UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF AEROSOLIZED NIOSOME FORMULATION CONTAINING GEMCITABINE AND CISPLATIN FOR *IN-VITRO* CYTOTOXICITY AGAINST MRC5 AND A549 CELL LINES

NORFATIN IZZATIE BINTI MOHAMAD SAIMI

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By

NORFATIN IZZATIE BINTI MOHAMAD SAIMI

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NURFATIN IZZATIE BINTI MOHAMAD SAIMI

November 2020

Chair : Norazlinaliza binti Salim, PhD
Faculty : Science

Gemcitabine (Gem) and cisplatin (Cis) are currently being used for lung cancer treatment has been proven to improve the life expectancy of cancer patients, but they are highly toxic in high dosages. Aerosolized niosome formulation containing a low-dosage Gem and Cis (NGC), as an alternative formulation for lung cancer chemotherapy treatment was developed. The idea of aerosolization is to able direct delivery of a niosome formulation to the smaller airways of the lung. Niosome is a closed-bilayer vesicle in aqueous media that formed from the self-assembly of nonionic surfactant with cholesterol (Chol). NGC was prepared using a very simple heating method and was further optimized by D-optimal mixture design. The optimized NGC with 2.00 wt.% of surfactant (Tween 65 : Span 60 with ratio of 2:1), 1.01 wt.% of cholesterol and 63.06 wt.% of glycerol solution was obtained, where the other components were kept constant. The actual particle size showed good correlation with the predicted particle size with residual standard error (RSE) value less than 5%. The physicochemical characterization of optimum NGC formulation showed that the particle size, polydispersity index (PDI), and zeta potential were 166.45 nm, 0.16, and −15.28 mV, respectively. Zeta potential obtained indicates good stability against aggregation meanwhile if the zeta potential approaching zero value will lead to aggregation. The optimized NGC remained stable at 27°C with no phase separation for up to 90 days. Optimized NGC surface tension was 35.49 mN/m with an aerosol output of 96.22%, which indicates its suitability as aerosolized formulation. An in vitro drug release study using the dialysis bag diffusion technique showed controlled release for both drugs for up to 24 h penetration. The result showed that percentage of Gem release in pH 7.4 (64.71%) was 2-fold than Gem in pH 6.7 (30.38%). Meanwhile, for Cis, the percentage drug release in pH 7.4 was lower (53.55 %) than in pH 6.7 (99.58%) after 24h. This was due to the nature of drug and pH of the release

medium affect the percentage of drug release. A cytotoxicity study against normal lung (MRC5) and lung cancer (A549) cell lines were performed by diluting and pipetting the formulation onto the cells. The results showed that the optimized NGC had reduced the cytotoxicity effects against both MRC5 and A549 cell lines when compared with the control (Gem + Cis alone) from very toxic (IC_{50} < 1.56 µg/mL) to weakly toxic (IC_{50} = 280.00 µg/mL) and moderately toxic (IC_{50} = 46.00 µg/mL), after 72 h of treatment. These results suggested that optimized NGC has the potential to be used for aerosolized chemotherapy treatment which will be promising less toxicity toward normal cell and able to inhibit cancer cell with low multidrug dosage.

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

PEMBANGUNAN FORMULASI EROSOL NIOSOM MENGANDUNGI GEMCITABINE DAN CISPLATIN UNTUK KESITOTOKSIKAN *IN-VITRO* TERHADAP TITISAN SEL MRC5 DAN A549

Oleh

NORFATIN IZZATIE BINTI MOHAMAD SAIMI

November 2020

Pengerusi : Norazlinaliza binti Salim, PhD
Fakulti : Sains

Gemcitabine (Gem) dan Cisplatin (Cis) yang kini digunakan dalam rawatan kanser paru-paru telah terbukti dapat meningkatkan jangka hayat pesakit kanser, tetapi ianya sangat toksik dalam dos yang tinggi. Formulasi niosom erosol yang mengandungi dos Gem dan Cis yang rendah (NGC), sebagai formulasi alternatif bagi rawatan kemoterapi kanser paru-paru telah dikaji.Idea erosol ini adalah bagi membolehkan penghantaran terus formulasi niosom kepada bahagian saluran udara paru-paru yang paling kecil. Niosom adalah vesikel dwilapisan tertutup dalam medium akues yang terbentuk daripada pengumpulan kendiri surfaktan bukan ionik dengan kolesterol (Chol). NGC telah disediakan dengan menggunakan kaedah pemanasan yang sangat ringkas dan kemudiannya dioptimumkan dengan reka bentuk campuran D-optimum. NGC optimum yang mengandungi 2.00 wt.% surfaktan (Tween 65 : Span 60 dengan nisbah 2:1), 1.01 wt.% kolesterol dan 63.06 wt.% larutan gliserol telah dihasilkan, di mana kandungan komponen lain adalah tetap. Saiz zarah sebenar dan ramalan saiz zarah menunjukkan tiada perbezaan yang ketara dengan baki ralat piawaan (RSE) kurang daripada 5%. Perincian fizikokomia terhadap formulasi NGC optimum menunjukkan saiz zarah, indeks kepoliserakan (PDI), dan potensi zeta masing-masing adalah 166.45 nm, 0.16, dan −15.28 mV. Potensi zeta yangdiperoleh menunjukkan tahap kestabilan yang baik melawan pengagregatan manakala sekiranya potensi zeta menghampiri nilai kosong akan menyebabkan pengagregatan berlaku. NGC optimum kekal stabil pada suhu 27°C tanpa pemisahan fasa selama 90 hari. Ketegangan permukaan NGC optimum adalah 35.49 ± 0.01 mN/m dengan keluaran erosol sebanyak 96.22% yang menunjukkan kesesuaianya sebagai formulasi erosol. Kajian pelepasan ubat secara in-vitro menggunakan teknik resapan beg dialisis menunjukkan pelepasan terkawal bagi kedua-dua ubat tersebut selama 24 jam penembusan. Keputusan menunjukkan kadar pelepasan Gem dalam pH 7.4 (64.71%) adalah 2 kali ganda berbanding Gem

dalam pH 6.7 (30.38%). Manakala bagi Cis, kadar pelepasan dalam pH 7.4 lebih rendah (53.55%) berbanding dalam pH 6.7 (99.58%) selepas 24 jam. Ini adalah bergantung kepada sifat natural ubat dan pH medium pelepasan yang mempengaruhi kadar pelepasan ubat. Kajian kesitotoksikan terhadap titisan sel paru-paru normal (MCR5) dan kanser paru-paru (A549) telah dilakukan. Hasil kajian menunjukkan bahawa NGC optimum telah mengurangkan kesan kesitotoksikan terhadap kedua-dua garis sel MRC5 dan A549 berbanding kawalan (Gem + Cis bersendirian) daripada sangat toksik (IC_{50} < 1.56 µg/mL) kepada toksik lemah (IC_{50} = 280.00 µg/mL) dan toksik sederhana (IC_{50} = 46.00 µg/mL), selepas rawatan selama 72 jam. Keputusan ini mencadangkan bahawa NGC optimum boleh digunakan sebagai rawatan kemoterapi secara erosol yang akan menjanjikan ketoksikan yang lebih rendah terhadap sel normal dan mampu untuk merencat sel kanser dengan dos pelbagai ubat yang rendah.

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Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

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:

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

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

Noraini binti Ahmad, PhD
Senior Lecturer
Faculty of Science
Universiti Malaya
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Signature: _____
Name of Member of Supervisory Committee: Mohd Basyaruddin bin Abdul Rahman

Signature: _____
Name of Member of Supervisory Committee: Noraini binti Ahmad

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
Au	Uranyl acetate
Cis	Cisplatin
CSC	Cancer stem-like cells
°C	Degree Celsius
DLS	Dynamic Light Scattering
DOX	Doxorubicin
DNA	Deoxyribonucleic acid
EE	Entrapment efficiency
g	Gram
Gem	Gemcitabine
h	Hour
HA-Pt	Cisplatin-hyaluronan
HLB	Hydrophile-lipophile balance
IC_{50}	Concentration of an inhibitor where the response (or binding) is reduced by half
M˚	Initial concentration
MDR	Multidrug resistance
MED	Mixture Experimental Design
mg/L	Milligram/liter
min	Minute
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
mV	Milivolt
NaCl	Sodium chloride
nm	Nanometer
NGC	Niosome formulation containing gemcitabine and cisplatin
NSCLC	Non-small cell lung carcinoma
PAMAM	Polyamidoamine
PBS	Phosphate buffer saline
PDI	Polydispersity index
PEG	Polyethylene glycol
rpm	Revolutions per minute
RSE	Residual standard error
RT	Room temperature
R^2	Coefficient of determination
SCLC	Small-cell lung carcinoma
SD	Standard deviation
SDS	Sodium dodecyl sulfate
SLF	Simulated lung fluid
SLN	Solid lipid nanoparticles
SPIONS	Superparamagnetic iron oxide nanoparticles
TEM	Transmission electron microscopy
UV/Vis	Ultraviolet–visible

CHAPTER 1

INTRODUCTION

1.1 Background of Research

Over the past fifty years, the main public health concern for cancer diseases has increased especially lung cancer which is the most common cancer diagnosed in the world followed by colorectal, liver and breast cancer and contributing to 37% of the leading cause of cancer-related death worldwide from total death in 2018 (Bray *et al*., 2018) . There are two main categories of lung cancer, which are non-small cell lung carcinoma (NSCLC), which contributes 85% of cases while small-cell lung carcinoma (SCLC) contributes 15% cases from all lung cancer cases (Zappa & Mousa, 2016).

A significant factor that leads to lung cancer is cigarette smoking (Hammerschmidt & Wirtz, 2009). However, increasing lung cancer cases among non-smokers are quite alarming nowadays (Planchard & Besse, 2015). Different stages of lung cancer with different treatments are the main reason for the low survival rate of cancer patients. Likewise, in other cancer cases, detection and confirmation usually can only be made at stage four (IV) (Akhter, 2015). The current treatments used for lung cancer are surgery, chemotherapy and radiation therapy, depending on the stage and overall performance of cancer cells. For the advanced stage of lung cancer, chemotherapy is the first-line treatment where most of the treatment is applied as intravenous (IV) formulations into systematic circulation (Quan *et al*., 2019).

Cancer chemotherapeutic drugs are usually used to destroy cancer cells by preventing the cancer cell from growing, dividing, and producing more cells (Lee *et al*., 2015). Conventionally, a patient who undergoes chemotherapy will be given a single or multi-drug at a time. For example, it is either cisplatin (Cis) or gemcitabine (Gem) alone or a combination of both drugs (Ma *et al*., 2017). The combination with other cancer treatments such as radiation therapy, surgery followed by several cycles of chemotherapy has also been applied (Khuda-Bukhsh *et al*., 2014). The current drugs used for lung cancer chemotherapy treatment are cisplatin, carboplatin, paclitaxel, gemcitabine, docetaxel, and vinorelbine (Zappa & Mousa, 2016).

The demand for nano-carriers for drug administration in medical applications, especially in chemotherapy treatment, has increased as drug development is advancing. Nano-carriers are believed to have great potential in the delivery of single or multiple drugs (at low dosage) to tissue tumours by overcoming biological barriers and can reach the tiniest area in the body due to their small

particle size. Furthermore, most of the nanocarrier systems increase the effectiveness of chemotherapy and minimize side effects by enhancing the deposition of the drug at the tumour based on their stability and permeability (Majumder, Taratula, & Minko, 2019).

Nanocarriers provide a larger surface area, have the potential to increase solubility, improve the controlled release of the drug, and enhance the bioavailability in the delivery of chemotherapy drugs to the targeted tumour area (Majeed *et al*., 2016). There are a few of nano-carriers used as targeting drugs delivery systems such as micelles, dendrimers, nanoparticles, liposomes and niosomes (Kang *et al.*, 2015; Khodabandehloo *et al.,* 2016). Among those nano-carriers, liposomes and niosomes have great potential in the delivery of multiple drug. Both have efficiencies in encapsulating hydrophilic and hydrophobic drugs into the aqueous layer and the lipid bilayer, respectively (Saraswathi *et al*., 2019). However, liposomes are less suitable because of their instability due to the oxidation or hydrolysis of phospholipids, where they require special storage conditions in a dark area sealed with nitrogen, and the materials used to produce liposomes are expensive (Wen *et al*., 2018).

Niosome is a system with bilayer spherical vesicles formed by self-assemblies of nonionic surfactant and cholesterol in an aqueous medium (El-badry *et al*., 2014; Ertekin *et al*., 2015). Nonionic surfactants are commonly used in the preparation of niosome due to their high degree of compatibility with other ingredients. As membrane additives to the bilayer composition of niosome, cholesterol enhances the stability and reduces leakage of vesicles which will increase the entrapment efficiency of the drug (Gharbavi *et al*., 2018). Niosomes are chemically stable, have high compatibility with biological systems, and low toxicity because of their nonionic nature (Ge *et al*., 2019). Therefore, it is not surprising that niosomes (as nanocarrier) are currently being used to deliver drugs such as (i) 5-Fluorouracil, increasing drug penetration in skin cancer treatment; (ii) tamoxifen citrate, providing higher cytotoxicity against breast cancer cells; and (iii) curcumin, giving more significant apoptotic effect towards ovarian cancer cells.

1.2 Problem Statements

Generally, Gem and Cis are administered at a higher dosage of 1.250 and 0.075 g/m^2 per cycle, respectively, which will lead to higher toxicity (Fan *et al*., 2010). However, it was found that the combination of drugs (Gem + Cis) improved the survival rate among cancer patients compared to the use of a single drug (Pande *et al*., 2012). This has shown that the optimum dosage of the combination of drugs can be effective in increasing the survival rate of lung cancer patients as well as helping to reduce side effects such as vomiting, sore throat, chest congestion, and nausea (Liu *et al*., 2015).

Most of the chemotherapeutics drugs are unstable with a short half-life and fast clearance from the body system. Furthermore, cancer chemotherapeutic drugs that are administered orally are always limited due to the first-pass metabolism, where the drug concentration is usually reduced as it passes through the gastrointestinal tract before the drug can access the systematic circulation (Sohail *et al*., 2018). Multi-drug resistance (MDR) in lung cancer stem-like cells (CSC) becomes a limitation to the combination of cancer therapy even though the dual drug has the potential to improve cancer treatment by reducing the drug dosage which leads to less side effects (Huang *et al*., 2016). These problems led to less effective lung cancer chemotherapy treatment. Thus, a more efficient carrier for this combination of drugs should be developed to improve the delivery of both drugs to the lung (targeted site) via the alternative route of delivery.

1.3 Scope of Study

In this study, aerosolized niosome (NGC) formulation containing Gem and Cis was prepared using the heating method (hydration method of niosome component without using any hazardous chemical). Screening of the compositions of the formulation used has been performed. The optimization of NGC formulation compositions was carried out using a mixture experimental design (MED). The physicochemical characterization and stability of the optimized NGC formulation were investigated. *In-vitro* drug release study in simulated lung fluid was performed at pH 6.7 and 7.4 using dialysis bag method, and a cytotoxicity study against normal healthy MRC5 and lung cancer A549 cells was further investigated. The aerosol output was determined in order to calculate the percentage of the aerosolized formulation.

1.4 Objectives

The main objective of this study was to develop aerosolized niosome formulation containing gemcitabine and cisplatin (NGC). In order to successfully achieved the main objective, the following specific objectives have been carried out:

1. To formulate and optimize niosome formulation containing gemcitabine and cisplatin (NGC) using a mixture experimental design (MED).
2. To characterize the physicochemical properties and evaluate the stability of the optimized NGC formulation.
3. To determine the *in vitro* cytotoxicity and drug release of the optimized NGC.

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BIODATA OF STUDENT

Norfatin Izzatie binti Mohamad Saimi was born in Pasir Mas, Kelantan on 11st May 1992. She received her primary in Sekolah Kebangsaan Temin and secondary education in MRSM Kuala Lipis and MRSM Tun Ghafar Baba. She completed her Matriculation of Science Programme at Matriculation College Pahang in 2011 and was offered to pursue her degree at Universiti Putra Malaysia (UPM) and obtained her Bachelor of Science (Honours) degree in Chemistry in 2016. Then, she pursued her Master's Degree in Nanomedicine under supervision of Dr. Norazlinaliza Salim and co-supervisor of Prof Dr Basyaruddin Abdul Rahman and Dr. Noraini Ahmad at Department of Chemistry, Faculty of Science, Universiti Putra Malaysia. She was offered Graduated Research Foundation under UPM, NanoMITe Research Grant (Vot. No 5526306) and UMRG (RG395-17AFR).

LIST OF PUBLICATIONS

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List of Conferences/Congress

National Conference (2015-2019)

1. Norfatin Izzatie Mohamad Saimi, Norazlinaliza Salim, Mohd Basyaruddin Abd Rahman, and Noraini Ahmad, 2019, Development of Aerosolized Niosome Formulation Containing Gemcitabine and Cisplatin for Lung Cancer Treatment. NanoMITe Annual Symposium & Nanotechnology Malaysia Annual Symposium (NanoSym 2019). (Oral presentation)

International Conference (2015-2019)

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3. Norfatin Izzatie Mohamad Saimi, Norazlinaliza Salim, Mohd Basyaruddin Abd Rahman, and Noraini Ahmad, 2019. Niosome Encapsulation of Gemcitabine-Cisplatin: Characterization, Stability and Cytotoxicity Effect on Lung Cancer Cell, 7th International Symposium on Applied Engineering and Sciences (SAES2019). (Oral presentation)

Awards

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