

VIRGIN COCONUT OIL BASED
NANOSTRUCTURED LIPID CARRIER LOADED WITH
FICUS DELTOIDEA EXTRACT FOR SKIN BARRIER IMPROVEMENT

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To the most special ones, mama and ah.

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ABSTRACT

Ficus deltoidea (FD) is a medicinal herb which had been discovered to possess antioxidant and anti-inflammatory activities. Thus, it has the potential to be a good active ingredients for improving skin barrier function. Nanostructured lipid carrier (NLC) is a promising delivery system to transport FD extract through the skin as it is composed of biocompatible lipids, which are similar to the intercellular part of the stratum corneum. The objective of this research is to formulate and characterize physicochemical and biological properties of virgin coconut oil (VCO) based NLC loaded with FD extract to improve skin barrier function. The FD loaded NLC (FDNLC) formulation was prepared using melt emulsification homogenization technique with glycerol monostearate as solid lipid, VCO as liquid lipid and combination of Tween 80 and soy lecithin as surfactant. The delivery system had the particle size of 158.033 ± 10.53 nm, polydispersity index of 0.153 ± 0.06 , zeta potential of -42.32 ± 1.54 mV, and encapsulation efficiency of $87.401 \pm 7.33\%$. Transmission electron microscopy images indicated that the prepared NLCs were spherical in shape with even size distribution. The formulation was stable for at least 40 days. Diffusion experiments showed that FDNLC diffused through the skin had the steady state flux of 12.727 mg/cm².h, lag phase of 0.023 h, and permeability coefficient of 0.098 cm/h. The results showed better penetration in FDNLC compared to non-encapsulated FD. The skin test study in term of transepidermal water loss, hydration, elasticity, melanin and erythema showed significant improvement between week 0 and week 4 with the usage of cream loaded with FDNLC. Taken together, the formulation of FDNLC can be concluded to be efficient in improving skin barrier function.

ABSTRAK

Ficus deltoidea (FD) adalah sejenis ubatan herba yang telah dikenal pasti untuk mempunyai aktiviti antioksidan dan anti-radang yang tinggi. Ini menjadikan ia sesuai sebagai bahan aktif untuk meningkatkan fungsi rintangan kulit. Pembawa lipid nanostruktur (NLC) adalah pembawa yang sesuai untuk ekstrak FD memandangkan ianya terdiri daripada lipid bioserasi sama sifat dengan bahagian ruang antara sel pada lapisan *stratum corneum*. Objektif penyelidikan ini adalah untuk merumuskan dan mencirikan sifat fizikokimia dan sifat biologi NLC yang dimuatkan dengan ekstrak FD berasaskan minyak kelapa dara (VCO) untuk meningkatkan fungsi rintangan kulit. FD yang dimuatkan ke dalam NLC (FDNLC) telah disediakan menggunakan teknik penghomogenan pengemulsian cecair dengan menggunakan gliserol monostearat sebagai lipid pepejal dan VCO sebagai lipid cecair serta gabungan Tween 80 dan lesitin soya sebagai surfaktan. Sistem penghantaran ubat ini mempunyai ciri-ciri berikut iaitu saiz partikel 158.033 ± 10.53 nm, indeks poliselerakan 0.153 ± 0.06 , potensi zeta -42.32 ± 1.54 mV dan kecekapan pengkapsulan $87.401 \pm 7.33\%$. Imej NLC daripada mikroskop elektron penghantaran menunjukkan partikel NLC berbentuk sfera dengan agihan saiz yang sekata. Formulasi ini stabil dalam tempoh sekurangnya selama 40 hari. Kajian resapan menunjukkan FDNLC yang diresap ke dalam kulit mempunyai fluks berkeadaan mantap 12.727 mg/cm².jam, fasa lag 0.023 jam dan pekali kebolehtelapan 3.19 ± 0.098 cm/jam. Keputusan kajian menunjukkan FDNLC adalah lebih bagus dari segi penyerapan berbanding FD yang tidak dienkapsulasi. Kajian kulit pula mendapati kehilangan transepidermal air, hidrasi, keanjalan kulit, melanin dan eritema kesemuanya menunjukkan peningkatan yang signifikan antara minggu kosong dan ke empat dengan penggunaan krim FDNLC. Kesimpulannya, formulasi FDNLC adalah efisien untuk meningkatkan fungsi rintangan kulit.

TABLE OF CONTENT

CHAPTER	TITLE	PAGE
	DECLARATION	ii
	DEDICATION	iii
	ACKNOWLEDGEMENT	iv
	ABSTRACT	v
	ABSTRAK	vi
	TABLE OF CONTENTS	vii
	LIST OF TABLES	xiii
	LIST OF FIGURES	xv
	LIST OF ABBREVIATIONS	xvii
	LIST OF SYMBOLS	xviii
1	INTRODUCTION	1
	1.1 Background of the Study	1
	1.2 Problem Statement	5
	1.3 Objective	7
	1.4 Scope of the Research	7
2	LITERATURE REVIEW	8
	2.1 Human skin	8
	2.1.1 Skin barrier function	9

2.2	Natural drugs for Treatment of Diseases	14
2.2.1	<i>Ficus deltoidea</i> (FD)	15
2.2.2	Chemical Compound of FD	16
2.2.3	Potential Effect of FD on Skin Barrier Function	17
2.2.4	Anti-inflammatory Activity of FD	19
2.2.5	Antioxidant Properties of FD	20
2.2.6	Anti-microbial Activity of FD	21
2.2.7	Application of FD	22
2.2.8	Toxicological Study of FD	23
2.3	Virgin Coconut Oil (VCO)	25
2.3.1	Chemical Compound in Virgin Coconut Oil	26
2.3.2	Advantages of Virgin Coconut Oil	27
2.3.3	Potential Effect of Virgin Coconut Oil on Skin Barrier Function	29
2.4	Topical Drug Delivery	29
2.5	Nanostructured Lipid Carrier System	34
2.5.1	Mechanism of Permeation of Drug from NLC System	36
2.5.2	Components in NLC System	37
2.5.3	Preparation of NLC System	38
2.5.4	Characterizations of NLC System	40
2.5.4.1	Particle Size and Polydispersity Index (PDI)	40
2.5.4.2	Zeta Potential	41
2.5.4.3	Entrapment Efficiency and Drug Loading	41
2.5.4.4	Electron Microscopy	42
2.5.4.5	Penetration Study	42
2.5.5	Stability Study of NLCs	43
2.5.6	Application of NLC System	44
3	RESEARCH METHODOLOGY	46
3.1	Introduction	46

3.2	Materials	48
3.3	Preparation of FD Extract	49
3.3.1	Detection of Bioactive Marker in FD Extract	50
3.3.2	Particle Size and PDI Analysis of FD Extract	50
3.3.3	Antioxidant Activity of FD Extract	50
3.4	Preparation of FD Loaded Nanostructured Lipid Carrier	51
3.5	Characterization of FD Loaded Nanostructured Lipid carrier	53
3.5.1	Measurement of Particle Size and Polydispersity Index	53
3.5.2	Encapsulation Efficiency and Drug Loading	53
3.5.3	Determination of Zeta Potential	54
3.5.4	Determination of Morphology	55
3.6	Chromatography Analysis of FD Loaded Nanostructured Lipid Carrier	55
3.6.1	High Performance Liquid Chromatography (HPLC) Analysis	55
3.7	In Vitro Evaluation of FD Loaded Nanostructured Lipid Carrier	56
3.7.1	Antioxidant Activity	56
3.7.2	Cell Proliferative Study	57
3.7.2.1	Cell Line	57
3.7.2.2	MTT Assay	57
3.8	Skin Permeation Study	58
3.9	Stability Study	59
3.10	In Vivo Study	59
3.10.1	Sample Preparation	59
3.10.2	Volunteers Recruitment	60
3.10.3	Protocol of Study	60
3.10.4	Tape Stripping	61
3.10.5	Biophysical Measurements	62
3.10.5.1	TEWL Measurements	62

	3.10.5.2	Skin Hydration Measurement	62
	3.10.5.3	Elasticity Measurement	62
	3.10.5.4	Skin pH Measurement	63
	3.10.5.5	Melanin and Erythema Measurement	63
	3.11	Statistical Analysis	63
4		RESULT AND DISCUSSION	64
	4.1	Introduction	64
	4.2	Properties of FD Extract	65
	4.2.1	Physicochemical Properties of FD Extract	65
	4.2.2	Yield of FD Extract Using High Performance Liquid Chromatography (HPLC) Analysis	66
	4.3	Determination of Composition of FD Loaded Nanostructured Lipid Carrier Formulation	67
	4.3.1	Effect of Amount of Solid Lipid on Particle Size and PDI	67
	4.3.2	Effect of Amount of Liquid Lipid on Particle Size and PDI	68
	4.3.3	Effect of Amount of Surfactant on Particle Size and PDI	69
	4.3.4	Effect of Composition of FD on Particle Size and PDI	70
	4.4	Characterization of FD Loaded Nanostructured Lipid Carrier	72
	4.4.1	Physicochemical Properties	72
	4.4.2	Particle Size and PDI of FD Loaded Nanostructured Lipid Carrier	73
	4.4.3	Zeta Potential of FD Loaded Nanostructured Lipid Carrier	74
	4.4.4	Active Ingredients Loading and Encapsulation Efficiency of FD Loaded Nanostructured Lipid Carrier	75
	4.4.5	Transmission Electron Microscopy (TEM)	76

4.5	Detection of Vitexin and Isovitexin in FDNLC Using High Performance Liquid Chromatography Analysis	77
4.6	Stability of FD Loaded Nanostructured Lipid Carrier	77
4.7	<i>In Vitro</i> Study of FD Loaded Nanostructured Lipid Carrier	80
4.7.1	Antioxidant Activity of FD Loaded Nanostructured Lipid Carrier	80
4.7.2	Cell Proliferative Assay	82
4.8	<i>In Vitro</i> Skin Permeation Study	84
4.9	In Vivo Skin Test	86
4.9.1	FDNLC Cream Preparation	86
4.9.2	Biophysical Measurements	86
4.9.3	Transepidermal Water Loss (TEWL)	87
4.9.4	Skin Hydration	89
4.9.5	Elasticity	91
4.9.6	pH Index	92
4.9.7	Melanin and Erythema Index	93
4.10	Summary	96
5	CONCLUSIONS AND RECOMMENDATIONS	97
5.1	Conclusions	97
5.2	Recommendations	98
	REFERENCES	99
	Appendices (A-D)	119-128

LIST OF TABLES

TABLE NO.	TITLE	PAGE
2.1	Chemical and nutritional constituents of FD	17
2.2	Potential pharmaceutical and cosmeceutical applications of FD	22
2.3	Quantitative physio-chemical analysis of leaves of FD.	24
2.4	Contamination of microbial in the leaves of FD.	24
2.5	Heavy metal content of leaves of FD	24
2.6	Fatty acid found in VCO and its chemical formula	27
2.7	Potential pharmaceutical and cosmeceutical applications of VCO	28
2.8	Various nanotherapeutics as topical drug delivery system	31
2.9	Summary of several nanocarriers used for topical therapy	32
2.10	List of components used in NLCs	37
2.11	Methods for preparation of NLCs	39
2.12	Possible application of NLC system in topical drugs formulations and cosmetic products.	44
3.1	Materials used in the study	48
4.1	Composition of final formulation of FDNLC	71
4.2	Comparison of particle size and PDI between FDNLC and blank	73
4.3	Comparison of zeta potential between FDNLC and blank	74
4.4	Yield of vitexin and isovitexin in FD extract and FDNLC	77
4.5	IC50 value of sample and standards used in DPPH assay	81

4.6	Permeation parameters for FDNLC and FD extract for penetration study using Strat-M as membrane.	84
4.7	Percentage change of skin biophysical parameters from week 0 to week 4	95

LIST OF FIGURES

FIGURE NO	TITLE	PAGE
2.1	Layers of human skin	9
2.2	Schematic diagram of stratum corneum	9
2.3	Functions of the epidermal ‘inside-outside’ and ‘outside inside’ barrier	10
2.4	Clinical appearance of damaged skin	15
2.5	<i>Ficus deltoidea</i> plant	16
2.6	Biomarkers for FD	19
2.7	Possible effect of FD on skin barrier function	19
2.8	Living Active Virgin Coconut Oil	26
2.9	Structure of SLN and NLC	35
2.10	Franz diffusion cells schematic diagram	43
3.1	Flowchart of experiment	47
3.2	Step by step of preparation for FDNLC	52
3.3	D-squame tape	61
3.4	Tape stripped site	61
4.1	FD extract	65
4.2	HPLC chromatograms (a) and (b) (absorbance at 340 nm) of vitexin and isovitexin from FD extract	66
4.3	Effect of composition of solid lipid (GMS) on size and PDI of FDNLC.	68
4.4	Effect of composition of liquid lipid (VCO) on size and PDI of FDNLC.	69

4.5	Effect of composition of surfactant (soy lecithin and tween80) on size and PDI of FDNLC	70
4.6	Effect of composition of active (FD) on size and PDI of FDNLC.	71
4.7	FDNLC formulation	72
4.8	Morphology of FDNLC from TEM	76
4.9	Size of FDNLC at 25°C, 4°C and 40°C through 40 days study	79
4.10	PDI of FDNLC at 25°C, 4°C and 40°C through 40 days study.	79
4.11	Percentage of DPPH inhibition by FDNLC and standards (Trolox and ascorbic acid).	81
4.12	Cell viability of fibroblast cells (HSF 1184) cultured with increasing concentrations of FDNLC using MTT assay.	82
4.13	The effect of FDNLC on cell viability of fibroblast cells (HSF 1184) after UVB irradiation (15.0 mJ/cm ² , 320 nm).	83
4.14	Cumulative amount of FD permeated for 24 hours using Strat-M as membrane	84
4.15	FDNLC cream	86
4.16	Comparison of TEWL value on skin surface in short term study	88
4.17	Percentage recovery of skin in 7 days after tape stripping.	89
4.18	Short term hydration study	90
4.19	Percentage change of hydration value after 4 weeks of application.	91
4.20	Percentage change of elasticity value after 4 weeks of application.	91
4.21	Percentage change of pH value after 4 weeks of application	92
4.22	Percentage change of melanin value after 4 weeks of application	93
4.23	Percentage change of erythema value after 4 weeks of application	94

LIST OF ABBREVIATIONS

DL	-	Drug loading
DMEM	-	Dulbelcco's modified Eagle's medium
DMSO	-	Dimethyl sulfoxide
DPPH	-	2,2-diphenyl-2- picrylhydrazyl
EE	-	Encapsulation efficiency
FBS	-	Fetal bovine serum
FD	-	<i>Ficus deltoidea</i>
FDNLC	-	<i>Ficus deltoidea</i> loaded Nanostructured Lipid Carrier
GCMS	-	Gas chromatography mass spectroscopy
GMS	-	Glyceryl monostearate
HPLC	-	High performance liquid chromatography
MTT	-	3-(4,5-dimethylthiazol-2-Y1)-2,5-diphenyltetrazolium bromide
PBS	-	Phosphate buffered saline
PDI	-	Polydispersity index
SLN	-	Solid lipid nanoparticles
VCO	-	Virgin Coconut Oil
ZP	-	Zeta potential

LIST OF SYMBOLS

cm	-	Centimeter
µg/ml	-	Microgram per millilitre
%	-	Percent
°C	-	Degree celcius
mg/ml	-	Milligram per millilitre
µL	-	Microlitre
nm	-	Nanometer
mM	-	Millimolar
µM	-	Micromolar
mm	-	Millimetre
ml	-	Millilitre
mV	-	Millivolts
g	-	Gram
rpm	-	Rotation per minute

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Skin is the largest organ in human which covers almost the whole body. The skin is a protective barrier against external mechanical, chemical, microbial and physical harms (Desai *et al.*, 2010). It is made up of three layers: epidermis, dermis and hypodermis. Stratum corneum (SC) is the outermost layer of epidermis and it is very important in permeation of drugs into our body. SC acts as formidable barrier to dermal absorption which specifies the rate of dermal penetration (Eman *et al.*, 2016). SC is also the barrier to loss of body water. In addition, SC produces a protective shield against the admission of harmful materials, such as bacteria or allergens, from the surrounding environment. This barrier fulfills an entire set of critical defensive functions including deflecting the ultraviolet light, refining most of it before it penetrates even deeper into the skin.

Luebberding *et al.* (2012) stated that the skin barrier function is the natural boundary between the inner organism and the surroundings, and this function is mainly formed by the epidermis. However, skin barrier function could be depleting due to many factors such as chronic stress. Animal studies performed by Denda *et al.* (1998; 2000) proved that stress can weaken the regaining of skin barrier function from barrier disruption by tape stripping. A study by Altemus *et al.* (2001) proposed the deterioration of skin permeability barrier homeostasis caused aggravation of inflammatory skin diseases.

Skin barrier disruption is related with both an increase in keratinocyte proliferation (Proksch *et al.*, 1991; Denda *et al.*, 1996) and an increase in production of inflammatory cytokine in the local tissue (Nickoloff and Naidu, 1994; Wood *et al.*, 1997). Both of these consequences could probably worsen inflammatory skin diseases such as psoriasis, eczema, and atopic dermatitis, and also aggravate contact dermatitis (Altemus *et al.*, 2001). Besides, the skin barrier function could be depleted as it is exposed to various exogenous sources of oxidative stress, such as ultraviolet radiation and pollutants. Reactive oxygen species (ROS) and other free radicals are generated in the skin as response to these oxidative attacks, (Dreher and Maibach, 2001). To curb the harmful effects of ROS, antioxidants is present in the skin and is responsible for the balance between pro-oxidants and antioxidant (Thiele *et al.*, 2000). An impairment of this balance, due to an increased exposure to exogenous sources of ROS, has been defined as “oxidative stress” and involves oxidative damages of lipids, proteins and DNA (Sies, 1985). On top of that, age is one of the factors which contributes to the declining of skin barrier functions. Although researches by Ghadially *et al.* (1995); Roskos and Guy (1989), showed that there is no change in water loss with ageing, barrier in aged skin has been claimed to be more vulnerable to penetration. The susceptibility to damage increased and there is setback in barrier recovery (Ghadially *et al.*, 1995).

Ficus deltoidea (FD) or widely known as Mas Cotek in Malaysia is a plant originated from Moraceae family. It had been traditionally used as medicine for many diseases including diabetes and relieving pain. Ramamurthy *et al.*, (2014) stated that

FD is also used for migraines, skin diseases, and diarrhea, pneumonia and heart problems. The active compounds in the extract of the plant are proven to possess anti-inflammatory, antinociceptive, anti-cancer, anti-oxidant and anti-photoaging effects (Bunawan *et al.*, 2014). Haron (2014) reported that among the chemicals found in FD are naringin and polyphenols which are useful for /anti-inflammatory effect. There are many mechanisms that are responsible for the anti-inflammatory activity based on the phytochemical compound found in FD. Meotti *et al.* (2005) found out flavonoids could inhibit protein kinase C and L-arginine/NO pathways. FD also possessed high antioxidant activity. Tannins present in FD might be responsible in preventing lipid oxidization as a reducing agent, free radical scavengers and chelators of pro-oxidant catalytic metals. Tannins are tightened over relaxed tissue, to dry excessive watery secretion and protects damage tissues like eczema or burnt (Ramamurthy *et al.*, 2014).

Many studies were done on the application of FD, for instance, a study by Abdula *et al.*, (2010) showed enhancement in wound healing in rats treated with FD. The results had proved the effectiveness of FD extract to speed up the rate of wound healing enclosure in the experimentally-induced wounds in rats. Along with that, a study by Hasham *et al.*, (2013) proposed that FD extract prevents the inflammatory cytokines production and might be an efficient protective agent to cure skin diseases. The research concluded that FD extract may be beneficial against UVB induced skin damage and is functional for anti-photoaging cosmetic products.

However, using plant extracted with water or ethanol had some limitations. In which the delivery of the extracts is slow and poor dosing of the extracts in human body (Caldorera-Moore and Peppas, 2009). It is also difficult for biologically active water-soluble extracts to permeate through human skin which naturally has hydrophobic characteristics. Another setback of using plant extract is the bioactive substances are unstable when exposed to light and could lose activity during storage (Vinardell and Mitjans, 2015).

Virgin coconut oil (VCO) is defined as the oil resulting from the fresh and mature kernel of the coconut (*Cocos nucifera L.*) through mechanical and natural means, whether with the use of heat or not, as long as it does not lead to alteration of the oil (Mansor *et al.*, 2012). Recently, VCO is recognized for its ample advantages. Marina *et al.* (2009a) confirmed VCO has higher antioxidant activity than refined coconut oil. A research by Nevin and Rajamohan (2006) had shown that VCO is capable in enhancing anti-oxidant enzymes activity and inhibition of lipid peroxidation in mice. In cosmetics industry, VCO is an excellent ingredient which functions as a skin moisturizer and softener (Rohman and Man, 2009). Kim *et al.* (2017) demonstrated that the oil increased expression of cornified envelopes (CE) components, thereby contributing to protective barrier functions of the SC. In addition, VCO had been used as co-carrier for nanostructured lipid carrier (NLC) system in several studies (Pamudji *et al.*, 2016; Rosli *et al.*, 2014). This is because with the listed quality it has, VCO does not only act as liquid lipid in NLC but also complements the system excellently.

Some procedures have been examined to increase the penetration of therapeutic molecules through the skin (Desai *et al.*, 2010). Solid lipid nanoparticles (SLN) were developed at early 1990s as a possible substitute carrier system to emulsions, liposomes and polymeric nanoparticles (Muller *et al.*, 2002). However, some problems were identified in SLN which are drugs load are too low and drug expulsion could happen during storage (Pardeshi *et al.*, 2012). Nanostructured lipid carrier system (NLCs) is composed of liquid lipid blended with a solid lipid to form a nanostructured solid particle matrix. Liquid lipid in NLC is used to alter the formation of SLN. This structure enhances loading of the drug and incorporates the drug securely during storage. However, there is not much study on association of lipid nanocarriers with plant medicine in the bio-nanotechnology field (Lacatusu *et al.*, 2014). With the health advantages and improved delivery features it brings, usage of suitable renewable vegetable sources is highly possible to comply with both industrial and customer demands. Final solid lipid core should contain structural imperfections to increase the incorporation of the drugs into the system. The system has been portrayed as an effective system to enhance skin hydration, due to their physiological lipid composition and occlusive effect properties (Tichota *et al.*, 2014). The small size of

NLCs ensures a close contact to the stratum corneum and can increase the amount of the active compound penetrating the skin (Li and Ge, 2012). NLCs are novel drug delivery systems for the delivery of actives with high solubility, stability, powerful skin penetration, and low skin discomfort (Muller *et al.*, 2007).

NLC incorporated with FD could be a promising treatment for improving skin barrier function. The incorporation of VCO as liquid lipid further added the value of the system. Therefore, the combination of all the powerful ingredients supposed to give good effect to skin in term of barrier function

1.2 Problem Statement

The function of skin barrier is to act as natural boundary between the inner organism and the environment. Nevertheless, the skin barrier function could decline due to several factors such as aging and stress. When the skin barrier function is damaged or depleted by application of harsh products, handling, or environmental conditions, the skin loses water and gets dried out faster, thus becomes more permeable to irritants and allergens. Once irritants or allergens penetrate the epidermis, they may trigger inflammation and this would lead to many skin problems such as dry skin, atopic dermatitis and psoriasis.

There are currently a lot of treatments and ingredients available in the market which could improve skin barrier function. However, the ingredients such as corticosteroids sometimes might also give off side effects to the body such as inflammation, wrinkling and thinning of skin to the site of application (Abraham and Roga,2014). As these side effects are of synthetic drugs, there is a need for safer and efficient treatment of these conditions. So, natural actives from herbs and plants could be an alternative for the treatment. This is because they produce no or fewer side

effects compared to synthetic drugs. In addition, natural drugs from the plants are gaining popularity because of several advantages such as better patient tolerance, being relatively less expensive and acceptable due to a long history of use (Tabassum and Hamdani, 2014). Also, an increased reliance on the use of medicinal plants in industrialized societies can be attributed to the extraction and development of a number of drugs and chemotherapeutics from plants, as well as herbal remedies. In industrial societies, herbal remedies have become more common in the treatment of minor ailments, due to increasing of cost of maintaining personal health (Hoareau and Dasilva, 1999). Other than that, Malaysia had an extensive variety of herbs and plants which possessed a lot of phytochemical constituents that has not been fully explored. It would be a waste if local researchers did not utilize the existing treasure in the country.

In this research, FD, a Malaysian herbs had been chosen to be encapsulated into NLCs as it had shown no toxicity and it is rich in anti-inflammatory and antioxidant compounds. It had been proved that FD can induce wound healing and act as protective agent in healing skin diseases. However, FD extract exhibits hydrophilic behavior which will make it difficult to penetrate human skin which are lipophilic in nature. To overcome this problem, NLC which are lipophilic will be used to encapsulate FD and it is expected to penetrate well into the human skin. NLCs had been chosen because of its efficacy to deliver the active ingredients with high solubility, stability, powerful skin penetration, and low skin discomfort. Furthermore, the small size of NLCs will establish a close contact to the stratum corneum as well as improve the quantity of the active compound penetrated into the skin. To improve the system, virgin coconut oil (VCO) is used as the liquid lipid in NLC system. VCO is highly known for its antioxidant effects and as moisturizer. The unique properties of VCO as co-carrier, excellently complement NLC system. In addition, coconut oil is proven to increase expression of cornified envelope (CE) components which could contribute in improving skin barrier function. Therefore, with the listed advantages, VCO based NLC loaded FD extract is highly potential to enhance skin barrier function.

1.3 Objective

The objective of this research is to formulate and characterize physicochemical and biological properties of Virgin Coconut Oil based Nanostructured Lipid Carrier loaded with *Ficus Deltoidea* extract to improve skin barrier function.

1.4 Scope of Research

In order to achieve the objective of the study, the following scopes have been identified as below:

1. Preparation of Nanostructured lipid carrier based on VCO as co-carrier system using melt emulsification homogenization technique.
2. Encapsulation of FD extract into VCO based NLC.
3. Characterization of formulation of VCO based NLC loaded with FD extract using Zetasizer Nano S, Zetasizer Nano Z, High performance liquid chromatography (HPLC), Transmission electron microscopy (TEM).
4. Study on the penetration ability of the formulation of VCO based NLC loaded with FD extract using Franz type diffusion cell.
5. Evaluation of stability of VCO based NLC loaded with FD extract at three different temperatures (4, 25 and 40°C) in term of size and PDI.
- 6 Analysis of topical cream incorporated with VCO based NLC loaded FD extract on skin barrier function, stratum corneum hydration, erythema, elasticity, pH and melanin index using multifunctional skin physiology monitor.

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