FORMULATION OF WATER-IN-OIL NANOEMULSION CONTAINING ROSELLE EXTRACT FOR CONTROLLED DELIVERY

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DEDICATION

To my beloved parents and siblings
My awesome supervisor, Dr Roswanira Abdul Wahab,
And all of my lovely friends,
Without whom none of my success would be possible

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ABSTRACT

The anthocyanin-rich roselle extract has the potential to inhibit lung cancer. However, the compounds demonstrate poor bioavailability and low stability in a biological application. Therefore, the present study proposed the formulation of a roselle extract containing W/O nanoemulsion (NE) as a nanocarrier for pulmonary delivery. This study utilized an integrated low and high energy methods of ultrasonication, Ultra-homogenizer, and hot temperature inversion methods to prepare the w/o roselle extract. Composition of the stable w/o formulation comprised roselle extract (0.04 w/w%), sodium chloride solution (3.0 w/w%), medium-chain triglyceride (81.93 w/w%), a ratio of surfactants Tween 80:Span 80 (15 w/w%) at 22.5:77.5, which gave a HLB of 6.7. Next, the corresponding physicochemical and morphological characterizations showed the NE has a mean droplet size of 298 ± 9 nm, a zeta potential of −49± 0.05 mV, and a polydispersity index (PDI) of 0.61 ± 0.009. Most importantly, the produced droplets were spherically shaped without any aggregation. The NE's pH was found to be in the range of 6.1−5.8 after 30 days of observation, agreeing well with the recommended range for safe delivery into the human lung. The low conductivity (0.009 mS/cm) of the roselle extract w/o NE verified its W/O characteristic, while the rheological test proved its shear-thinning (pseudoplastic) behaviour. The W/O NE remained stable without phase separation in the accelerated stability tests (centrifugation test, freeze-thaw cycle) and the long-term storage stability test at 4°C, 25°C, and 35°C, done at 60 days. The *in vitro* release of the entrapped roselle extract at different pH buffer solutions showed that their release at pH 6.5 was 45.19%. The percentage release seen here was higher than at pH 7.4 (40.2%). Pertinently, the two release kinetics behaviour adhered to the Korsmeyer-Peppas kinetic mechanism (R^2 = 0.9702 for pH 7.4 and R^2 = 0.9722 for pH 6.5). The Korsmeyer–Peppas Model of the roselle extract w/o NE gave a release exponent (n) of 0.77 at pH 6.5 and 0.49 at pH 7.4. The study results verified that the release pattern of the extracts at both pH conditions followed non-Fickian diffusion mechanism. This meant that more than one type of release phenomenon might be involved in the case of the roselle extract, in which diffusion along with erosion through the simulated lung fluid could be the mechanism of release. In conclusion, the present study collectively showed the successful development of the W/O nanoemulsion containing the roselle extract. Thus, the results support its potential as a nanocarrier for pulmonary delivery application for lung cancer treatment.

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ABSTRAK

Ekstrak roselle yang kaya dengan antosianin berpotensi untuk menghalang barah paru-paru. Walau bagaimanapun, sebatian tersebut menunjukkan ketersediaan bio yang rendah dan kestabilan rendah dalam aplikasi biologi. Oleh itu, kajian ini mencadangkan formulasi emulsi nano ekstrak roselle air-dalam-minyak (W/O) sebagai pengangkut nano untuk penghantaran paru .Kajian ini menggunakan kaedah bersepadu tenaga rendah dan tinggi ultrasonikasi, ultrapenghomogen, dan inversi suhu panas untuk menyediakan ekstrak roselle (W/O). Komposisi yang stabil formulasi w/o terdiri daripada ekstrak roselle (0.04 w/w%), larutan natrium klorida (3.0 w/w%), trigliserida rantai sederhana (81.93 w/w%), suatu nisbah surfaktan Tween 80:Span 80 (15 w/w%) pada 22.5:77.5, yang memberikan HLB 6.7. Seterusnya, ciri fizikokimia dan morfologi yang berkaitan menunjukkan NE mempunyai ukuran titisan min 298 ± 9 nm, suatu potensi zeta −49 ± 0.05 mV, dan indeks penyebaran (PDI) 0.61 ± 0.009. Yang paling penting, titisan yang dihasilkan berbentuk bulat tanpa apa-apa pengagregatan. PH NE berada di dalam julat 6.1−5.8 setelah 30 hari pemerhatian, bersetuju dengan julat yang disyorkan untuk penghantaran selamat ke paru-paru manusia. Kekonduksian rendah (0,009 mS / cm) ekstrak roselle NE mengesahkan ciri w/onya, sementara ujian reologi membuktikan tingkah laku penipisan ricih (pseudoplastik). NE W/O kekal stabil tanpa fasa pemisahan dalam ujian kestabilan dipercepat (ujian sentrifugasi, kitaran pembekuan-pencairan) dan ujian kestabilan penyimpanan jangka panjang pada suhu 4° C, 25° C, dan 35° C, yang dilakukan pada 60 hari. Pelepasan *in vitro* ekstrak roselle yang terperangkap pada larutan buffer pH yang berbeza menunjukkan bahawa pelepasan pada pH 6.5 adalah 45.19%. Peratusan pelepasan yang dilihat di sini lebih tinggi berbanding pada pH 7.4 (40.2%). Sesungguhnya, tingkah laku kinetik pelepasan mematuhi mekanisme kinetik Korsmeyer-Peppas (R^2 = 0.9702 untuk pH 7.4 dan R^2 = 0.9722 untuk pH 6.5). Model Korsmeyer – Peppas ekstrak roselle tanpa NE memberikan eksponen pelepasan (n) 0.77 pada pH 6.5 dan 0.49 pada pH 7.4. Hasil kajian mengesahkan bahawa corak pelepasan ekstrak pada kedua-dua keadaan pH mematuhi penyebaran bukan-Fickian. Ini bermaksud bahawa lebih daripada satu jenis fenomena pelepasan mungkin terlibat di dalam kes ekstrak roselle, di mana penyebaran bersama hakisan melalui simulasi cecair paru-paru dapat menjadi mekanisme pelepasan.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACN	-	Anthocyanin
MCT	-	Median chain triglyceride
NE	-	Nanoemulsion
SCLC	-	Small cell carcinoma
NSCLC	-	Non–small cell carcinoma
O/W	-	Oil in water
W/O	-	Water in oil
W/O/W	-	Water-in-Oil-in-Water
Hs	-	Hibiscus sabdariffa
HLB	-	Hydrophile-Lipophile Balance
D3S	-	Delphinidin-3-sambubioside
C3S	-	Cyanidin-3-sambubioside
PDI	-	Polydispersity index
DLS	-	Dynamic light scatter
CVD	-	Cardiovascular disease
DI	-	Deionized water
FPF	-	Finer Particle Fraction
TEM	-	Transmission Electron Microscopy
PBS	-	Phosphate Buffer Saline
PB	-	Phosphate buffer
ZP	-	Zeta Potential
EE	-	Encapsulation Efficiency
PIC	-	Phase Inversion Composition
PIT	-	Phase Inversion Temperature
MDS	-	Mean Droplet Size
T80	-	Tween 80
S80	-	Span 80

LIST OF SYMBOLS

T	-	temperature
ρ	-	density
r	-	radius value after a certain time
r_o	-	radius value at time zero
t	-	frequency of rupture per unit of the dialysis bag surface
ω	-	the frequency of rupture per unit surface of the dialysis bag
$C(\infty)$	-	bulk phase solubility
V_m	-	molar volume of the internal phase
D	-	diffusion coefficient of the dispersed phase in the continuous phase
µg	-	microgram
ml	-	millilitre
min	-	minute
nm	-	nanometer
rpm	-	rotation per minutes
µL	-	microliter
mg	-	milligram
cm	-	centimetre
h	-	hour
µM	-	micro molar
mOsm	-	miliosmolar
mV	-	millivolt
mS	-	milisiemens
min	-	minute
w/w	-	weight/weight
w/v	-	weight/volume

CHAPTER 1

INTRODUCTION

1.1 Background of Research

Globally, cases and deaths from lung cancer are on the rise. In 2018, GLOBOCAN recorded 2.09 million new cases and 1.76 million deaths, more than those reported in 2012, making it the most persistent and cause of cancer death in both males and females (Bray et al., 2018). This number of cases is expected to grow in the next 15 years(Abdelaziz et al., 2018; Meghani et al., 2018). While lung cancer has been linked to tobacco smoking, it also affected non-smokers. In Malaysia, only 15% of lung cancer patients survived more than five years after diagnosis (Rajadurai et al., 2020). Visibly, current therapies for lung cancer, viz. surgical resection, radiation, and chemotherapy, are far from effective (Neal, Gubens, & Wakelee, 2011). Systemic delivery of chemotherapeutic drugs is rarely effective even at high concentrations as only a small quantity targets the tumor sites in the lungs (Patra et al., 2018). Unfortunately, most of the administered chemotherapy drugs attack the normal cells and inhibit their development, further weakening the patient and led to their eventual death (Dietrich & Gerber, 2016). Therefore, effective treatment regimens must be developed to overcome this issue.

Pulmonary drug delivery has recently drawn the attention of the scientific community. Pulmonary drug delivery has various merits over other delivery routes that include a wide surface area in the alveolar sacs and high vascularization. This is because the lungs being the respiratory system's main component, offers a fascinating route to non-invasive local and systemic drug administration (Javadzadeh & Yaqoubi, 2017; Sung, Pulliam, & Edwards, 2007). The features allow targeted drug delivery and hence, reduce unwanted symptoms (Beck-Broichsitter et al., 2009). Pulmonary drug delivery takes advantage of the comparatively low local

metabolic activity in the lungs. Unlike the oral route, pulmonary drug delivery is not subjected to first-pass metabolism, and the needle-free approach is better accepted by patients (Pilcer & Amighi, 2010). Pulmonary drug delivery also lowers non-reversible tissue impairment due to drug cytotoxicity, and the drugs are better absorbed by the exceptional ultra-thin alveolar epithelium(Sung et al., 2007). Notably, particles between 10−20 nm in size deposited in the alveolar region are nearly four times more effective than micron-size ones (Onischuk et al., 2014). . From this perspective, pulmonary delivery of the chemotherapy drug nanoemulsion is a promising strategy for anti-lung cancer therapy.

Chemotherapeutic approaches using natural molecules are widely used to inhibit or reverse carcinogenesis (Maiuthed, Chantarawong, & Chanvorachote, 2018). A survey of the literature has shown the phenolic compounds, anthocyanin (ACNs) have therapeutic benefits and disease-preventing properties, such as anti-tumor (P.-N. Chen et al., 2006). ACNs can interfere with the proliferation of multiple cancer cell types, including lung cancer (P.-N. Chen et al., 2006; J. N. Lu et al., 2017; L.-S. Wang & Stoner, 2008). and exhibit cardiovascular and neuroprotective effects on humans (Kalt et al., 2020; Zhang et al., 2019). Other therapeutic properties of ACNs include antibacterial, anti-inflammatory, antioxidant, and antifungal (Demirbas, Yilmaz, Ildiz, Baldemir, & Ocsoy, 2017; Jurikova, Skrovankova, Mlcek, Balla, & Snopek, 2019; Sabatini et al., 2020). A good source of ACNs is the calyces of the *Hibiscus sabdariffa* Linn, a shrub of the Malvaceae family and that grow well in Asia or Tropical Africa. The bright-red calyxes of the plant are rich in anthocyanins, particularly the ephinidin 3-sambubioside or hibiscus, as well as the major pigments cyanidin 3-sambubioside, alongside minor compounds, namely the delphinidin 3-glucoside and cyanidin 3-glucoside. Anthocyanins are naturally highly reactive, being the derivatives of the alkaline, electron-deficient nucleus flavylium cation structure. Preserving the pH-dependent activity (pH 2.0 − 7.0) of the extract is germane as the compounds' anti-oxidative power decline with increasing pH (Chumsri, Sirichote, & Itharat, 2008).

However, the application of ACNs in the medicinal and clinical treatments of lung cancers has been problematic and are rather limited due to the physiological

instability of the drug formulation and a low oral bioavailability (Kalam Azad, Lim, Park, & Kang, 2018; Lila, Burton-Freeman, Grace, & Kalt, 2016).One possible intervention of the aforesaid issue and boosting the bioavailability of drug to affected lung cells is by a novel therapeutic carrier system, i.e., nanoemulsion. A new generation hybrid of nanotechnology and emulsion technology has facilitated the manipulation to deliver bioactive compounds to get the best outcome of the treatment (MOHAMAD, ABD GANI, WAHAB, & ZAIDAN). Nanoemulsions of chemotherapeutic cancer drugs are a promising treatment because of the minute size of the droplets (20−500 nm) (Bernardi et al., 2011), unlike the classically formulated macroemulsions and microemulsions. Generally, there are two different types of nanoemulsions: 1) oil in water (O/W) nanoemulsion where the oil is dispersed in the continuous aqueous phase and, (2) water in oil (W/O) nanoemulsion where water droplets are dispersed in the continuous oil phase. In many cases, the o/w nanoemulsion is often used for the delivery of hydrophobic active substances. Conversely, w/o nanoemulsion is for the delivery of hydrophilic active substances (Aswathanarayan & Vittal, 2019a). Nanoemulsions can vary in shape and stability; their high solubilizing capability and drug loading efficiency facilitate efficient transport of the drugs to the lungs (Amani, York, Chrystyn, & Clark, 2010). It also can ameliorate pulmonary deposition and retention for the prolonged interval in the lung tissues when inhaled. Nanoemulsions are kinetically stable due to absence of gravitational separation and droplet aggregation from the reduced attractive force between the small-sized droplets (Aswathanarayan & Vittal, 2019a; Solans, Izquierdo, Nolla, Azemar, & Garcia-Celma, 2005). Nanoemulsions are also easy to formulate as they mostly require a low energy input (Jasmina, Džana, Alisa, Edina, & Ognjenka, 2017).

1.2 Problem Statement

Lung cancer remains one of the most malignant cancer till today, but the treatment regimen for this disease remains challenging for oncologists (Abdelaziz et al., 2018; Meghani et al., 2018). Conventional treatment by oral and intravenous route leads to poor bioavailability of the synthesized drug to the targeted sites due to the first-pass

metabolism and blood resistance (Neal et al., 2011; Patra et al., 2018). and adversely affecting healthy tissues (Neal et al., 2011). In this perspective, this study proposes the direct delivery of a water-in-oil (W/O) nanoemulsion inhalant containing the natural therapeutic agent containing anthocyanins from roselle extract . These bioactive ingredients are extremely unstable and susceptible to degradation as well as have low bioavailability . This route is feasible for delivering higher contents of the bioactive ingredients by circumventing the first-pass metabolism responsible for the profound reduction of components to the affected lung cells alongside fewer systemic side effects to the patient (Javadzadeh & Yaqoubi, 2017). Through the inhalation method, pulmonary delivery avoids first-pass metabolism, fewer systemic side effects, and a needle-free approach to patients (Sung et al., 2007).

In the present research, the ACNs were extracted from the *H. sabdariffa* Linn plant's calyces or natively known as roselle. This study then identifies the best route to formulate a stable water-in-oil roselle extract for an inhalant system. Literature has shown that anthocyanins are potential bioactive agents against lung cancer (P.-N. Chen et al., 2006; J. N. Lu et al., 2017; L.-S. Wang & Stoner, 2008). given that the poor bioavailability and poor stability of this compound are overcome (Kalam Azad et al., 2018; Lila et al., 2016). It is hypothesized that the nano formulated ACN extract of roselle provides better bioavailability and imparts a more controlled release of the bioactive agents. The approach taken in this study is somewhat possible since nanoemulsions have been found suitable for pulmonary delivery administration of bioactive agents or drugs for lung-related complications or diseases(Andrade, Rodrigues, & Martins, 2020; Ngan & Asmawi, 2018).

1.3 Objectives of research

This study aimed to prepare a stable, nano-sized emulsion containing the crude roselle extract. To achieve this, the following objectives were proposed:

i. To screen and optimize the parameters to formulate a stable W/O nanoemulsion containing the crude roselle extract for controlled pulmonary delivery.

ii. To characterize the physicochemical properties and stability study of the W/O nanoemulsion containing the crude roselle extract

iii. To investigate the mechanism of in-vitro control release study of roselle extract containing W/O nanoemulsion.

1.4 Scopes of the Study

The first part of this research first obtained the crude extract of roselle by refluxing in ethanol/water solvent to extract the anthocyanins alongside polyphenols. The extractant was lyophilized into powder before storage in the chiller. The following part of the formulation activity began by identifying the optimal i) hydrophilic/hydrophobic balance (HLB) of the crude roselle extract containing nanoemulsion, ii) the type of surfactant and oils, and iii) amount of water to be incorporated into the nanoemulsion. An adequate ratio of Tween 80 and Span 80 was used as the surfactants in this formulation. The nanoemulsion was prepared by combining a high-energy and low-energy technique, namely the ultrasonic and hot-temperature method. The correct protocol of the integrated mixing method was explored and repeated for the i) order to mixing and ii) the duration of mixing using each method until a suitably stable nanoemulsion was obtained.

The second part of this research involves the stability characterization of the nanoemulsion, namely by freeze-thaw cycle, centrifugation test at 4000 rpm, pH (5.8−6.1), and storage stability for over 60 days at (35, 25 and 4 C°). Formulations that passed the tests above are then physicochemically characterized by the Zetasizer Nano ZSP Instrument for particle size and PDI. Finally, the in vitro assessment of the crude roselle extract containing nanoemulsion was tested for aerosol delivery by using the dialysis bag diffusion technique in which the samples are withdrawn from the medium at different intervals and analyzed for the amount of drug released.

1.5 Significance of the Study

This study to discover the most kinetic stable roselle extract containing W/O nanoemulsion as a drug to cure lung cancer treatment and also the identifical formulation provides a sustained release of the anti-cancer active ingredients to increase residence time on the target site and improve their bioavailability and stability of the active ingredient in the roselle extract.

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