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DEVELOPMENT, CHARACTERISATION AND TRANSLOCATION OF VALPROIC ACID-ENCAPSULATED NANOEMULSION ACROSS BLOOD-BRAIN BARRIER

TAN SUK FEI

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By

TAN SUK FEI

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 this thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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Chairman : Professor Hamidon Bin Basri, M.D. M. Med
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Valproic acid (VPA) is a widely used antiepileptic drug (AED) for epilepsy especially in generalized and absence seizures. However, VPA has high plasma protein binding (90 % - 95 %) so only low amount of free VPA were able to reach the brain. An increase in therapeutic dose is not feasible as it will further aggravate the toxicity problem because VPA has a narrow therapeutic window range of 50-150 µg/mL in plasma. The presence of brain-to-blood efflux transporter in blood-brain barrier (BBB) further reduces the bioavailability of VPA in the brain. Taken together, the efficacy of VPA in treating epilepsy is hampered by high plasma protein binding nature, narrow therapeutic window and low brain bioavailability. The currently marketed parenteral VPA only enhances the solubility of the drug in water. Therefore in this study, a formulation of parenteral nanoemulsion of VPA was developed to reduce the clearance of VPA, to improve the tolerable concentration of VPA and the brain bioavailability of VPA.

In our study, valproic acid-encapsulated nanoemulsions (VANE) were formulated by dispersing an oil phase containing VPA and lecithin into an aqueous phase containing tween 80 (T80). Among all types of oils studied, safflower seed oil was used as an oil phase in VANE as it formed the smallest droplet size of VANE. Alpha-tocopherol were also added into the oil phase to reduce the lipid peroxidation of oil phase in VANE. To further reduce the droplet size of VANE, the optimum processing conditions of ultrasonicator were studied (temperature, energy intensity and time) and used to further emulsify the VANE. Next, four VANEs with different percent composition (F1, F2, F3 and F4) were formulated to study the effect of oil phase content and drug-to-oil phase ratio on the physical properties of VANE (droplet size, polydispersity index (PDI) and zeta potential). Eventually, two nanoemulsions namely F3 VANE and F4 VANE out of these four formulations were selected to be studied in the following studies as they had higher drug content at desirable physical characteristic (droplet size <200 nm, PDI <0.2).

Both VANEs had physiologically compatible pH (around 8), osmolarity and viscosity. Both VANEs were spherical in shape and encapsulated more than 97% of VPA. Stability studies showed that F3 VANE was more stable than F4 VANE as F3 VANE showed only little changes in droplet size and PDI at storage of high temperature (45 °C) over five months. The *in vitro* drug release also indicated F3 VANE had more and faster VPA release compared to F4 VANE. This was probably due to lower surfactant-to-oil ratio and higher percentage of oil in F3 VANE, exhibited less barrier for VPA release. F3 VANE (IC_{50}: 633.19 µg/mL) also had less cytotoxic effect on hCMEC/D3 cells compared to F4 VANE (IC_{50}: 402.69 µg/mL). Next, the *in vitro* BBB model was successfully developed with appropriate optimization and characterization. It was then used to assess the *in vitro* drug penetrability of F3 and F4 VANE where both VANEs penetrated the *in vitro* BBB as freely as VPA.

Comparing both of the VANEs, F3 VANE was physically and biologically more attractive as it had higher drug content, better stability and less cytotoxic effect. Hence, only VPA and F3 VANE were studied in *vivo* studies. F3 VANE had improved the total bioavailability of VPA, reduced the clearance of VPA, and prolonged the half life of VPA in the blood from F3-treated rats compared to VPA-treated rats. The improvement of bioavailability of F3 VANE in the brain was also observed. This is possibly due to (a) higher bioavailability of F3 VANE in blood (b) lower clearance rate of F3 VANE in the brain by possible inhibition of T80 to P-gp. Overall, F3 VANE had successfully reduced the cytotoxicity of VPA, the clearance of VPA and prolonged the half-life of VPA in the blood, subsequently improved the brain bioavailability of VPA significantly.

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

PEMYEDIAAN, PENCIRIAN DAN TRANSLOKASI VALPROIC ASID-TERKANDUNG NANOEMULSI MELALUI PENGHALANG DARAH-OTAK

Oleh

TAN SUK FEI

Januari 2017

Pengerusi : Profesor Hamidon Bin Basri, MDM Med
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Asid valproik (VPA) adalah sejenis ubat epilepsi yang digunakan untuk merawat penyakit sawan. Walau bagaimanapun, kecenderungan VPA untuk mengikat protein serum adalah tinggi (90% - 95%) dan ini telah menyebabkan kekurangan jumlah VPA dalam darah untuk tujuan teraputik. Peningkatan dos teraputik VPA untuk tujuan rawatan sawan tidak dapat dilaksanakan kerana VPA mempunyai julat teraputik yang terhad (50-150 μg/mL) dalam darah. Kewujudan penghadang di persimpangan otak telah menurunkan bioketersediaan VPA dalam otak. Ringkasannya, keberkesanan VPA untuk merawat epilepsi terjejas disebabkan kecenderungan VPA untuk mengikat protein serum, julat teraputik yang sempit dan bioketersediaan VPA yang rendah dalam otak. Natrium valproate, ubat parental yang terdapat di pasaran hanya meningkatkan kelarutan ubat tersebut dalam air. Oleh yang demikian, formulasi nanoemulsi parenteral telah direka untuk mengkapsulkan VPA dalam nanoemulsi untuk mengurangkan kadar penyingkiran VPA, meningkatkan kadar toleransi VPA dan bioketersediaan VPA dalam otak.

Dalam kajian ini, nanoemulsi yang mengandungi asid valproik (VANE) telah diformulasi dengan memencarkan fasa minyak yang mengandungi VPA dan lesitin dalam fasa akueus yang mengandungi tween 80 (T80). Minyak kesumba telah digunakan sebagai fasa minyak sebab ia mempunyai saiz titisan yang paling kecil antara semua minyak yang diformulasi. Trigliserida rantaian sederhana (MCT) dan α-tokoferol juga digunakan sebagai fasa minyak untuk mengurangkan pengoksidaan fasa minyak dalam VANE. Untuk mengurangkan saiz titisan VANE, parameter optimum pemprosesan ultrasonik telah dikaji (suhu, intensiti tenaga, masa) dan digunakan untuk memprosesan VANE. Seterusnya, empat VANE dengan komposisi yang berlainan telah diformulasikan untuk mengkaji kesan–kesan peratusan fasa minyak dan nisbah ubat kepada minyak terhadap sifat fizikal VANE (saiz titisan, indeks kepoliserakan dan potensi zeta). Akhirnya, dua nanoemulsi iaitu F3 dan F4 VANE telah dipilih untuk kajian yang seterusnya kerana kedua-duanya mengandungi VPA yang tinggi dan sifat-sifat fizikal yang diingini (saiz titisan <200nm, PDI <0.2).

Kedua-dua F3 dan F4 VANE mempunyai pH 8, osmolariti dan kelikatan yang serasi dengan fisiologi manusia. Kedua-duanya adalah berbentuk sfera dan telah mengkapsulasi lebih daripada 97% VPA. Kajian kestabilan menunjukkan F3 VANE adalah lebih stabil daripada F4 VANE kerana ia hanya menunjukkan sedikit perubahan dalam saiz titisan dan PDI pada suhu yang tinggi (45 °C) dalam masa lima bulan. Analisis pelepasan ubat telah menunjukan kadar pelepasan ubat F3 VANE adalah lebih cepat dan banyak berbanding dengan F4 VANE. Ini mungkin disebabkan F3 VANE mempunyai nisbah surfaktan-minyak yang rendah dan peratusan minyak yang tinggi, sejurusnya menyebabkan kekurangan halangan untuk melepaskan VPA. F3 VANE (IC_{50}: 633.19 µg/mL) adalah juga kurang sitotoksik terhadap sel hCMEC/D3 berbanding dengan F4 VANE (IC_{50}: 402.69 µg/mL). Seterusnya, model *in vitro* penghalang darah-otak telah dibinakan dengan pengoptimuman dan pencirian yang sesuai bagi pengajian penembusan ubat F3 dan F4 VANE, dimana kedua-duanya menunjukan keupayaan penembusan yang setara dengan VPA.

F3 adalah lebih berpotensi dari segi fizikal dan biologi kerana ia mempunyai lebih VPA, lebih stabil dan kurang sitotoksik berbanding dengan F4 VANE. Oleh itu, hanya VPA dan F3 VANE telah dikaji dalam *in vivo*. F3 VANE telah meningkatkan jumlah bioketersediaan VPA, mengurangkan penyingkiran VPA dan melanjutkan separuh hayat VPA dalam darah yang disampel daripada tikus yang dirawati F3 VANE berbanding dengan tikus yang dirawati VPA. Bioketersediaan F3 VANE dalam otak juga dipertingkatkan. Ia mungkin disebabkan oleh (a) peningkatan bioavaibiliti F3 VANE dalam darah. (b) penguranggan kadar penyingkiran F3 VANE dalam otak melalui perencatan P-gp oleh T80. Sebagai kesimpulannya, proses enkapsulasi VPA dalam nanoemulsi telah berjaya mengurangkan sitotoksiksiti dan kadar penyingkiran serta melanjutkan separuh hayatnya. Ini membawa kepada peningkatan bioketersediaan VPA dalam otak.

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I certify that a Thesis Examination Committee has met on 10 January 2017 to conduct the final examination of Tan Suk Fei on her thesis entitled "Development, Characterisation and Translocation of Valproic Acid-Encapsulated Nanoemulsion Across Blood- Brain Barrier" 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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ABC	ATP-binding cassette
AED	Antiepileptic drug
AGM-2	Astrocyte growth medium
ALP	Alkaline phosphotase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BBB	Blood-brain barrier
BNE	Blank nanoemulsion
BM	Basement membrane
cAMP	cyclic adenosine monophosphate
CCD	Central composite design
CC-2565	Human astrocytes
Col4	Collagen type IV
CREB	cAMP-responsive element binding protein
CrEL	Cremophor® EL
CNS	Central nervous system
COV	Coefficient of variance
CYP	Cytochrome P450 enzyme
CPP	Critical packing parameter
DEX	Dexamethasone
DMSO	Dimethyl sulfoxide
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid disodium salt
EGM-2	Endothelial growth medium
GABA	γ-aminobutyric acid
GPI	Glycerophosphoinositol
hCMEC/D3	Immortalized human cerebral endothelial cells
hEGF	Human epidermal growth factor
HLB	Hydrophilic-lipophilic balance
HPLC	High-performance liquid chromatography
hEGF	human epidermal growth factor
hTERT	Human telomerase
IFG-1	Insulin-like growth factor
IgG	Immunoglobulin G
K_p	Brain-to-plasma ratio
LCT	Long chain triglyceride
LDL	Low-density lipoprotein
LOD	Lower limit of quantification
LLOD	Lower limit of detection
MAP	Mitogen-activated protein kinases
MCT	Medium chain triglyceride
MDR	Multidrug resistance
MES	Maximal electroshock seizure
MRI	Magnetic resonance imaging
MRP	Multidrug resistance-associated protein
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
NMDA	N-methyl- D,L-aspartic acid
OA	Octanoic acid

O/W	Oil-in-water
PBS	Phosphate-buffered saline
PDA	Photodiode array
PDI	Polydispersity index
P-gp	P-glycoprotein
PHS	Plasma derived human serum
PIC	Phosphatase inhibitor
PKA	Protein kinase A
pNP	p-Nitrophenol
PTZ	Pentylenetetrazole
PUFA	Polyunsaturated fatty acid
RES	Reticuloendothelial system
RSM	Response surface methodology
SE	Status epilepticus
SDS	Sodium dodecyl sulphate
SDS-PAGE	SDS-polyacrylamide gel electrophoresis
T80	Tween 80
TEER	Trans-endothelial electrical resistance
TEM	Transmission electron microscopy
TEMED	Tetramethylethylenediamine
Tween 20	Polyoxyethylene sorbitan monolaurate
UGT	Uridine 5'-diphospho-glucuronosyltransferase
VPA	Valproic acid
VANE	Valproic acid-encapsulated nanoemulsion
VEGF	Vascular endothelial growth factor
W/O	Water-in-oil

CHAPTER 1

INTRODUCTION

1.1 Background of Study

According to the World Health Organization (2012), it is estimated that 50 million people in the world have epilepsy. Epilepsy is a common and serious neurological disorder which is characterised by recurrent unprovoked seizures of the cerebral, it is widespread throughout the world. It is a disorder resulting from an imbalance of neurotransmission signals and requires long-term treatment with one or more antiepileptic drug (AED) (Baker *et al*., 1997). The quality of life for epileptic patient is lower than the rest of the population (Baker *et al*., 1997) because they have to live with anxiety, social stigma and often unemployed compared to a healthy person. Epileptic patients also have a higher incidence rate of cardiovascular and cerebrovascular disease, hence they have higher mortality rates compared to healthy people (Olesen *et al*., 2011). This might be due to long-term use of a few selected AED, which causes a higher incidence of vascular disease (Chuang *et al*., 2012).

1.2 Problem Statements

Almost 70% of patients are seizure-free with the right medication after the first onset of incidence. Hence, medication is usually the first therapy provided by the healthcare professionals. However, the efficacy of the drug would be hampered if there is an insufficient amount of the drug at the site of action. In the epilepsy, the presence of the blood-brain barrier (BBB) often limits the bioavailability of AED in the brain. In order to reach the therapeutic dose in the brain, a higher dose has to be injected intravenously. However, this is dangerous due to the lack of target specificity (Minko *et al.*, 2013). Adverse side effects of the drugs are often due to the non-specific distribution of the drug (Tan *et al*., 2016). Hence, it is not wise to deliver a higher dose of drug to the patient unless the local targeting properties of a drug can be assured. On top of that, the aqueous solubility of hydrophobic therapeutic agents is often low that a high dose of intravenous injection can cause local venous irritation and phlebitis (Hippalgaonkar *et al.*, 2010) Hence to deliver a high dose of hydrophobic therapeutic agent via parenteral route is rather challenging due to its physicochemical properties such as viscosity and pH issue.

Multidrug resistance (MDR) is one of the most common obstacles which limit the therapeutic efficacy of the treatments of CNS disease. One of the mechanisms of MDR is the up-regulated expression of efflux protein, P-glycoprotein (P-gp). It is a transmembrane protein, ATP-coupled transporter family that pumps xenobiotic out from the brain back into the bloodstream through active transport. This results in a low brain bioavailability of the drug. A circulating drug must enter the brain and exert its therapeutic effect by, for example suppressing excitatory neurotransmission. Many studies have explored the development of P-gp inhibitors such as verapamil, tariquidar,

cyclosporine A to inhibit the efflux pump system, in an attempt to prevent drugs from sweeping out from the brain (Gottesman *et al.*, 2002). However, these have not been successful clinically because of severe side effects and adverse influence on the pharmacokinetic profile of therapeutic agent (Dong *et al*., 2009).

Valproic acid (VPA) is one of the AED that have the widest spectrum against different types of seizures including life-threatening epilepsy, status epilepticus (SE). Furthermore, kindling animal studies have also suggested VPA might have antiepileptogenetic effects in addition to anticonvulsant effects (James & McNamara, 1991). It is also good in the sense that its efficacies remain the same in spite of long-term administration. Structurally, it is a small and lipophilic molecule that can enter the brain easily. However, it has low brain bioavailability due to high plasma protein binding and higher efflux: influx activities of VPA across the BBB (Cornford *et al*., 1985). In addition, it is also known to produce serious hepatotoxicity issue due to its downstream metabolites (Ghodke-Puranik *et al*., 2013).

1.3 Significance of the Study

There is a growing body of evidence on the use of nanotechnology uses in medicine to improve the bioavailability of drugs. Different nanocarriers such as polymer-drug conjugates and lipid nanoparticles have been formulated and used (Cho *et al.*, 2008). Receptor-mediated endocytosis involves the interaction of a ligand and its receptor which changes the process of endocytosis can be employed to transport drugs into the brain. Hence, in our study, nanoemulsion will be used to encapsulate VPA to improve its biological fates and properties.

1.4 Hypothesis

a) The formulated valproic acid-encapsulated nanoemulsion (VANE) will be physically more stable and biocompatible compared to VPA
b) VANE will be less cytotoxic than VPA
c) The bioavailability of VANE in plasma and brain will be higher than VPA.

1.5 Objective of the Study

The general objective of this study is to produce a nanoemulsion loaded with VPA to be delivered to the brain via parenteral route.
The specific objectives are as follows:
a) To produce a stable and biocompatible nanoemulsion loaded with VPA.
b) To reduce the cell toxicity issue of VPA by encapsulation of it within nanoemulsion.
c) To improve the half-life of VPA in biological systems by encapsulation of it within nanoemulsion.
d) To improve the concentration of VPA in the brain by increasing free VPA in plasma.

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