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MONTE CARLO SIMULATION OF MICELLE FORMATION IN MIXED SURFACTANTS AND PALM-KERNEL OIL ESTERS-BASED NANOEMULSION

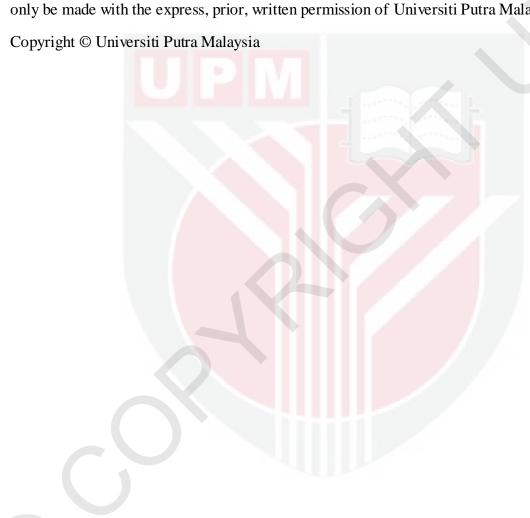**RUZANNA BINTI YAHYA**

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MONTE CARLO SIMULATION OF MICELLE FORMATION IN MIXED SURFACTANTS AND PALM-KERNEL OIL ESTERS-BASED NANOEMULSION

By

RUZANNA BINTI YAHYA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science.

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Master of Science.

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December 2014

Chairman : **Roghayeh Abedi Karjiban, PhD**

Faculty : **Science**

For several years, the experimental laboratory and Molecular Dynamics (MD) simulation works was used to determine the behaviour and structural properties of nanoemulsions. In order to solve the problems related to transdermal drug nano-delivery system, the palm-kernel oil esters (PKOEs) nanoemulsion can act as chemical penetration enhancers with the help of non-ionic surfactants properties. Here, the stochastic numerical methods or Monte Carlo (MC) was suggested to develop new configurations of a system of interest. The physical properties of the mixed surfactants and nanoemulsions formulation were studied using the Metropolis Monte Carlo (MMC) algorithm while grand canonical Monte Carlo (GCMC) simulation was applied to investigate the displacements of critical micelle concentration (CMC) for both systems. Seven set of mixed surfactants (Brij 92, Brij 96 and water) models and five simulation sets of PKOEs nanoemulsion (PKOEs, Brij 92, Brij 96, isopropanol as co-surfactant and water) which were adapted from the experimental phase diagram was simulated using MMC algorithm up to 10 and 20 million MC steps, respectively in order to determine the most suitable composition of mixed surfactants and PKOEs nanoemulsion with water molecules.

The chemical potential for both model systems were calculated using Reference Interaction Site Model (RISM) module. The most suitable composition from MMC simulations was then grouped to five systems of mixed surfactants and six systems for PKOEs nanoemulsion with a series of different values of temperature and chemical potential resulted from the histogram-reweighting. The latest model systems were used to simulate in grand canonical ensemble for 10 million MC steps with 50% of insertion and removal of molecules and 50% of reptation moves. From the results, the acceptance ratio for single atom moves of the mixed surfactants was increased as the percentage of surfactants was increased from 0.429 to 0.591 meanwhile the acceptance ratio for single atom moves for PKOEs nanoemulsion was decreased as the number of molecules increased from 0.600 to 0.587 due to the different composition of the surfactants and PKOEs nanoemulsion with water molecules where both systems formed spherical shape.

The physical properties of models such as radius of gyration, solvent accessible surface area, radial distribution function and total energy were also determined. The chemical potential for the mixed surfactants was produced at the range of 0.77 - 2.06 J/mol while for the PKOEs nanoemulsion the value was ranged from 3.17 - 5.00 J/mol. The displacement of CMC was increased while the insertion and deletion ratio movement were decreased as the temperature and chemical potential increased due to the drop of density in the cubic box during the simulation. Therefore these observations indicated that the physical properties of mixed surfactant and PKOEs nanoemulsion systems were adequately described by the simulation. The acceptance ratio for displacement movement critical micelle concentration (CMC) for the mixed surfactants and PKOEs nanoemulsion systems was also considered accepted with reasonable values produced.

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Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk Ijazah Master Sains.

SIMULASI *MONTE CARLO* BAGI PEMBENTUKKAN MISEL DIDALAM CAMPURAN SURFAKTAN DAN NANOEMULSI YANG BERASASKAN ESTER MINYAK ISIRONG SAWIT

Oleh

RUZANNA BINTI YAHYA

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Sejak beberapa tahun kebelakangan ini, kaedah ujikaji makmal dan simulasi Dinamik Molekul (MD) telah digunakan untuk mengkaji sifat dan struktur nanoemulsi. Bagi menyelesaikan masalah yang berkaitan dengan sistem nano-penghantaran ubatan melalui kaedah transdermal, nanoemulsi ester minyak isirong sawit (PKOEs) boleh bertindak sebagai bahan kimia peningkat penerobosan dengan bantuan sifat-sifat surfaktan bukan ion. Di dalam penyelidikan ini, kaedah berangka stokastik atau simulasi *Monte Carlo* (MC) telah dicadangkan untuk membangunkan konfigurasi yang baru bagi sistem yang dikehendaki. Sifat fizikal bagi formulasi campuran surfaktan dan nanoemulsi telah dikaji menggunakan kaedah algoritma *Metropolis Monte Carlo* (MMC) manakala simulasi *grand canonical Monte Carlo* (GCMC) telah digunakan untuk mengkaji sesaran kepekatan misel kritikal (CMC) bagi kedua-dua system. Tujuh set model campuran surfaktan (Brij 92, Brij 96 dan air) dan lima set simulasi nanoemulsi PKOEs (PKOEs, Brij 92, Brij 96, isopropanol sebagai ko-surfaktan dan air) yang berdasarkan gambar rajah fasa yang diperolehi daripada ujikaji makmal telah disimulasi menggunakan algoritma MMC selama 10 dan 20 juta langkah MC masing-masing untuk mendapatkan komposisi yang paling sesuai bagi campuran surfaktan dan nanoemulsi PKOEs dengan molekul air.

Keupayaan kimia bagi kedua-dua model sistem telah dikira menggunakan modul Rujukan Interaksi Tapak (RISM). Komposisi yang paling sesuai daripada simulasi MMC kemudiannya telah dibahagikan kepada lima sistem untuk campuran surfaktan dan enam system untuk nanoemulsi PKOEs menggunakan dengan bacaan suhu dan keupayaan kimia yang berbeza secara bersiri yang dihasilkan daripada *histogram-reweighting*. Sistem model yang terkini telah digunakan untuk simulasi bagi ensembel *grand canonical* untuk 10 juta langkah MC dengan penambahan dan penyingkiran molekul sebanyak 50% dan pergerakan *reptation* sebanyak 50%. Hasil kajian yang diperolehi menunjukkan nisbah penerimaan bagi pergerakan atom tunggal bagi campuran surfaktan telah meningkat seiring dengan peningkatan kepekatan surfaktan yang telah meningkat daripada 0.429 sehingga 0.591, sementara itu nisbah penerimaan bagi pergerakan atom tunggal untuk nanoemulsi PKOEs pula telah berkurangan daripada 0.600 sehingga 0.587 seiring dengan peningkatan bilangan molekul yang meningkat berdasarkan perbezaan komposisi surfaktan dan nanoemulsi PKOEs dengan molekul air yang mana bentuk sfera telah diperolehi daripada kedua-dua sistem.

Sifat-sifat fizikal bagi model seperti jejari putaran, permukaan boleh akses pelarut dan fungsi taburan radial dan jumlah tenaga juga telah ditentukan. Keupayaan kimia bagi campuran surfaktan yang diperolehi ialah dalam julat 0.76510 – 2.05767 J / mol manakala nilai bagi nanoemulsi PKOEs adalah dalam julat 3.17152 – 5.00000 J / mol. Nilai sesaran CMC telah meningkat sementara nisbah penambahan dan penyingkiran pergerakan telah menurun selaras dengan peningkatan suhu dan keupayaan kimia berdasarkan kepada penurunan ketumpatan didalam kotak kubik semasa simulasi. Oleh itu, hasil pemerhatian menunjukkan bahawa sifat fizikal bagi sistem campuran surfaktan dan nanoemulsi PKOEs telah berjaya dibincangkan dengan menggunakan kaedah simulasi. Nisbah penerimaan bagi sesaran CMC untuk sistem campuran surfaktan dan nanoemulsi PKOEs juga telah dapat diterima dengan penghasilan nilai yang munasabah.

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I certify that an Examination Committee has met on 15th December 2014 to conduct the final examination of Ruzanna binti Yahya on her thesis entitled "Monte Carlo Simulation of micelle formation in mixed surfactants and Palm-Kernel Oil Esters-based nanoemulsion" in accordance with 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 Master of Science.

Members of the Thesis Examination Committee were as follows:

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Date: 19 March 2015

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

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Date:

Declaration by Members of Supervisory Committee:

This is to confirm that:
- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____

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LIST OF ABBREVIATIONS

ABNR	adopted basis Newton-Raphson
ARM	Acceptance Ratio Method
ASAXS	anomalous small-angle X-ray scattering
Brij 92	Polyoxyethylene (2) oleyl ether
Brij 96	Polyoxyethylene (10) oleyl ether
CG-MD	Coarse-grained Molecular Dynamics
CHARMM	Chemistry at Harvard Macromolecular Mechanics
CMC	Critical Micelle Concentration
CPE	Chemical Penetration Enhancer
DOMC	Dynamically Optimized Monte Carlo
GAMESS	General Atomic and Molecular Electronic Structure System
GCMC	Grand Canonical Monte Carlo
HLB	Hydrophile-lipophile balance
LJ	Lennard-Jones
MC	Monte Carlo
MD	Molecular Dynamics
MMC	Metropolis Monte Carlo
MOFs	Metal-organics Frameworks
MOI	Moment of Inertia
NMF	Natural Moisturizing Factor
O/W	Oil in water emulsion
PKOEs	Palm-kernel Oil Esters
PME	Particle Mesh Ewald
POEs	Palm Oil Esters
RESP	Restrained Electrostatic Potential
RISM	Reference Interaction Site Model
SANS	Small Angle Neutron Scattering
SASA	Solvent Accessible Surface Area
SAXS	Small Angle X-ray Scattering
TTAB	Tetradecyltrimethylammonium Bromide
W/O	Water in Oil emulsion

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CHAPTER 1

INTRODUCTION

Nanoemulsions of palm-kernel oil wax esters (PKOEs) is considered as active ingredients' carriers and chemical penetration enhancers (CPEs) due to their amphiphilic esters properties (Keng *et al.*, 2009; Salim *et al.*, 2011). The palm-kernel oil esters based nanoemulsions can be described structurally as dispersions of self-assembled structures of surfactant molecules and palm kernel oil esters in water as a result of solubilization of surfactant aggregates in the nanoemulsions' formulation. For example, it has been shown that spherical and cylindrical micelles are superior for acting as a good CPE due to their size (permeability), the mobility of the drug and the release of drug (Peltola *et al.*, 2003).

Micelle is known as an inexactly bound aggregation of several tens or hundreds of atoms, ions, or molecules to form a colloidal molecule. An aggregation of micelles can adequately reduce vascular leakage at inflamed spots due to the suitability of micelle as nanocarriers for several anti-flammatory compounds and local delivery of drugs (Rosen, 2004). The main properties of micelles are the critical micelle concentration (CMC) values, the aggregation number, size, and shape. The micelle shape depends on the temperature, the concentration, and the type of surfactants used during nanoemulsion formulation. The size of micelles allows their selective accumulation in sites with leaky vasculature, through upgraded permeability and maintenance effect (Husseini and Pitt, 2008).

Surfactants are chemical compounds that can possibly change the properties of fluid interfaces. For example surfactants will diffuse in water and absorb at the interface between oil and water, in the case where water is mixed with oil. Surfactants molecules can lower the surface tension between two liquids or liquid and solid phase. This can be done by re-orientating of the surfactant molecules inside the water system and disturb their bonding so that the electrostatic forces will be decreased. Surfactants are categorized into four groups which are anionic, nonionic, cationic, and amphoteric or zwitterionic. The categorizations of surfactants depend on whether the polar head group can be dissociated in water or not (Yu *et al.*, 2008). Surfactants show several important properties such as foaming or anti-foaming, emulsifying, dispersing, and wetting behaviours. They are widely used in the management of soil water repellence (Kostka, 2000), petroleum industry (Schramm, 2000), personal care, cosmetics, food industry, pharmaceuticals, and agrochemical (Tadros *et al.*, 2004).

For several years, experimental laboratory researchers have been estimating the shape and structural properties of nanoemulsions by observing the spectrum data using the Small Angle Neutron Scattering (SANS) and Small X-ray Neutron Scattering (SAXS). However, the data cannot precisely describe the physical properties of these systems (Thomas and Olivier, 2010). Hence, computational simulation techniques can be an alternative approach to produce a detail description of nanoemulsions systems.

The structural properties of swollen micelles of oleyl oleate (OE) at different micelle composition, and also an addition of OE and surfactants were used to investigate the molecular dynamics (MD) simulations that produced valid results to be compared with the experimental data (Abdul Rahman *et al.,* 2010). Wahab *et al.* (2001) proved that the behaviour of the chemical penetration enhancers could be successfully predicted and simulated by computational approach.

The size and the ability of different aggregation numbers of the palm-oil esters (POEs) and surfactant molecules were also observed through the Molecular Dynamic simulation (Abdul Rahman *et al.*, 2009). Therefore, the stochastic numerical methods or Monte Carlo (MC) can be suggested to develop new configurations of a system of interest. Sampling method can be employed to examine the behaviour of a deterministic system based on Monte Carlo or stochastic numerical experiments. As a result, the structural and translational degrees of freedom of the model systems can be obtained (Woo *et al.*, 2004). The average properties of molecular system were effectively contributed to generate new configuration of states. The acceptance ratio is equivalent to the proportion of their weight at equilibrium which is an example of each configuration that can produce from previous state with transition probability (Hu *et al.*, 2006).

In Monte Carlo, the configurations are selected regardless of bias and the important consideration is to evaluate the energetic of the model system. Furthermore, this can be a good advantage of MC in comparison with other molecular simulation methods, for example molecular dynamics (MD) where the calculation of the first derivative of force is done and it is time consuming, especially when the model system is so big or complex. The reason is that, during MC calculation a single particle is moved in each step, so that the energy associates with this move will be calculated based on the total energy that obeys the Metropolis probabilities for the molecular system. Hashemianzadeh *et al.* (2008) implemented the Metropolis Monte Carlo (MMC) simulation of surfactants aggregation in binary mixtures of water and an ionic surfactant that resulted in decreasing critical micelle concentration (CMC) as the surfactant chain length increased and the CMC increased with an enhancement in solvent dipole moment.

For several years, the micellization process was used to examine using lattice Monte Carlo simulation method. Poorgholami-Bejarpasi *et al.* (2010) studied a model of two surfactants molecules with similar structures. The results show that the thermodynamic properties could be likely affected by the interactions between head groups or tail groups. Grand canonical Monte Carlo simulation was used to study the micelles formation in larger surfactant model system hence the size distribution of micellar aggregates was investigated using appropriate chemical potential values (Floriano *et al.*, 1999). Mixed amphiphile systems using three-dimensional lattice-based Monte Carlo simulations showed that the interaction between head to head could affect the CMC value in addition to the aggregate structure and size (Zaldivar and Larson, 2003).

This research investigated the mixed surfactant behaviour in water and the self-assembly of palm-kernel oil esters (PKOEs) nanoemulsions using MC technique. The experimental phase diagram was consisted of PKOEs, nonionic surfactants (Brij 92 and Brij 96) with an additional of isopropanol and water molecules (Chong, 2013). The PKOEs are usually applied as an oil phase in nanoemulsions formulation because of their unique wetting behaviour without any creamy feeling. Additionally, PKOEs are colourless liquids with low viscosity with a lot of applications in cosmetic and pharmaceutical products (Park *et al.*, 2000). Furthermore, it was shown that PKOEs could effectively penetrate the skin during drug delivery (Mahdi *et al.*, 2011).

In the formulations of nanoemulsion, nonionic surfactants were used to reduce the interfacial tension between oil phase and water phase due to their amphiphilic properties. The nonionic surfactants used in this research were Polyoxyethylene (2) oleyl ether, Brij 92, and Polyoxyethylene (10) oleyl ether, Brij 96. The Brij 92 and Brij 96 mixtures can produce the hydrophilic-lipophilic balance (HLB) value ranging from 4.9 to 12.4 to stabilize the nanoemulsion formulation. A maximum stability were observed when a mixture of two different nonionic surfactants was used at a certain HLB (Seiller *et al.*, 1970) and these surfactants have been widely used in pharmaceutical industry as a drug carrier (Lawrence, 1994). The isopropanol was proposed as cosurfactants to improve the common dispersion of PKOEs and water in the present of Brij® surfactants because alcohol shows poor solubility in PKOEs but high solubility in water (Acharya *et al.*, 2002).

1.1 Research Objectives

The main objective of this project was to model the self-assembly of the palm-kernel oil esters (PKOEs) nanoemulsion system using Monte Carlo technique. Therefore, the following specific objectives were undertaken:

1. To determine the physical behaviour of mixed nonionic surfactants (Brij 92 and Brij 96) in aqueous solution.

2. To study the self-assembly of palm kernel oil-based nanoemulsion system using experimentally determined phase diagram.

3. To estimate the shape and physical properties of the selected model systems.

4. To calculate the displacement of critical micelle concentration (CMC) for the surfactants mixture and nanoemulsion system.

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