UNIVERSITI PUTRA MALAYSIA

DOCETAXEL-LOADED MAGNETIC NANOSTRUCTURED LIPID CARRIER FUNCTIONALIZED WITH FISH OIL-COATED IRON OXIDE NANOPARTICLES INTENDED FOR LUNG CANCER TREATMENT

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By

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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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Chair :Mohd Basyaruddin bin Abdul Rahman, PhD
Faculty :Science

Lung cancer is currently the most prevalent cause of cancer mortality due to late diagnosis and lack of curative therapies. Docetaxel (Dtx) is clinically proven to be effective, but poor aqueous solubility and non-selective cytotoxicity limit its therapeutic efficacy. Increasing the bioavailability of Dtx while potentially monitoring the therapeutic response via Magnetic Resonance Imaging is an appropriate strategy for effective drug delivery. In this work, a nanostructured lipid carrier (NLC) loaded with iron oxide nanoparticles (IONP) and Dtx (Dtx-MNLC) was developed as a potential theranostic agent for lung cancer treatment. The IONP was synthesised from thermal decomposition of iron oxyhydroxide (Fe(O)OH) and functionalised with Menhaden fish oil (MFO). Its physicochemical properties, cytotoxicity, and potential as contrast agents were then evaluated. The NLC was optimised using Response Surface Methodology. The amount of IONP and Dtx loaded into the Dtx-MNLC was quantified using Inductively Coupled Plasma Optical Emission Spectroscopy and high-performance liquid chromatography. Dtx-MNLC was then subjected to assessment of physicochemical characteristics, in vitro drug release, and cytotoxicity. IONP having 10 nm size was synthesised at 60 minutes aging time and 400 rpm stirring rate. The MFO-coated IONP (MFO-IONP) showed excellent aqueous dispersibility and good negative contrast with transverse relaxation rate of 9.85 $mM^{-1}s^{-1}$. MFO-IONP exhibited dose-dependent toxicity with higher toxicity on human lung carcinoma cells (IC_{50} = 41 µg/mL) than human lung fibroblast cells (IC_{50} = 494 µg/mL) within 72 hours exposure. The RSM model suggested the NLC formulated with 6% w/w lipid (MCT/ Precirol ATO 5) and 7.7% w/w emulsifier (TPGS/ Lipoid S75), with 20 minutes stirring time and 400 rpm stirring rate to achieve 187 nm particle size. Dtx loading percentage was determined at 3.98% w/w, and 0.36 mg/mL MFO-IONP was loaded into the Dtx-MNLC. The formulation showed a biphasic drug release in a simulated cancer cell environment, where 40% of Dtx was released for the first 6 hours, and 80% cumulative release was achieved after 48 hours. Dtx-MNLC exhibited higher

cytotoxicity to A549 cells than MRC5 in a dose-dependent manner. Furthermore, the toxicity of Dtx-MNLC to MRC5 was lower compared to the commercial formulation. In conclusion, Dtx-MNLC shows the efficacy to inhibit lung cancer cells growth, yet reduced toxicity on healthy lung cells and potentially capable as a theranostic agent for lung cancer treatment.

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

MAGNETIK LIPID BERSTRUKTUR NANO MENGANDUNGI DOCETAXEL DAN FERUM OKSIDA BERSALUT MINYAK IKAN SEBAGAI AGEN RAWATAN KANSER PARU-PARU

Oleh

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Kanser paru-paru menjadi punca kematian yang tertinggi di antara jenis kanser yang lain disebabkan kelewatan diagnosis dan kekurangan terapi penyembuhan yang berkesan. Docetaxel (Dtx) ialah antikanser yang berkesan secara klinikal, tetapi sifat tidak larut air dan kesitotoksikan yang tidak selektif telah mengehadkan keberkesanannya. Satu strategi yang efektif ialah dengan meningkatkan bioketersediaan Dtx dan memantau kesan terapi terhadap tumor melalui pengimejan resonans magnetik. Dalam kajian ini, Dtx dan magnetik ferum oksida nanopartikel (IONP) dimuatkan dalam lipid berstruktur nano (NLC) dan dijadikan Dtx-MNLC sebagai agen teranostik yang berpotensi merawat kanser paru-paru. IONP disintesis melalui penguraian terma ferum oksihidroksida (Fe(O)OH) dan permukaannya difungsikan dengan minyak ikan Menhaden (MFO-IONP). Sifat fizikokimia, kesitotoksikan dan ciri agen kontras kemudiannya dinilai. Formulasi NLC dioptimakan melalui Metodologi Respons Permukaan manakala jumlah kandungan IONP dan Dtx ditentukan menggunakan plasma induksi optik pelepasan spektrometri dan kromatografi cecair prestasi tinggi. Pencirian fizikokimia, kadar pelepasan dos dan kesitotoksikan kemudian dilakukan. IONP bersaiz 10 nm disintesis dalam masa 60 minit dan kadar pengadukan 400 rpm. MFO-IONP dapat diserakkan dalam air dan menunjukkan kontras negatif dan kadar relaksasi melintang sebanyak 9.85 $mM^{-1}s^{-1}$. Kesitotoksikan MFO-IONP bergantung kepada dos, dan ketoksikannya lebih tinggi kepada sel karsinoma paru-paru manusia (IC_{50} = 41 µg/mL) berbanding sel fibroblas paru-paru (IC_{50} = 494 µg/mL) dalam tempoh 72 jam. Berdasarkan model RSM, formulasi NLC dihasilkan secara optima dengan 6% lipid (MCT/Precirol ATO 5) dan 7.7% pengemulsi (TPGS/Lipoid S75) dengan 20 minit masa pengadukan dan 400 rpm kadar pengadukan untuk mendapatkan saiz nanopartikel sebesar 187 nm. Sebanyak 3.98% b/b Dtx dan 0.36 mg/mL MFO-IONP berjaya dimuatkan dalam Dtx-MNLC. Formulasi ini melepaskan dos secara dwifasa dalam persekitaran sel kanser simulasi, iaitu 40% Dtx dilepaskan pada 6 jam pertama dan 80% pelepasan

kumulatif sepanjang 48 jam. Bergantung kepada dos, Dtx-MNLC adalah lebih toksik kepada A549 berbanding MRC5. Dtx-MNLC juga kurang toksik kepada MRC5 berbanding formulasi komersial. Kesimpulannya, Dtx-MNLC berkesan untuk merencatkan pertumbuhan sel kanser tetapi kurang toksik kepada sel tubuh yang sihat dan berpotensi sebagai agen teranostik untuk rawatan kanser paru-paru.

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

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LIST OF ABBREVIATIONS

A549	Human lung carcinoma cell
ADC	Adenocarcinoma
ALK	Anaplastic lymphoma kinase
AMF	Alternating magnetic field
ANOVA	Analysis of Variance
ATCC	American Type Culture Collection
ATR-FTIR	Attenuated total reflection - fourier transform infrared spectroscopy
CCD	Central Composite Design
CCM	Cell Culture Media
CT	Computed Tomography
DDS	Drug Delivery System
DL	Drug loading
DLS	Dynamic Light Scattering
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DSC	Differential scanning calorimetry
Dtx	Docetaxel
EE	Entrapment efficiency
EGFR	Epidermal Growth Factor Receptor
EPR	Enhanced permeabilty and retention
FDA	Food and Drug Administration
GRAS	Generally Recognized as Safe

HLB	Hydrophile-lipophile balance
HPLC	High Performance Liquid Chromatography
HRTEM	High resolution transmission electron microscopy
ICP-OES	Inductively Coupled Plasma Optical Emission Spectroscopy
IONP	Iron oxide nanoparticles
ISO	International Organization of Standardization
LBF	Lipid-based formulation
LCC	Large cell carcinoma
LP	Lipoid S75
MAR	Motion averaging regime
MCT	Medium chain triglyceride
MFO	Menhaden fish oil
MFO-IONP	Menhaden fish oil-coated iron oxide nanoparticle
MNLC	Magnetic nanostructured lipid carrier
MPS	Mononuclear phagocytic system
MRC5	Human lung fibroblast cell
MRI	Magnetic resonance imaging
MWCO	Molecular weight cut-off
NLC	Nanostructured lipid carrier
NSCLC	Non-small cell lung cancer
OA	Oleic acid
OA-IONP	Oleic acid-coated iron oxide nanoparticle
PBS	Phosphate buffer saline
PdI	Polydispersity index

PET	Positron emission tomography
PMS	phenazine methosulfate
PS	Particle size
PTFE	Polytetrafluoroethylene
PXRD	Powder X-ray diffracion
R2	Transverse relaxtion rate
RES	Reticuloendothelial system
RF	Radiofrequency
RPMI	Roswell Park Memorial Institute
RSM	Response Surface Methodology
SBRT	Stereotactic body radiotherapy
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SDR	Static dephasing regime
SLF	Simulated lung fluid
SLN	Solid lipid nanoparticle
SMR	Slow motion regime
T1	Longitudinal relaxation time
T2	Transverse relaxation time
TFA	Trifluoroacetic acid
TGA	Thermogravimetric analysis
TME	Tumour microenvironment
TNM	Tumour-Node-Metastatis
TPGS	D-α-tocopheryl polyethylene glycol succinate

VSM	Vibrating sample magnetometer
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Research Background

Until 2020, global lung cancer prevalence was estimated to increase to 2.2 million cases compared to 2.1 million cases in 2018 (Bray et al., 2018). The exact cause of lung cancer is unknown, but high-risk lifestyle such as cigarette smoking has been identified as a major risk factor. Symptoms of lung cancer are similar to other respiratory and lung diseases, which complicates a correct diagnosis; thus, it is often confirmed when the patients have reached stage III and IV. According to Sung et al. (2021), it was estimated that most lung cancer patients die within one year of diagnosis, and only 18% survived within five years due to poor prognosis and less effective treatment.

Standard therapy for lung cancer patients includes surgery, chemotherapy, and radiotherapy. Surgery and radiotherapy are often combined with chemotherapy to avoid recurrent tumour progression for more effective treatment. Anticancer agents such as doxorubicin, cisplatin, and docetaxel (Dtx) have been shown to inhibit solid tumor progression in the lungs, breasts, and prostates, among others (Montero et al., 2005). Nevertheless, clinical applications of these drugs are limited due to low aqueous solubility, serious side effects, and non-specific distribution of the body. For example, the commercial formulation of Dtx (Taxotere®) contains a high amount of surfactant (Tween 80) to increase its aqueous solubility. Although this formulation is proven effective in cancer therapy, it has caused dose-limiting toxicity, and hypersensitivity reactions in patients, as both cancer cells and healthy cells are exposed to the toxicity effects, leading to severe adverse effects such as neurotoxicity and neutropenia (Ho & Mackey, 2014).

The development of nanotechnology in pharmaceutical sciences has opened up endless possibilities for improving cancer treatment. Various colloidal drug delivery systems (DDS) such as micelles, polymeric nanoparticles, dendrimer, and solid lipid nanoparticles (SLN) have shown promising results to entrap hydrophobic and hydrophilic chemotherapeutics for improved biodistribution and better therapeutic response. Among these nanoparticulate delivery systems, lipid-based formulations designed as respirable nanocarriers, such as liposomes (Lin et al., 2017), nanoemulsions (Asmawi et al., 2019), solid lipids nanoparticles (SLN) (Bakhtiary et al., 2017), and nanostructured lipid carrier (NLC) (Ong et al., 2020) were reported to have good lung tolerability and low toxicity due to the biocompatible lipid used in the formulations.

Nanoparticles formulated from solid lipid, e.g., SLN, present high stability in vivo and often demonstrate controlled release kinetics (Duan et al., 2020). However, premature drug leakage from their solid lipid during storage and low drug loading appear to limit their potential as DDS. In 2002, Müller et al. started incorporating liquid lipid in the solid lipid to form NLC, which resulted in higher loading capacity and better stability than SLN. The types of lipid and the ratio of solid and liquid lipid selected to produce NLC were observed to significantly impact their polymorphism, possible existence of supercooled melts, and presence of other colloidal species. Therefore, careful selection of formulation excipients and investigations on their physicochemical properties are required to develop a suitable formulation designed as lung cancer therapy.

Current chemotherapy effectiveness can only be determined upon treatment completion by physical examinations, X-ray/ Computed Tomography (CT) scan, or blood tests. The treatment protocol would be changed later if inadequate chemotherapy response was measured, which consequently could cause the tumour to progress further before an effective treatment regime can be prescribed. Theranostic in oncology offers unique opportunities to provide diagnostic imaging and therapeutic molecules in a single platform. Functionalisation of nanocarriers with magnetic nanoparticles such as iron oxide nanoparticles (IONP) will enable visualisation of tumours and metastases in various organs such as the liver, spleen, and lymph nodes using Magnetic Resonance Imaging (MRI) (Dadfar et al., 2019). A theranostic approach to continuously monitor the treatment response is beneficial for measuring chemotherapy effectiveness.

1.2 Research Objectives

This work describes the development of magnetic nanostructured lipid carrier (MNLC) loaded with Dtx for potential theranostic application in lung cancer treatment. This study is designed to achieve the following objectives:

I. To optimise the synthesis protocol of oleic acid-coated iron oxide nanoparticles (OA-IONP) using thermal decomposition method based on their measured size and magnetic properties

II. To determine the physicochemical properties of Menhaden fish oil-coated IONP (MFO-IONP) after ligand exchange

III. To assess the suitability of MFO-IONP for Magnetic Resonance Imaging (MRI) using agarose phantom

IV. To develop the formulation of MNLC loaded with MFO-IONP and Dtx with an understanding of its physicochemical properties, release kinetics of drugs and short-term storage stability of formulated MNLC

V. To study the in vitro cytotoxicity of MFO-IONP and MNLC on non-small cell lung carcinoma (A549) and lung fibroblast cells (MRC5) using colorimetric assay

1.3 Scope of the Study

IONP were used as magnetic nanoparticles in this work. The IONP was chemically synthesised using thermal decomposition of iron oxyhydroxide in the presence of oleic acid as the capping agent and 1-octadecene. The oleic acid coating was then substituted with Menhaden fish oil to improve the biocompatibility of the IONP. The IONP was further embedded in lipid vesicles composed of Precirol ATO 5 as solid lipid, medium chain triglyceride (MCT) as oil, Vitamin E TPGS (TPGS) and soy lecithin (Lipoid S75) as the emulsifier. Dtx, an antineoplastic agent, was used as active pharmaceutical ingredient in this formulation and was solubilised in the lipid component to form MNLC.

Various characterisation techniques were used to investigate the physicochemical properties of the IONP and MNLC. Particle size and dispersity were determined using High Resolution Transmission Electron Microscope (HRTEM) and dynamic light scattering (DLS). Chemical bonding was analysed by Attenuated Reflection-Fourier Transform Infrared spectroscopy (ATR-FTIR). Crystallinity and solid state of the nanoparticles were studied using powder X-ray diffraction (PXRD), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Magnetic properties of IONP and MNLC were characterised by Vibrating Sample Magnetometry (VSM). Concentration of Dtx in the formulation was determined using high performance liquid chromatography equipped with UV detector (HPLC-UV).

In vitro tests were carried out to study the drug release profile of MNLC in simulated lung fluid (SLF) at pH 7.4 and in pH 6.0 to simulate the cancerous microenvironment. Cytotoxicity tests of IONP and MNLC were performed on the normal human fibroblast lung cell (MRC-5) and adenocarcinomic human alveolar basal epithelial cells (A549) using colorimetric cell viability assay.

1.4 Limitation of the Study

This study is only limited to the development, physicochemical analysis, in vitro drug release and in vitro cytotoxicity of IONP and MNLC. The assessment of their aerodynamic properties for inhalational delivery route, in vivo toxicity and MRI-monitored magnetic targeting performance are beyond the scope of this work.

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