UNIVERSITI PUTRA MALAYSIA

OPTIMIZATION AND CHARACTERIZATION OF NANOEMULSION CONTAINING ARIPIPRAZOLE AND ITS TOXICITY ON ZEBRAFISH

WAN SARAH BINTI SAMIUN

FS 2020 38

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By

WAN SARAH BINTI SAMIUN

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

October 2019

DEDICATION

This work is dedicated to Almighty Allah, my family and all those who stand for truth and justice.

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

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WAN SARAH BINTI SAMIUN

October 2019

Chairman : Siti Efliza binti Ashari, PhD
Faculty : Science

Poorly water soluble drugs have been a major problem in the development of drug formulation. Thus, the main aim of this study is to optimize the composition of formulation and the preparation conditions of nanoemulsion containing aripiprazole which is a poorly water-soluble drug.

In the optimization study, Mixture Experimental Design (MED) and Artificial Neural Networks (ANNs) were carried out to formulate nanoemulsion compounds containing aripiprazole by varying five components of mixture composition. Estimation of particle size of nanoemulsion containing aripiprazole by MED and ANN were 64.24 nm and 64.38 nm, respectively. The results showed that MED model predicted is more accurate as compared to ANN since MED model has a lower percentage of RSE (2.01%). The optimum compositions of the model were 3.00% of palm kernel oil ester (PKOE), 2.00% of lecithin, 1.00% of Tween 80, 2.25% of glycerol and 91.75% of deionized water.

Response Surface Methodology (RSM) was used to optimize the process parameter conditions in preparation of the optimum nanoemulsion formulation. This design was used to study the effects of four independent variables: the stirring time, shear rate, shear time, and the number of cycle of high-pressure homogenizer with the function of particle size as the response. The optimum process parameter conditions obtained were 120 min of stirring time, 15 min of shear time, 4400 rpm of shear rate and 11 cycles of high pressure homogenizer. By using RSM, the experimental value of the particle size was 64.52 nm which was very close to the predicted value (62.59 nm) with 1.93% of RSE value.

The physicochemical properties of optimized nanoemulsions revealed the particle size of 62.23 nm, polydispersity index (PDI) of 0.18, zeta potential of -31.6 mV, pH of 7.45, viscosity of 3.72 cps and osmolality of 297 mOsm/kg, suggesting their compatibility for parenteral administration. Aripiprazole was incorporated into nanoemulsion system with an entrapment efficiency of 97.3% and a relatively high drug loading of 93.14%. The optimized formulation demonstrated sufficient physical stability upon long-term storage at 4 °C, 25 °C and 45 °C. The ability of nanoemulsion to deliver aripiprazole through was assessed *in vitro* using Franz diffusion cell and showed the permeability of aripiprazole was significantly increased from 2.22% at 1 h to 93.06% after 24 h drug release.

In the toxicity study, the toxic effect of nanoemulsion containing aripiprazole, blank nanoemulsion and aripiprazole were tested by using zebrafish embryos and larvae (*Danio rerio*) during 120 hours post exposure. From this assessment, aripiprazole showed LC_{50} value of 473.7 µg/mL towards zebrafish embryos. Nanoemulsion containing aripiprazole and blank nanoemulsion showed LC_{50} value of 140.2 µg/mL and 78.21 µg/mL towards zebrafish embryos, respectively. However, during the developmental toxicity, all the survived zebrafish larvae showed severe toxicity effect at high concentration of samples more than 250 µg/mL such as chronic pericardial edema, bradycardia, scoliosis and non-detachment of tail. Regardless of the presence of surfactant toxic effect, surfactant must be chosen wisely within the optimum concentration in producing formulation nanoemulsion.

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

PENGOPTIMUM DAN PENCIRIAN NANOEMULSI YANG MENGANDUNGI ARIPIPRAZOLE DAN KESAN KETOKSIKAN KEATAS ZEBRAFISH

Oleh

WAN SARAH BINTI SAMIUN

Oktober 2019

Pengerusi : Siti Efliza binti Ashari, PhD
Fakulti : Sains

Ubat yang tidak larut dalam air merupakan masalah terbesar dalam penciptaan formula ubat. Oleh itu, matlamat utama kajian ini adalah untuk mengoptimumkan komposisi formulasi dan kondisi semasa penyediaan nanoemulsi yang mengandungi aripiprazole iaitu ubat yang tidak larut dalam air.

Dalam kajian pengoptimuman, Mixture Experimental Design (MED) and Artificial Neural Networks (ANNs) telah dijalankan untuk mengoptimumkan komposisi nanoemulsi yang mengandungi aripiprazole dengan memvariasikan komposisi campuran menggunakan lima komponen. Anggaran saiz partikel nanoemulsi yang mengandungi aripiprazole oleh MED dan ANN adalah masing-masing 64.24 nm dan 64.38 nm. Keputusan menunjukkan bahawa ramalan oleh model MED lebih tepat berbanding model ANN kerana model MED mempunyai peratusan RSE yang paling rendah iaitu 2.01%. Komposisi optimum model yang telah dicadangkan adalah 3.00% ester minyak isirong sawit (PKOE), 2.00% lesitin, 1.00% daripada Tween 80, 2.25% gliserol dan 91.75% daripada air yang telah dinyah-ionkan.

Response Surface Methodology (RSM) telah digunakan untuk mengoptimumkan keadaan parameter proses dalam penyediaan formulasi nanoemulsi yang optimum. Reka bentuk ini digunakan untuk mengkaji kesan empat pembolehubah bebas: masa mengacau, kadar ricih, masa ricih, dan bilangan kitaran alat penghomogenan bertekanan tinggi terhadap saiz partikel sebagai tindak balas. Kondisi parameter proses optimum yang diperolehi adalah 120 minit masa mengacau, 15 minit masa ricih, 4400 rpm kelajuan ricih dan 11 bilangan kitaran alat penghomogenan bertekanan tinggi. Dengan menggunakan RSM, nilai saiz partikel semasa eksperimen ialah 64.52 nm

manakala nilai saiz partikel yang diramalkan dari model adalah 62.59 nm iaitu tidak jauh bezanya dengan data eksperimen dengan nilai RSE 1.93%.

Nanoemulsi yang dioptimumkan telah dikaji dari pelbagai sudut sifat fizikokimianya. Penciriannya menunjukkan saiz partikel 62.23 nm, indeks kepoliserakan (PDI) 0.18, keupayaan zeta -31.6 mV, pH 7.45, kelikatan 3.72 cps dan keosmolalan 297 mOsm/kg, yang mana ia bersesuaian dengan aplikasi parenteral. Aripiprazole telah berjaya dimuatkan ke dalam sistem nanoemulsi dengan pengkapsulan secara efisien iaitu 97.3% dan kandungan ubat yang agak tinggi sebanyak 93.14%. Formulasi tersebut menunjukkan kestabilan fizikal yang baik dalam penyimpanan jangka masa yang panjang dalam tempoh 3 bulan penyimpanan pada suhu 4 °C, 25 °C dan 45 °C. Keupayaan nanoemulsi untuk menyampaikan aripiprazole melalui *in vitro* telah dinilai dengan menggunakan sel peresapan Franz dan menunjukkan bahawa ketelapan aripiprazole meningkat dengan ketara daripada 2.22% pada jam yang pertama kepada 93.06% selepas pembebasan ubat selama 24 jam.

Dalam kajian ketoksikan, kesan toksik nanoemulsi yang mengandungi aripiprazole, nanoemulsi tanpa aripiprazole dan aripiprazole telah diuji dengan meggunakan embrio dan larva ikan zebra (*Danio rerio*) dalam 120 jam selepas pendedahan. Dari ujian ini, aripiprazole menunjukkan nilai LC_{50} 473.7 µg/mL ke atas embrio ikan zebra. Nanoemulsi yang mengandungi aripiprazole menunjukkan nilai LC_{50} 140.2 µg/mL, manakala nanoemulsi tanpa aripiprazole menunjukkan nilai LC_{50} 78.21 µg/mL ke arah embrio ikan zebra. Walau bagaimanapun, semasa ujian ketoksikan keatas perkembangan embrio/larva ikan zebra,semua larva yang masih hidup menunjukkan kesan ketoksikan yang teruk pada kepekatan yang melebihi 250 µg/mL seperti edema perikardium yang kronik, bradikardia, skoliosis dan pemisahan ekor yang tidak sempurna. Kepekatan surfaktan perlu dipilih dengan sebaiknya untuk mengurangkan kesan toksik oleh surfaktan dalam penghasilan formulasi nanoemulsi.

ACKNOWLEDGEMENTS

In the name of Allah, the Most Loving and the Most Merciful. All praises goes to Allah for the strength, health and passion. He has given to me to complete this thesis. I would like to take this opportunity to express my gratitude to those who have contributed directly or indirectly in this thesis.

My deepest gratitude and sincere appreciation is owed to my previous supervisor, late Prof. Dr. Mahiran binti Basri for her invaluable guidance, continuous support, patience and encouragement from the beginning of this journey. Many thanks and genuine appreciation is also extended to my current supervisor, Dr. Siti Efliza binti Ashari for her aspiring guidance, numerous support, and assistance throughout this research journey. I would like to express my cordial and sincere gratitude to my co-supervisors, Dr. Norazlinaliza binti Salim and Dr. Syahida binti Ahmad for their consultancy, constant support and troubleshooting during my course of study.

A special thanks to late Dr. Hamid Reza Fard Masoumi, for his invaluable guidance and insightful comments that assist me throughout my research and publications. My appreciation also goes to all my colleagues in the Research Laboratory of Chemical Synthesis and Nanomolecular (Lab 401), especially Nurshafira Khairudin, Shazwani Samson, Zahra Izadiyan, Lim Chaw Jiang, and Nur Syafiqah Rizalman. Thank you for making my stay during this research a bearable one with countless sweet memories.

Last but not least, love and thanks to my families especially my mother for their endless supports, concerns as well as their truly understanding throughout the years of my study. I believed this journey is not only about me, but also about us. Alhamdulillah.

To all, I am wholeheartedly grateful.

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:

Siti Efliza binti Ashari, PhD
Senior Lecturer
Centre of Foundation Studies for Agricultural Science
Universiti Putra Malaysia
(Chairperson)

Norazlinaliza binti Salim, PhD
Senior Lecturer
Centre of Foundation Studies for Agricultural Science
Universiti Putra Malaysia
(Member)

Syahida binti Ahmad, PhD
Associate Professor
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Member)

_____
ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 9 January 2020

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Signature: _____
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Signature: _____
Name of Member of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAD	Absolute average aeviation
ADME	Absorption, Distribution, Metabolism and Excretion
ANNs	Artificial Neural Networks
ANN-BBP	Artificial Neural Network- Batch Back Propagation
ANN-GA	Artificial Neural Network- Genetic Algorithm
ANN-IBP	Artificial Neural Network- Incremental Back Propagation
ANN-LM	Artificial Neural Network- Levenberg Marquardt
ANN-QP	Artificial Neural Network- Quick Propagation
ANOVA	Analysis of variance
BBB	Blood-brain barrier
CCD	Central Composite Design
CCRD	Central Composite Rotatable Design
CNS	Central nervous system
CV	Coefficient variation
dpf	Days post fertilization
DLS	Dynamic light scattering
DMSO	Dimethyl sulfoxide
DOE	Design of experiments
EC	Endothelial cells
EE	Entrapment efficiency
EPS	extra-pyramidal side effects
FFAs	Free fatty acids
HPLC	High Performance Liquid Chromatography
LC_{50}	Concentration that cause 50% mortality

MCT	Medium-chain triglycerides
MED	Mixture Experimental Design
NE	Nanoemulsion
OECD	Organization for controlled Economic Cooperation and Development
PBS	Phosphate Buffered Saline
PCCS	Photon Cross Correlation Spectroscopy
PDI	Polydispersity Index
PKOE	Palm kernel oil ester
PRESS	Prediction Error Sum of Squares
R^2	Correlation of determination
R_t	Retention time
r.p.m	Rotation per min
RMSE	Root Mean Square Error
RSM	Response Surface Methodology
SD	Standard Deviation
TEER	Transendothelial Electric Resistance
TEM	Transmission Electron Microscope
UV-Vis	Ultraviolet-visible

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Schizophrenia is a serious psychiatric condition that affects ~1% of worldwide population (McGrath et al., 2008). This mental illness is characterized by positive symptoms (such as hallucinations, delusions, and deranged thoughts), negative symptoms (such as loss of motivation, restricted emotional experience, and poverty of speech), and cognitive impairment. In recent years, a medication (aripiprazole) has received growing attention for the treatment of schizophrenia. Aripiprazole has been demonstrated to be effective for the treatment of positive and negative symptoms in the schizophrenia or schizoaffective disorder for acute and long-term treatment in adults at doses of 10–30 mg/d (Pigott et al., 2003, Potkin et al., 2003, Chan et al., 2007, McEvoy et al., 2007, Li et al., 2014).

Aripiprazole is an atypical antipsychotic drug with D2 partial agonist properties and high D2 receptor affinity. This partial agonist can reduce D2 hyperactivation in the mesolimbic pathway, thus alleviating positive symptoms of schizophrenia, but provide enough D2 receptor stimulation in the mesocortical pathway and the nigrostriatal pathway to prevent, respectively, negative symptoms and extrapyramidal side effects (Wood and Reavill, 2007, Bhattacharjee and El-Sayeh, 2008, Mailman and Murthy, 2010, Stip and Tourjman, 2010). Initially developed for the treatment of schizophrenia, it is also used to treat bipolar I disorder (acute treatment of manic and mixed episodes and maintenance treatment of bipolar I disorder), major depressive disorder (as an adjunctive therapy to antidepressant), and irritability associated with autistic disorder. Finally, aripiprazole injection is indicated for the acute treatment of agitation associated with schizophrenia or bipolar disorder (Gaboriau et al., 2014).

Despite these vast gains, aripiprazole is insoluble in water, which makes it very challenging to incorporate it in pharmaceutical products. For enhancing the dissolution rate of poorly water soluble molecule, the surface area is purposely increased by reducing the droplet size of drug molecule. Increasing the surface area can affect the performance extremely (Merisko Liversidge and Liversidge, 2011). An alternative route of application can be considered where oil as a biocompatible carrier for aripiprazole in the composition of a nanoemulsion. This is able to improve the solubility as well as bioavailability of aripiprazole.

A nanoemulsion-based aripiprazole carrier could improve the solubility of the drug in the dispersed phase and drug penetration into the blood–brain barrier and target cells due to its extremely small size. Thus, a smaller dose of aripiprazole is preferred to reduce the side effects. In this context, the development of new drug nanodelivery systems to increase drug bioavailability and reduce adverse effects has been claimed as a good option.

The study of the influence of the mixture composition and parameter condition in preparation nanoemulsion formulation should be addressed by using Mixture Experimental Design (MED), Response Surface Methodology (RSM) and Artificial Neural Networks (ANNs). Besides helping to maximize the amount of acquired information and minimize the number of experiments to be carried out, these designs allow characterization and identification of synergistic and antagonistic interaction effects between different components. Nevertheless, some studies revealed on the study of formulation composition through these techniques in recent years that formulation investigations would be more suitable if these techniques were utilized more frequently (Seabra et al., 2012, Musa et al., 2013, Kamairudin et al., 2014, Ngan et al., 2014, Woo et al., 2015).

1.2 Problem statements

Aripiprazole is one of the CNS-acting drugs which are possessed poorly-water soluble characteristics (Mihajlovic et al., 2012). Thus, it has become a problem to pharmaceutical industries to incorporate aripiprazole in a formulation due to the low bioavailability and solubility. The surface area is purposely enlarged by minimizing the particle size of the drug molecule to maximize the dissolution rate of poorly water-soluble drug (Merisko Liversidge and Liversidge, 2011). By introducing the aripiprazole in the nanoemulsion system for an effective parenteral delivery, it can increase the possibility of the drug to pass through the BBB.

The stability of emulsion is an ultimate concern during development of a new formulation design. Maintaining the particle size in nanoscale range and physical stability for a long period of time have been a biggest challenge while formulating a nanoemulsion system. Thus, the development of suitable composition of formulations is very important to achieve stable nanoemulsion system with recommended physicochemical characteristics for parenteral delivery.

The evaluation of relationship between each component involved in this design has been examined individually. This process of experiment was time consuming and highly costing due to a large number of experiments involved. Thus, by using multivariate statistical techniques as the optimization tools, the processes of data collection in the experiment would be easier and high success rates could be achieved.

1.3 Objectives of the study

The aim of this study is to develop parenteral nanoemulsions formulation containing aripiprazole with the specific objectives as follows:

a) To prepare and optimize the nanoemulsion formulation containing aripiprazole.
b) To characterize the physicochemical properties of the optimized nanoemulsion.
c) To investigate the permeability of aripiprazole in the optimized nanoemulsion.
d) To evaluate the toxicity effects of the optimized nanoemulsion containing aripiprazole on zebrafish embryo (Danio rerio).

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