Equilibration	176
D8	Parameter file for Production runs	178
E1	Radius of gyration (R_g) of the PKOEs and T80 molecules in the PKOEs/T80 model	180
E2	Radius of gyration (R_g) of the PKOEs, T80 and IBU molecules in the PKOEs:IBU/T80 model	180
E3	A mean square displacements (MSD) analysis of the PKOEs and the T80 molecules in PKOEs/T80 aggregate during 50 ns	180
E4	A mean square displacements (MSD) analysis of the PKOEs, T80 and IBU molecules in PKOEs:IBU/T80 during 50 ns	180

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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