UNIVERSITI PUTRA MALAYSIA

FORMULATION OPTIMIZATION OF PALM-BASED NANOEMULSION CONTAINING LEVODOPA, AN ANTI-PARKINSON'S DRUG

SYAFINAZ BINTI ZAINOL

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By

SYAFINAZ BINTI ZAINOL

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirement 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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SYAFINAZ BT ZAINOL

August 2014

Chair: Professor Mahiran Basri, PhD
Faculty: Science

The great challenges in drug delivery to the brain is the existence of blood-brain barrier (BBB) which controls the drug penetration to the brain, hence limiting the therapeutic effect of the drug for treatment of BBB diseases such as Parkinson's disease. An anti-Parkinson's drug, levodopa is the "gold standard" of anti-parkinsonian therapy. Only a small fraction of levodopa reaches the brain, since most is decarboxylated by enzymes and is taken up by skeletal muscle, liver, and kidney. The alternative to increase the effectiveness of levodopa is by application of efficient drug carrier systems such as nanoemulsion, solid lipid nanoparticle and liposome through parenteral delivery.

Nanoemulsion is one of the potential strategies for efficient delivery of levodopa across BBB due to advantages such as nano-sized, biocompatible, biodegradable and physically stable. Various types of emulsion composition, excipients and emulsification methods were studied to produce formulation with desirable properties. High energy emulsification method was the best method to form nanoemulsions when compared to low energy emulsification method. Lecithin and Cremophor EL found to be the most suitable surfactant and co-surfactant, respectively, for the formation of stable formulation.

Response surface methodology (RSM) was utilized to investigate the influence of the main emulsion composition; mixture of palm oil and medium-chain triglyceride (MCT) oil (6%–12% *w*/*w*), lecithin (1%–3% *w*/*w*), and Cremophor EL (0.5%–1.5% *w*/*w*) as well as the preparation method; addition rate (2–20 mL/min), on the physicochemical properties of palm-based nanoemulsions. The response variables were the three main emulsion properties namely : particle size, zeta potential and polydispersity index. Optimization of the four independent variables was carried out to obtain an optimum formulation palm-based nanoemulsion. The response surface analysis showed that the variation in the three responses could be depicted as a quadratic function of the main composition of the emulsion and the preparation method. The experimental data could be fitted sufficiently well into a second-order polynomial model.

Nanoemulsions with particle size of 107 nm, zeta potential of -31.4 mV, polydispersity index of 0.174, viscosity of 1.6 cps were successfully produced. The Transmission Electron Microscopy (TEM) analysis revealed that the nanoemulsion droplets were spherical in shape and homogenous in distribution. The entrapment efficiency study exhibited that 43.99 % levodopa was present in the oil phase of nanoemulsion. The *in vitro* drug release profile suggested that there was sustained release of the levodopa from the nanoemulsion system. The nanoemulsion loaded with levodopa exhibited highest cell viability for the cytotoxicity study compared to levodopa solution. The optimized formulation was stable for 11 months at 4 °C. The studies demonstrated the feasibility of palm-based nanoemulsion system as the parenteral levodopa delivery system.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains.

PENGOPTIMUMAN FORMULASI NANOEMULSI BERASASKAN SAWIT YANG MENGANDUNGI LEVODOPA, DADAH ANTI-PARKINSON'S

Oleh

SYAFINAZ BINTI ZAINOL

Ogos 2014

Pengerusi: Profesor Mahiran Basri, PhD
Fakulti: Sains

Cabaran besar dalam penghantaran ubat ke otak adalah kewujudan penghalang darah-otak yang mengawal penembusan ubat ke otak, oleh itu menghadkan kesan teraputik ubat untuk rawatan penyakit penghalang darah-otak seperti penyakit Parkinson. Ubat anti-Parkinson, levodopa adalah 'piawaian emas' terapi *anti-parkinsonian.* Hanya sebahagian kecil daripada levodopa sampai ke otak, memandangkan kebanyakannya dinyahkarboksilat oleh enzim dan diambil oleh otot rangka, hati dan buah pinggang. Alternatif untuk meningkatkan keberkesanan levodopa adalah dengan aplikasi sistem pembawa ubat yang cekap seperti nanoemulsi, nanozarah lemak pepejal dan liposom melalui penghantaran parenteral.
Nanoemulsi adalah strategi berpotensi untuk penghantaran levodopa yang cekap menembusi penghalang darah-otak disebabkan kelebihan seperti saiz nano, bioserasi, biodegradasi dan stabil secara fizikal. Pelbagai jenis komposisi emulsi, *excipients* dan kaedah pengemulsian telah dipelajari untuk menghasilkan formulasi dengan ciri-ciri yang diinginkan. Kaedah pengemulsian tenaga tinggi adalah kaedah terbaik untuk menghasilkan nanoemulsi apabila dibandingkan dengan kaedah pengemulsian tenaga rendah. Lesitin dan *Cremophor EL* telah dipilih sebagai surfaktan dan kosurfaktan paling sesuai, masing-masing, untuk pembentukan formulasi yang stabil.

Kaedah Permukaan Respons (RSM) telah digunakan untuk mengkaji pengaruh komposisi utama emulsi; campuran minyak sawit dan minyak rantaian sederhana trigliserida (6%–12% *w*/*w*), lesitin (1%–3% *w*/*w*), *Cremophor EL* (0.5%–1.5% *w/w)* dan kaedah persediaan; kadar penambahan (2–20 mL/min), ke atas sifat-sifat fizikokimia nanoemulsi berasaskan sawit. Pemboleh ubah tindak balas adalah tiga ciri utama emulsi; saiz zarah, keupayaan zeta dan indeks polisebaran. Pengoptimuman empat pemboleh ubah bebas dijalankan untuk mendapat formulasi nanoemulsi berasaskan sawit yang optimum. Analisis tindak balas permukaan menunjukkan variasi dalam ketiga-tiga tindak balas boleh digambarkan sebagai fungsi kuadratik bagi komposisi utama emulsi dan kaedah penyediaan. Data eksperimen dapat dimuat secukupnya dengan baik ke peringkat kedua dalam model polinomial.

Nanoemulsi dengan saiz zarah 107 nm, potensi zeta -31.4 mV, indeks polisebaran 0.174, kelikatan 1.6 cps telah berjaya dihasilkan. Analisis Mikroskopi Elektron Penghantaran (TEM) menunjukkan titisan emulsi adalah berbentuk sfera dan homogen dalam taburan. Kajian kecekapan pemerangkapan menunjukkan 43.99 % levodopa telah wujud di dalam fasa minyak nanoemulsi. Profil pelepasan ubat *in vitro* mencadangkan terdapat pengekalan pelepasan levodopa dari sistem nanoemulsi. Nanoemulsi yang dimuatkan dengan levodopa menunjukkan daya maju sel tertinggi dalam kajian *cytotoxicity* berbanding larutan levodopa. Formulasi yang optimum stabil untuk 10 bulan pada 4 °C. Kajian menunjukkan kebolehlaksanaan sistem nanoemulsi berasaskan sawit sebagai sistem penghantaran levodopa secara parenteral.

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I certify that a Thesis Examination Committee has met on 14 August 2014 to conduct the final examination of Syafinaz binti Zainol on her thesis entitled "Formulation Optimization of Palm-based Nanoemulsion Containing Levodopa, an anti-Parkinson's Drug" 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 Master of Science.

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Professor
Universiti Kebangsaan Malaysia
Malaysia
(External Examiner)

_____
NORITAH OMAR, PhD
Associate Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 19 September 2014

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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Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

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Associate Professor
Faculty of Pharmacy,
Universiti Kebangsaan Malaysia
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Committee: **Prof. Dr. Mahiran Basri**

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Member of
Supervisory
Committee: **Assoc. Prof. Dr. Ahmad Fuad Shamsuddin**

Signature: _____
Name of
Member of
Supervisory
Committee: **Dr. Siti Salwa Abd Gani**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BBB	Blood-brain barrier
CNS	Central Nervous System
cps	centipoises
LCT	Long-chain Triglyceride
MCT	Medium-chain Triglyceride
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
mV	millivolt
nm	nanometer
OFAT	One-Factor-At-a-Time
O/W	Oil-in-water
Pa	Pascal
Pa.s	Pascal second
PD	Parkinson's Disease
PBS	Phosphate buffer solution
PIC	Phase Inversion Composition
PIT	Phase Inversion Temperature
rpm	Revolution per minute
RSM	Response Surface Methodology
TEM	Transmission Electron Microscopy
UPLC	Ultra Performance Light Chromatography
w/w	weight/weight

CHAPTER 1

INTRODUCTION

1.1 Background of Study

The Blood-brain barrier (BBB) impede many live-saving medications from reaching the brain which include therapeutics for brain diseases such as brain tumor, Parkinson's, Alzheimer's, Huntington's and schizophrenia. Conventional therapeutics are still unable to achieve the level of optimum therapeutics efficacy. It has become critical as researchers realize that the barrier is not a static defence structure but it is an active and regulatory interface. It is identified that BBB is a dynamic system which has the capability to respond to local changes and environment as well as able to be regulated via some mechanism and cell type (Abbott *et al.*, 2010).

In the 21st century, the incidence of Parkinson's disease (PD) is expected to rise with increasing lifespan and population demographics. PD is a progressive disease with a mean age at onset of 55, and the prevalence ascend obviously with age, from 20/100,000 overall to 120/100,000 at age 70 (Dauer and Przedborski, 2003). In Malaysia, the prevalence of PD is unknown though it is believed to be rising with the country's growth (Razali *et al.*, 2011). The treatments that are available include pharmacological and non-pharmacological treatments, which are only for symptomatic relief (Katzung, 2001).

Currently, Levodopa remains as the most effective drug to treat PD (Stocchi *et al.*, 2010). An immediate-release (IR) oral dosage form was the first commercialized product which consists of combination of Levodopa and Carbidopa (peripheral decarboxylase inhibitor) with the name of Sinemet®. Another useful treatment for the fluctuating PD patients is enteral infusion of levodopa/carbidopa. A gel with water-based suspension of levodopa and carbidopa (Duodopa®, Solvay Pharmaceuticals) which was for intraduodenally administered was designed (Goole and Amighi, 2009). A long-term therapy, implantable system (microsphere) offers a continuous supply of loaded drug. Consequently, development of poly (butylenes succinate) (PBSu) microspheres-based levodopa delivery system was developed (Mohanraj *et al.*, 2013). However, the need to look for even better delivery system with improved efficacy and safety is always ongoing.

Nanotechnology has a vital role in the therapies of the future since nanomedicine could decrease doses required for efficacy, as well as enhance the therapeutic indices and safety profile of new therapeutics (Koo *et al.*, 2005). By application of nanotechnology in drug delivery and design, the potential of nanomedicine has been explored in term of capability to release the drug at a controlled rate, increase drug accumulation at targeted tissues and retain within the blood circulation system without degradation by opsonisation process (a process where the foreign molecule is marked for destruction by phagocyte). Moreover, nanomedicine having extremely

small size, can be injected without occluding the capillaries thus, allows targeted drug delivery.
Palm oil is a major source of renewable and sustainable raw materials for the world's oleochemical, food and biofuel industries (Basiron, 2007). It is produced from the fruit flesh of oil palm (*Elaeis guineensis)* which contain 45% palmitic acid (a fatty acid made by our body), 40% monounsaturated oleic acid, 10% polyunsaturated linoleic acid (an essential fatty acid) and 5% stearic acid. The application of palm oil in the pharmaceutical field has not been broadly discovered. Palm oil has potential to be applied in the pharmaceutical industry as it possesses desirable properties such as non-toxicity, low cost, oxidative stability, high thermal stability and high productivity. Linoleic acid, one of the fatty acid present in palm oil was reported to be able to cross the BBB (Yehuda *et al.*, 2005). Tocotrienol-rich fraction (TRF) from palm oil shows high capability as a chemopreventive and/or therapeutic agent against prostate cancer (Srivastava and Gupta, 2006). TRF from palm oil has been proven to consist potent antioxidant, anticancer, and cholesterol lowering activities (Wu *et al.*, 2008).

1.2 Problem Statements

BBB becomes the major entrance route for therapeutics to the brain. Drugs for treating brain disease need to be able to cross BBB (Li *et al.*, 2005). However, BBB limits the transfer of compound from blood to brain through two pathways; physical (tight junction) and metabolic (enzyme) barriers (Fernandes *et al.*, 2010). It acts as defensive tool by limiting the transport of compounds from blood to brain through the pathways. The impermeability of the BBB is due to the tight junction between the endothelial cells which are developed by cell adhesion molecules. BBB permits a selective entrance of nutrients and minerals and controls the entry of foreign substances like drugs due to the presence of numerous endogenous transporters. This leads to the ineffectiveness of brain disease treatments.

The initial marketed product of levodopa is in the form of oral dosage. It is estimated that less than 1 % of levodopa dose administered (without decarboxylase inhibitor) penetrate the brain. As levodopa is administered in the form of oral dosage, it is decarboxylated rapidly by an enzyme, dopa decarboxylase (DDC) (Singh *et al.*, 2007). The decarboxylation of levodopa generates dopamine which is unable to cross the BBB thus bring to severe peripheral adverse effect (Goole and Amighi, 2009). Levodopa is also almost completely absorbed in the small intestine and from the administered dose, only 30% is kept as the original compound in the periphery. The remains are metabolized in the kidneys, liver and the blood. Hence, to achieve the desired therapeutic effect, a large dose of levodopa is required.

Levodopa is extremely hydrophilic molecule which possesses the positive and negative charge at pH values of 3-9 (Merck Index, 1996). This property has contributed to the low solubility of levodopa within this pH range (Kankkunen *et al.*, 2002). Hydrophilic drug is commonly incorporated into aqueous phase of water-in-oil emulsion for intramuscular administration. However, the limitation due to the nature of levodopa and demand for patient convenience, leads to a need to develop a novel technology for the formulation of oil-in-water emulsion with poorly soluble drug for intravenous administration.

Active drug component could lead to the toxicity of a pharmaceutical product. Certain drugs which are used to give a therapeutic action could cause fatal or unfavourable adverse effect (Lim *et al.*, 2012). In order to overcome resistance due to the reaction such as hydrolysis, decarboxylation and oxidation of certain drugs when without any vehicle, higher drug dosage is required to give the significant therapeutic effect. However, this brings about further increase in systemic drug exposure and toxicity to healthy and normal tissues (Reddy, 2005). Therefore, such drugs need carrier systems that encapsulate them thus reduce the contact area between the drugs and the health cell as well as prevent the drugs from facing the resistance.

1.3 Scope of Study

In this work, palm-based nanoemulsion system loaded with an anti-Parkinson's drug, levodopa for parenteral administration was designed and developed. Various biocompatible materials and preparation methods which included low and high energy emulsifications were investigated to produce emulsion in nano-sized. Formulation optimization of nanoemulsion containing levodopa was performed using one-factor-at-a-time (OFAT) and Response Surface Methodology (RSM) method. The nanoemulsion formulation was characterized with respect to particle size, polydispersity index, zeta potential, viscosity, morphology analysis, encapsulation efficiency, stability evaluation, drug-loaded nanoemulsion release and toxicity.

1.4 Objectives

The objectives of this work are as follows:

1. To formulate nanoemulsion system containing levodopa using low and high energy emulsification method.
2. To optimize the condition for formulating nanoemulsion with nano-sized particle and good physical stability using Response Surface Methodology (RSM).
3. To characterize the properties of optimised levodopa-loaded nanoemulsion with respect to particle size, zeta potential, polydispersity index, viscosity, pH, morphology, encapsulation efficiency, drug-loaded nanoemulsion release and toxicity.

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