UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT AND CHARACTERIZATION OF DOCETAXEL AND CURCUMIN-LOADED AEROSOLIZED NANOEMULSION FOR PULMONARY CANCER

AZREN AIDA BINTI ASMAWI

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By

AZREN AIDA BINTI ASMAWI

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

DEVELOPMENT AND CHARACTERIZATION OF DOCETAXEL AND CURCUMIN-LOADED AEROSOLIZED NANOEMULSION FOR PULMONARY CANCER

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AZREN AIDA BINTI ASMAWI

July 2020

Chair : Mohd Basyaruddin Abdul Rahman, PhD
Faculty : Science

Lung cancer tops the cancer mortality rate with the lowest survival rate among all the cancers. The synergistic anticancer effect of docetaxel (DTX) and curcumin (CCM) emerges as an attractive therapeutic candidate in lung cancer treatment. However, the lack of optimal bioavailability due to poor solubility, low stability, and high toxicity have limited their clinical success. Hence, attention has been focused on the use of inhalable nanoemulsion systems for pulmonary delivery to alleviate the drawbacks. In this study, DTX and CCM-loaded nanoemulsions were formulated and optimized using Mixture Experimental Design (MED) and Response Surface Methodology (RSM) emphasizing the criteria for pulmonary applications. The drug content was quantified using a newly developed and validated high-performance liquid chromatography (HPLC) method. The formulated nanoemulsions were then subjected to physicochemical and aerodynamical characterizations. Investigation of their efficacy and nanotoxicity was also evaluated. The MED model exhibited that the optimum formulation for DTX and CCM-loaded nanoemulsions containing palm kernel oil ester and safflower seed oil (1:1, w/w; 6.00%), lecithin (2.50%), Tween 85 and Span 85 (9:1, w/w; 2.00%), glycerol (2.50%), α-tocopherol (0.05%) and water (86.95%) was achieved. The formulations were prepared using different process parameters having targeted size of 100, 150, and 200 nm as predicted by the RSM models. The developed HPLC method showed specificity with high linearity, good precision, and accuracy which are consistent with the International Conference on Harmonization (ICH) guidelines. All nanoemulsions exhibited desirable pH, viscosity, conductivity, and surface tension attributes for pulmonary administration. The nebulized nanoemulsions were mainly deposited in the deep lung regions with aerodynamic size ranging from 2.8 to 3.3 μm and a high percentage of FPF (>75%). Their aerodynamic characteristics were governed by the size, surface tension, and viscosity of the nanoemulsions in an inverse proportion. The formulated nanoemulsions exhibited

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sustained drug release and excellent physical stability against extreme conditions for nanoemulsion with the size 100 nm compared to 150 and 200 nm due to the Ostwald ripening process. Interestingly, *in-vitro* and *ex-vivo* experiments revealed that the combination of DTX and CCM in the nanoemulsion system was to reduce nanotoxicity and synergistically increase the efficacy. Similar results were obtained in zebrafish acute toxicity study as the nanotoxicity of the nanoemulsions was found to be dose and particle size dependents, and combined DTX and CCM-loaded nanoemulsion exhibited higher LC_{50} value compared to single and free drug solutions. Hence, these characteristics make the formulation to be a great candidate for potential use as a carrier system for DTX and CCM in lung cancer treatment via pulmonary delivery.

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PENGHASILAN DAN PENCIRIAN NANOEMULSI AEROSOL MENGANDUNGI DOCETAXEL DAN KURKUMIN UNTUK KANSER PULMONARI

Oleh

AZREN AIDA BINTI ASMAWI

Julai 2020

Pengerusi : Mohd Basyaruddin Abdul Rahman, PhD
Fakulti : Sains

Kanser paru-paru mendahului kadar kematian dengan kadar kelangsungan hidup yang terendah di kalangan semua kanser. Kesan sinergistik docetaxel (DTX) dan kurkumin (CCM) telah muncul sebagai calon terapeutik yang menarik dalam rawatan kanser paru-paru. Walau bagaimanapun, paras bioavailabiliti yang minima kerana kelarutan yang rendah, kestabilan yang rendah dan ketoksikan yang tinggi telah membataskan kejayaan klinikal mereka. Oleh itu, perhatian diberikan kepada penggunaan sistem nanoemulsi melalui penghantaran pulmonari untuk mengatasi kelemahan tersebut. Dalam kajian ini, DTX dan CCM-nanoemulsi telah diformulasi dan dioptimakan melalui Reka Bentuk Eksperimen Campuran (MED) dan Metodologi Tindak Balas Permukaan (RSM) dengan penekanan kepada kriteria terhadap aplikasi pulmonari. Kuantifikasi kandungan bahan aktif dianalisa dengan menggunakan kaedah kromatografi cecair prestasi tinggi (HPLC) yang baru dibangunkan dan divalidasikan. Formulasi tersebut kemudiannya tertakluk kepada pencirian fizikokimia dan aerodinamik. Penyiasatan terhadap keberkesanan dan ketoksikan nano mereka juga dinilai. Model MED telah menunjukan formulasi optima DTX dan CCM nanoemulsi mengandungi ester minyak isirong sawit dan minyak bunga kesumba (1:1, w/w; 6.00%), lesitin (2.50%), Tween 85 dan Span 85 (9:1, w/w, 2.00%), gliserol (2.50%), α-tokoferol (0.05%) dan air (86.95%). Formulasi tersebut disediakan dengan menggunakan parameter proses yang berbeza untuk saiz yang disasarkan 100, 150, dan 200 nm seperti yang diramalkan oleh model RSM. Kaedah HPLC yang dibangunkan menunjukkan pengkhususan dengan kelinearan yang tinggi, dan kejituan dan ketepatan yang baik selaras dengan garis panduan ICH. Semua nanoemulsi menunjukan nilai pH, kelikatan, kekonduksian dan ketegangan permukaan adalah bersesuaian untuk penghantaran pulmonari. Nanoemulsi yang dinebulasi deposit terutamanya ke bahagian dasar paru-paru dengan saiz aerodinamik dari 2.8 hingga 3.3 μm dan peratusan FPF yang tinggi (>75%). Ciri-ciri aerodinamik mereka dipengaruhi oleh saiz, ketegangan permukaan dan kelikatan nanoemulsi dalam kadaran songsang. Nanoemulsi yang telah dibangunkan mempamerkan pelepasan bahan aktif yang berterusan dan kestabilan fizikal yang sangat baik terhadap pelbagai keadaan untuk nanoemulsi yang yang bersaiz 100 nm dibandingkan dengan 150 dan 200 nm disebabkan oleh proses *Ostwald ripening*. Menariknya, kajian *in-*

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vitro dan *ex-vivo* mendedahkan bahawa gabungan DTX dan CCM di dalam sistem nanoemulsi dapat mengurangkan ketoksikan nano mereka dan meningkatkan keberkesanannya secara sinergi. Keputusan yang sama diperolehi dalam kajian ketoksikan ikan zebra di mana ketoksikan nano terhadap nanoemulsi adalah bergantung pada dos dan saiz partikel, dan gabungan DTX dan CCM nanoemulsi menunjukan nilai LC_{50} yang lebih tinggi berbanding dengan bahan aktif tunggal. Oleh itu, ciri-ciri ini menjadikan formulasi tersebut berpotensi besar untuk digunakan sebagai sistem pembawa bagi DTX dan CCM dalam rawatan kanser paru-paru melalui penghantaran pulmonari.

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Mohd Basyaruddin Abdul Rahman, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

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

Mas Jaffri Masarudin, 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

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Signature: _____
Name of Member of Supervisory Committee: Dr. Norazlinaliza Salim

Signature: _____
Name of Member of Supervisory Committee: Assoc. Prof. Dr. Mas Jaffri Masarudin

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LIST OF ABBREVIATIONS

A549	Human lung carcinoma cell
ACI	Anderson cascade impactor
CCD	Central composite design
CCM	Curcumin
CI	Combination index
COPD	Chronic obstructive pulmonary diseases
CSC	Cancer stem cells
CV	Coefficient of variation
DMEM	Dulbecco's modified eagle media
DMSO	Dimethyl sulfoxide
DTX	Docetaxel
ED	Emitted dose
EPR	Enhance permeability and retention
FBS	Fetal bovine serum
FPD	Fine particle dose
FPF	Fine particle fraction
GSD	Geometric standard deviation
HBSS	Hank's balanced salt solution
HLB	Hydrophilic-lipophilic balance
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
LCT	Long chain triglycerides
LOD	Limit of detection
LOQ	Limit of quantification

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MDR	Multidrug resistance
MED	Mixture experimental design
MMAD	Mass median aerodynamic diameter
MRC5	Human lung fibroblast cell
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NSCLC	Non-small cell lung cancer
OFAT	One-factor-at-a-time
PBS	Phosphate buffer saline
PCLS	Precision cut lung slice
PD	Percent dispersed
PDI	Polydispersity index
PI	Percent inhaled
PKOE	Palm kernel oil esters
RPMI	Roswell park memorial institute
RSE	Residual standard error
RSM	Response surface methodology
SCLC	Small cell lung cancer
SCT	Short chain triglycerides
TD	Total dose
TEM	Transmission electron microscopy
TMEM	Tumor microenvironment of metastasis
VMD	Volume median diameter

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CHAPTER 1

INTRODUCTION

1.1 Research background

Lung cancer is among the most prevalent cancers in the world and responsible for approximately 18.4% of cancer deaths in 2018 (Globocan, 2018). Since the 1930s, the incidence of lung cancer has been rising due to the widespread use of cigarette smoking (Ridge *et al.*, 2013). In Malaysia, the five-year survival rate for lung cancer has been the lowest among all the cancers, with only 11% of lung cancer patients survived after five years of diagnosis (MySCan, 2018). This trend is likely attributable to the poor prognosis, along with inadequate access to timely diagnosis and treatment due to no early obvious symptom. Therefore, it is usually only detectable at the later stages, where the cancerous cells or tissues are prevalent in large numbers and spread throughout the body. At this stage, chemotherapy is one of the most common treatment options for controlling the spreading of malignant tumors (Lee *et al.*, 2015).

Among the most potent chemotherapeutic drugs used for lung cancer treatment are taxanes, that comprises docetaxel (DTX). However, most chemotherapeutic drugs will end up with the development of drug resistance towards cancerous cells, which significantly reduces the efficacy of the chemotherapeutic-based treatment (Mansoori *et al*., 2017; Zhang *et al*., 2013). There is growing evidence indicating a mechanism derives from a subset of self-renewing cells, known as cancer stem cells (CSCs), which differ from the majority of cancer cells that are useful to be adapted in the mechanism of treatment. Although the cells mass is small in number, their self-renewal and differentiating properties may be similar to normal stem cells which makes them resistant to eradicate by chemotherapy and able to develop secondary tumors at other parts of the body (Housman *et al*., 2014; Zahreddine and Borden, 2013). Thus, to improve the efficacy of chemotherapy and minimize the emergence of drug resistance on growing cancer cells, targeting these populations of cells are essential in lung cancer treatment.

Recent progress in natural products has paved the way for the discovery of a novel chemotherapy adjunct for cancer treatment. A compound with medicinal properties known as Curcumin (CCM) extracted from the turmeric rhizome *Curcuma longa*, was identified for its potential as a chemosensitizer whereby the lung CSCs can be sensitized towards chemotherapy (Ahmad *et al.*, 2015; Mimeault and Batra, 2011). CCM is a multitargeting compound and able to suppress both function and expression of multidrug resistance (MDR) in CSCs which actively efflux drugs and enhance tumor cell proliferation (Lopes-Rodrigues *et al*., 2016; Yin *et al.*, 2012). The synergistic anticancer effect exhibited by DTX and CCM may potentiate the treatment of lung cancer and become an attractive therapeutic drug candidate. Nonetheless, the lack of optimal bioavailability in both DTX and CCM due to poor solubility and low stability have hampered their progression towards better development and clinical use. Moreover, the administration of this cytotoxic drug into the bloodstream and attaining the required dose

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at the target site are often marred by adverse side effects on healthy body tissues. This limits the dosage of taxanes that can be employed, and DTX has a dose limit of <100 mg/m^2 known to derive from hematologic toxicities (FDA, 2016).

At this juncture, the parenteral administration of chemotherapeutics through intravenous is a common route in treating lung cancer. The mechanism of chemotherapeutic drugs will be based on systemic circulation that needs to pass through several natural defense mechanisms before they reach the lungs. Furthermore, the non-specific distribution of the drugs across the human body may result in rapid clearance and poor pharmacokinetics. Hence, the focus of present research has been shifted to an alternative route that is via pulmonary, to mitigate the disadvantageous of the current course. Pulmonary drug delivery is a non-invasive intervention, which can be delivered through nasal or mouth by taking advantage of the physiological and nature of the lung environment. Lungs have a large contact surface area (140 m^2), high membrane permeability with thin alveolar epithelium (0.1 – 0.2 µm), making this as a domain of entry for pulmonary drug delivery (Fröhlich *et al*., 2016). Several types of respiratory diseases such as chronic obstructive pulmonary diseases (COPD), bronchitis, and asthma also have been conventionally treated via this route.

Direct deposition of drugs at the targeted region of the lungs can be achieved via inhalation therapy, which may be far effective with increasing local lung concentration. These lead to high systemic bioavailability, avoid first-pass metabolism and rapid onset of drug action. Prior to that, adverse effects caused by excessive drug dosage can also be prevented. However, due to the complexity of lung architecture and its clearance mechanisms, inhalations of drug solution may not be efficiently delivered to the deep lung region, where the tumors are normally found. Appropriate drug carrier systems to encapsulate drugs without affecting their primary bioactivity is therefore highly required in order to exploit the nature of respiratory transportation. The availability of biocompatible lipid excipients within the safety standards combined with their capability to improve drug bioavailability has made oil in water (O/W) nanoemulsion to be an ideal carrier to cater for these hydrophobic drugs.

1.2 Justification of the study

The focal interest in formulating an inhalable nanoemulsion system loaded with DTX and CCM is based on the presence of lipophilic core in the system, which can improve the drugs' solubility more than their aqueous solubility. This drug carrier system with a small particle size offers an increase in stability, dissolution rate and uniform distribution of drugs within the alveoli region due to the increased contact surface area. Also, the aerodynamic diameter of inhalable aerosols <5 µm containing drug loaded nanoemulsion particles is seen advantageous for effective deposition typically deposited in deep lung region and diffused preferentially into tumor tissue due to enhance permeability and retention (EPR) effect that allows nanosized particles to slip through the leaky tumor vessels. Eventually, this inhalable drug delivery system will enhance the bioavailability of the drug on the lung tumors and enable the use of a lower dosage than those currently employed.

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1.3 Scope of the study

In current state of invention, the combined delivery of a chemotherapeutic drug (DTX) and a chemosensitizer agent (CCM) encapsulated in an inhalable nanoemulsion system for enhancement of efficacy in lung cancer treatment via pulmonary route has been developed. An efficient screening and optimization method for the selection of pharmaceutically acceptable nanoemulsion excipients has been examined. The efficiency and suitability of inhalable DTX and CCM-loaded nanoemulsion were characterized physicochemically and aerodynamically with an emphasis on the required criteria for pulmonary delivery application through series of experiments including particle size, zeta-potential, surface tension, viscosity, osmolality, conductivity, stability, aerosolization properties. Besides, other assessments that involve *in-vitro* and *ex-vivo* experiments comprising drug permeability and nanotoxicity on normal cell lines (MRC5) and cancerous lung (A549) cell lines, rat precision-cut lung slices (PCLS) and zebrafish embryos with treatments of single and combined therapy in different sizes of nanoemulsion formulations and free drug solution have also been evaluated.

1.4 Objectives

The objective of this research is to design and develop an effective inhalable nanoemulsion system with the size of 100, 150 and 200 nm loaded with DTX and CCM for lung cancer treatment. Thus, the research embarks on the following specific objectives:

i. To formulate and model the influence of nanoemulsion excipients and process parameter interaction on the formation of an inhalable nanoemulsion system containing DTX and CCM.
ii. To develop and validate the high-performance liquid chromatographic (HPLC) method for the determination of single and combined DTX and CCM content in an inhalable nanoemulsion system.
iii. To characterize the physicochemical and aerodynamical properties of formulated nanoemulsion aerosols.
iv. To assess the *in-vitro* permeation and stability properties of the formulated nanoemulsion system.
v. To evaluate the efficacy and nanotoxicity of the formulated nanoemulsion system.

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BIODATA OF STUDENT

Azren Aida Asmawi was born on 19th March 1987 in Kuala Lumpur. She received her early education at Sekolah Rendah Kebangsaan Ampang Campuran, Ampang, Selangor. In 2000, she continued her secondary education at Sekolah Menengah Kebangsaan Taman Tasik, Ampang, Selangor and later at MARA Junior Science College Beseri, Perlis from 2003 to 2004. After completing her Malaysian Certificate of Education (SPM), she pursued her studies at INTEC Education College, Shah Alam under Australian Matriculation (AUSMAT) programme in 2005. She received her Bachelor of Biotechnology majoring in Biochemistry from Monash University, Australia in 2009. After graduation, she joined Biotechnology Corporation for special training programme and was assigned on attachment to BioNexus Research Company (Myagri Nutribio) for 3 months and then was offered a research executive position in the same company. Thereafter, in September 2011, she enrolled in Master of Science degree programme, at Faculty of Science, Universiti Putra Malaysia (UPM) and was awarded her Master degree in chemical synthesis under the supervision of Dr. Bimo Ario Tejo. Upon completion, in September 2016, she continued her studies in the same university and enrolled in Doctor of Philosophy programme majoring in Nanoscience under the supervision of Prof. Dr. Mohd Basyaruddin Abdul Rahman. She was awarded MyMaster and MyPhD scholarships under programme of MyBRAIN15 by Ministry of Education throughout her Master and PhD studies.

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LIST OF PUBLICATIONS

Research Papers

Azren Aida Asmawi, Norazlinaliza Salim, Emilia Abdulmalek, Mohd Basyaruddin Abdul Rahman (2020). Modeling the effect of composition on formation of aerosolized nanoemulsion system encapsulating Docetaxel and Curcumin using D-optimal Mixture Experimental Design. *International Journal of Molecular Sciences*, *21*(12), 4357.

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