NANOSTRUCTURED LIPID CARRIER LOADED WITH ZINGIBER OFFICINALE AND ZINGIBER ZERUMBET OIL FOR INDUCTION OF LIPOLYSIS IN SUBCUTANEOUS SKIN LAYER

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To my beloved husband, sons and family

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ABSTRACT

Body weight loss strategies include combination of nutrition consultation, regular exercise, drug prescription, invasive intervention and/or non-invasive intervention. A non-invasive intervention such as transdermal administration of active ingredients helps in reducing localized subcutaneous adipose tissue through lipolysis. *Zingiber officinale* (ZO) and *Zingiber zerumbet* (ZZ) belong to the Zingiberaceae family and both have been discovered to possess lipolysis activity. An efficient drug delivery system is required to encapsulate ZO and ZZ, and deliver these substances up to the subcutaneous skin layer. In this study, ZO and ZZ oil were successfully encapsulated in nanostructured lipid carrier (NLC) using hot homogenization technique followed by ultrasonication. D-optimal mixture design was used to optimize the NLC in which the composition of ZO and ZZ oil, solid lipid, and liquid lipid were the independent variables, while particle size, polydispersity index (PDI), zeta potential, and encapsulation efficiency were the dependent variables. From the study, the optimum formulation for NLC-ZO was 3.6% ZO oil, 1.4% glyceryl monostearate, and 5.0% virgin coconut oil, and the NLC-ZO obtained had the following properties: 90.7 nm particle size, 0.15 PDI, -45.7 mV zeta potential and 88.8% encapsulation efficiency. The optimum NLC-ZZ formulation was 3.7% ZZ oil, 1.3% glyceryl monostearate, and 5.0% virgin coconut oil, and the NLC-ZZ obtained had the following properties: 91.0 nm particle size, 0.17 PDI, -40.9 mV zeta potential and 94.4% encapsulation efficiency. Morphology study revealed the spherical shape of NLC-ZO and NLC-ZZ, and the particle size obtained through transmission electron microscope conformed with the size measured through dynamic light scattering technique. Thermogram profile of NLC showed incorporation of ZO and ZZ into NLC lowered the melting temperature of lipid mixture, thus producing a less ordered crystalline structure of NLC to accommodate the active ingredients. Fourier transform infrared spectroscopy analysis demonstrated an interaction existed between ZO/ZZ and the NLC system. *In vitro* penetration study using Strat-M® membrane and freshly excised rat skin showed NLC-ZO and NLC-ZZ had higher penetration flux compared to free ZO and ZZ. The release of ZO from NLC-ZO followed Korsmeyer-Peppas model, and the release of ZZ from NLC-ZZ followed zero order kinetic model. 90-day storage stability study showed no significant changes for both NLC-ZO and NLC-ZZ in terms of particle size, PDI and zeta potential. *In vitro* lipolysis study revealed the potential of NLC-ZO and NLC-ZZ as anti-obesity agents as they stimulated the release of glycerol in 3T3-L1 adipocytes cells. *In vivo* NLC distribution in female Sprague-Dawley rats showed penetration deep into the dermis layer after 12 h of application. Free fatty acid release was detected when the rats were treated with NLC-ZO and NLC-ZZ for 3 h. This study demonstrated that ZO and ZZ were successfully encapsulated in NLC and the nanoparticles were effectively utilized to enhance dermis penetration and induce lipolysis activity via *in vitro* and *in vivo*.

ABSTRAK

Strategi penurunan berat badan meliputi kombinasi perundingan pemakanan, kekerapan bersenam, preskripsi ubat-ubatan, campur tangan invasif dan/atau campur tangan tidak-invasif. Campur tangan tidak invasif seperti pengurusan bahan aktif secara transdermal membantu mengurangkan tisu adiposa subkutanus setempat menerusi lipolisis. *Zingiber officinale* (ZO) dan *Zingiber zerumbet* (ZZ) adalah daripada keluarga *Zingiberaceae* dan kedua-duanya ditemui mempunyai aktiviti lipolisis. Sistem penyampaian ubat yang cekap diperlukan untuk merangkum ZO dan ZZ dan menghantar bahan ini sehingga ke lapisan subkutanus kulit. Dalam kajian ini, minyak ZO dan minyak ZZ telah berjaya dimuatkan dalam pembawa lipid berstruktur nano (NLC) menggunakan teknik homogenisasi panas diikuti ultrasonik. Reka bentuk campuran D-optimal telah digunakan untuk mengoptimumkan NLC di mana komposisi minyak ZO dan ZZ, lipid pepejal dan lipid cecair sebagai pembolehubah tidak bersandar, manakala saiz zarah, indeks poliserakan (PDI), potensi zeta, dan kecekapan enkapsulasi sebagai pembolehubah bersandar. Dari kajian ini, rumusan yang optimum untuk NLC-ZO adalah 3.6% minyak ZO, 1.4% gliseril monostiarat, dan 5.0% minyak kelapa dara, dan NLC-ZO yang dihasilkan mempunyai sifat-sifat berikut: saiz zarah 90.7 nm, PDI 0.15, keupayaan zeta -45.7 mV, dan kecekapan pengkapsulan 88.8%. Rumusan NLC-ZZ yang optimum adalah 3.7% minyak ZZ, 1.3% gliseril monostiarat, dan 5.0% minyak kelapa dara, dan NLC-ZZ yang dihasilkan mempunyai sifat berikut: saiz zarah 91.0 nm, PDI 0.17, keupayaan zeta -40.9 mV dan kecekapan pengkapsulan 94.4%. Kajian morfologi menunjukkan yang NLC-ZO dan NLC-ZZ berbentuk sfera, dan saiz zarah yang diperolehi melalui analisis mikroskop transmisi elektron mengesahkan saiz yang diukur melalui teknik penyelerakan cahaya dinamik. Profil termogram NLC menunjukkan penggabungan ZO dan ZZ ke dalam NLC telah menurunkan suhu lebur campuran lipid, sehingga menghasilkan struktur kristal NLC yang kurang teratur untuk menampung bahan-bahan aktif. Analisis spektroskopi inframerah transformasi Fourier menunjukkan interaksi antara sistem ZO/ZZ dan NLC. Kajian penembusan secara *in vitro* menggunakan membran Strat-M® dan kulit tikus yang disiat segar menunjukkan NLC-ZO dan NLC-ZZ mempunyai fluks penembusan yang lebih tinggi berbanding ZO dan ZZ. Pelepasan ZO daripada NLC-ZO mengikuti model Korsmeyer-Peppas dan pelepasan ZZ daripada NLC-ZZ mengikuti model kinetik tertib sifar. Kestabilan penyimpanan selama 90 hari menunjukkan tiada perubahan ketara bagi NLC-ZO dan NLC-ZZ dari segi saiz zarah, PDI dan keupayaan zeta. Kajian lipolisis secara *in vitro* telah mendedahkan potensi NLC-ZO dan NLC-ZZ sebagai agen anti-obesiti yang meransang pembebasan gliserol dalam sel-sel adiposit 3T3-L1. Kajian penyebaran NLC secara *in vivo* pada tikus Sprague-Dawley betina telah menunjukkan penembusan sehingga ke lapisan dermis selepas 12 jam rawatan. Pembebasan asid lemak bebas telah dikesan apabila tikus dirawat dengan NLC-ZO dan NLC-ZZ selama 3 jam. Kajian ini menunjukkan bahawa ZO dan ZZ telah berjaya dirangkumkan dalam NLC dan zarah nano ini berkesan untuk meningkatkan penembusan sehingga ke lapisan dermis dan mendorong aktiviti lipolisis secara *in vitro* dan *in vivo*.

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11HSD1	-	11β-hydroxysteroids dehydrogenase
ABTS, 2,2'-azinobis	-	3-ethylbenzothiazoline-6-sulfonic acid
AC	-	adenyl cyclase
ACC	-	acetyl-CoA carboxylase
ACE	-	Angiotensin-1-converting enzyme
ADD1/SREBP-1c	-	adipocyte determination and differentiation factor 1
ALT	-	alanine aminotransferase
AOX	-	anti-oxidant capacity
aP2	-	fatty acid-binding protein
AST	-	aspartate aminotransferase
ATGL	-	Adipose triglyceride lipase
ATP	-	adenosine and three phosphate
ATR	-	attenuated total reflectance
BMI	-	body mass index
C/EBPα, C/EBPβ and C/EBPδ	-	CCAAT/enhancer binding proteins
cAMP	-	Cyclic adenosine monophosphate

CAT	-	catalase
cGMP	-	cyclic guanosine monophosphate
CMT-3	-	chemically modified tetracyclines
DAG	-	diacylglycerol
DEX	-	1μM dexamethasone
DI	-	deionized water
DL	-	drug loading
DLS	-	dynamic light scattering
DLX	-	duloxetine
DMEM	-	Dulbecco's modified Eagle's medium
DSC	-	differential scanning methods
EE	-	Encapsulation efficiency
EMEA	-	European Medicines Agency
ETH	-	Swiss Federal Institute of Technology
FAOSTAT	-	Food and Agricultural Organizations of the United Nations
FAS	-	fatty-acid synthase
F-C	-	Folin-Ciocalteu
FCS	-	fetal calf serum
FDA	-	Food and Drug Administration
FESEM	-	field-emission scanning electron microscopy
FFA	-	free fatty acids

FoxO1	-	forkhead box class O 1
FTIR	-	Fourier-transform infrared spectroscopy
GA	-	glycyrrhetinic acid
GAE	-	gallic acid equivalents
GC	-	guanylyl cyclase
GCI-58	-	comparative gene identification 58
GI	-	gastrointestinal
GMS	-	Glyceryl monostearate
GPx	-	glutathione peroxidase
GSH	-	glutathione
GTP	-	guanosine triphosphate
HIFU	-	high intensity focused ultrasound
HLB	-	hydrophile-lipophile balance
HMG-CoA	-	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HOMA-IR	-	homeostasis model assessment of insulin resistance
HPH	-	High pressure homogenisation
HSL	-	hormone sensitive lipase
IBMX	-	isobutylmethylxanthine
IL-1β	-	interleukin-1β
IL-6	-	interleukin-6
IL-8	-	interleukin-8
iNOS	-	inducible nitric oxide

IP3	-	inositol triphosphate
IR	-	Infrared
IR	-	Infrared
IRS-1	-	insulin receptor substrate 1
JAK	-	Janus kinase
JNK	-	c-Jun N-terminal kinase
LCAT	-	lecithin choline acyl transferase
LDL	-	low density lipoprotein
LLLT	-	low-level laser therapy
LPAAT	-	lysophosphatidic acid acyltransferase
LPL	-	lipoprotein lipase
MAG	-	monoacylglycerol
MALS	-	multi-angle light scattering
MaPk	-	mitogen-activated protein kinase
MCP-1	-	monocyte chemoattractant protein-1
MDA	-	malondialdehyde
MGL	-	monoacylglycerol lipase
Mo	-	molybdenum,
MTT	-	3-(4,5-Dimethylthiazol-2-yl, 5-diphenyltetrazolium bromide
MWCO	-	Molecular weight cut-off
NIH	-	National Institutes of Health

NLC	-	Nanostructured lipid carrier
NLC-ZO	-	Nanostructured lipid carrier loaded with Zingiber officinale
NLC-ZZ	-	Nanostructured lipid carrier loaded with Zingiber zerumbet
NMR	-	Nuclear magnetic resonance
NO	-	nitric oxide
o/w	-	oil in water
OAT 2	-	Organic Anion Transporter 2
OECD	-	Organisation for Economic Co-operation and Development
PCS	-	correlation spectroscopy
PDE	-	phosphodiesterase
PDI	-	polydispersity index
PDK	-	phosphoinositide-dependent kinase
PES	-	polyethersulfone
PKA	-	protein kinase A
PKB	-	protein kinase B
PKC	-	Protein kinase C
PKG	-	cGMP-dependent protein kinase
PLC	-	phospholipase C
PLIN	-	perilipin
PPAR-γ	-	peroxisome proliferator-activated receptor
QLS	-	quasi-light scattering
RF	-	radio frequency

SC	-	stratum corneum
SD	-	Standard deviation
SEM	-	scanning electron microscopy
SET	-	single electron transfer
SLN	-	solid lipid nanoparticles
SOD	-	superoxide dismutase
SREBP-1c	-	sterol regulatory element-binding protein-1c
STAT	-	signal transducers and activators of transcription
TAG	-	triacylglycerol
TBARS	-	thiobarbituric acid–reactive substances
TC	-	total cholesterol
TEM	-	transmission electron microscopy
TG	-	triglycerides
TNF-α	-	tumor necrosis factor alpha
VCO	-	Virgin coconut oil
w/o	-	water in oil
WHO	-	World Health Organization
ZO	-	Zingiber officinale
ZZ	-	Zingiber zerumbet

LIST OF SYMBOLS

cm	-	Centimeter
µg/ml	-	Microgram per mililitre
%	-	Percent
ºC	-	Degree celcius
mg/ml	-	Miligram per mililitre
µL	-	Microlitre
nm	-	Nanometer
mM	-	Milimolar
µM	-	Micromolar
nmole	-	Nanomole
mm	-	Milimetre
ml	-	Mililitre
rpm	-	Revolutions per minute
g	-	Gram

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Obesity has reached epidemic proportions and is a significant contributor to the global burden of chronic disease and disability. Currently, nearly two billion adults worldwide are overweight, and at least 600 million of them are clinically obese (WHO, 2016). Obesity often related to the appearance of excess fat or adiposities which may generate social distress, physiological embarrassment, affecting the quality of life and highlighting possible undetected metabolic disturbance. The modern lifestyle does take its toll on current generations, for instance, long working hours and less physical activities, as well as exposure to imbalanced high caloric diet. The imbalance of diet intake and energy expenditure are generating more obesity-prone individual. The excess of calories is naturally stored within adipocytes.

White adipose tissues provide insulation and serve as useful energy depot. It also plays a vital role in maintaining an excellent endocrine equilibrium and actively contributes to the control of lipid and glucose metabolism. However, excessive adipose tissue distribution in human bodies does affect negatively to appearance and health state of an individual. The adiposities have a number of side effect including skin barrier alterations, sebaceous gland hyperactivity, apocrine and eccrine sweat glands hyperactivity, impaired lymphatic drainage leading to inflammation and fibrosis, altered collagen structure, impaired wound healing, and decreased microvascular homeostatic efficiency (Sparagvina *et al*., 2012).

To date, there are two types of obesity-treatment drugs available in the market which is orlistat and sibutramine. Both drugs treat obesity through the gastrointestinal route in which they reduce energy intake. However, due to the dissatisfaction of high costs and potentially hazardous side effects of these drugs, numerous researches have reported potential plant extracts which may be an excellent alternative strategy for the anti-obesity drug (Yun, 2010). Alternatively, various non-invasive techniques in reducing localized subcutaneous adipose tissue were reported safe and effective, for example, low-level laser therapy (LLLT), cryolipolysis, radio frequency (RF) and high intensity focused ultrasound (HIFU) (Kennedy *et al*., 2015). On the other hand, liposuction surgery has been reported as extremely effective in reducing adiposities although the post-procedural pain may cause discomfort (Hunstad *et al*., 2018). Reports by Greenway *et al*., (1995) and Sparagvina *et al*., (2012) have proved a reduction of weight through transdermal administration of drug which promotes lipolysis of fat cell under the skin.

Subcutaneous adipose tissue constitutes the largest fat depot and altered distribution of subcutaneous fat may affect skin elasticity and cosmetically undesirable. Inefficient subcutaneous fat cell lipolysis also independently linked to long-term weight gain and disturbed glucose metabolism (Arner *et al*., 2018). It is well established that obesity is characterized by increased spontaneous (basal) but decreased hormone stimulated fat cell lipolysis. Major endogenous stimulators of lipolysis are catecholamines, which accelerates lipolysis after binding to beta-adrenergic receptors and stimulates the production of cyclic AMP (cAMP). The cAMP production activates lipases that hydrolyze fat cell triglycerides into glycerol and fatty acids. The energy-rich fatty acids are oxidized for energy consumption in skeletal muscle, heart, and liver. Therefore, it is possible that variation in basal and/or stimulated adipocyte lipolysis may impact weight development. On the other hand, reports by Roure *et al*., (2011) showed the potential of caffeine and forskolin as active ingredients which stimulated lipolysis through adenylate cyclase activation and inhibit phosphodiesterase. The lipolysis activity was measured from glycerol release after treated with active ingredients.

The treatment of obesity is commonly done together with regulation of diet and regular exercise. There are rising needs to manage obesity with low cost, high efficacy and give very fewer side effects. Oral drug delivery poses multiple challenges such as relatively low uptake and low bioavailability which is due to the absorption of the drug in digestive system and enters the hepatic portal system. As the liver metabolizes the drug, only a small amount of active drug emerges from the liver to the rest of the circulatory system. Therefore, transdermal drug delivery is a preferred candidate due to reduced systemic effect as compared to oral and parenteral drug delivery. However, very scarce data available on anti-obesity treatment strategy which utilizing local plants for transdermal drug delivery.

Zingiber officinale (ginger), ZO and *Zingiber zerumbet* (pinecone ginger), ZZ are common spices used around the world and long been used in traditional medicine as a cure for ailments. A recent study has shown the anti-obesity activity of ZO and its constituents through *in vitro* and *in vivo* studies. Consumption of ginger has significantly reduced lipid profile and reduce body weight of male Albino rats after four weeks of treatment (Mahmoud and Elnour, 2013). Similarly, Misawa *et al*., (2015) have reported the role of ginger extracts in preventing obesity via activation of peroxisome proliferator-activated receptor, PPAR-γ pathway in C57BL/6J mice treated with dietary ginger extract. In this study, the compound 6-gingerol and 6-shogaol acted as specific PPAR-γ ligands and stimulated PPAR-γ-dependent gene expression in cultured human skeletal muscle myotubes, therefore stimulating fat utilization. In another report, 6-gingerol reduced the expression of PPAR-γ associated genes and reduced adipogenesis in 3T3-L1 adipocytes (Isa *et al*., 2008). Obese rats treated orally with gingerol for 30 days have shown to reduce body weight and tissue lipid suggested ginger supplementation could suppress obesity induced by high-fat diet (Saravanan *et al*., 2014). Ethanol extract of ZZ has reported suppressing body weight gain and body fat accumulation by increasing fatty acid oxidation which likely mediated via up-regulation of PPAR-α in the liver of high fed diet male Wistar rats (Chang *et al*., 2012). The *in vivo* and *in vitro* data does support the potential of ZO and ZZ to induce the anti-obesity effect. Therefore, this study was designed to load ZO and ZZ extracts into a specific carrier to penetrate into the skin in an attempt to reduced localized subcutaneous adipose tissue.

The skin barrier is a major limitation for transdermal drug administration. The barriers generally designed to keep foreign material out and, in some cases, to allow highly regulated transfer of specific desired molecules. Different skin levels such as skin surface, epidermis, dermis, and hypodermis lower the chance for penetration of drug. Therefore, in drug delivery strategies, various types of carrier for transdermal drug delivery have been developed and colloidal vesicle carriers are one of them. The modern development of colloidal carriers started with the discovery of liposome. These vesicles act as drug reservoir and have the ability to control release rate for drug. They also assist the drug to reach the desired pharmacological site of action and have continuous duration of action. The other type of colloidal-based carriers is solid lipid nanoparticles (SLN) and nanostructured lipid particles (NLC). Prof R. Muller discovered SLN in 1995 and the successor of SLN was NLC which developed later in 1990s (Muller *et al*., 2007). SLN were developed to improve the stability issues arise from liposome and at the same time retain high absorption and biocompatibility properties. NLC is the improvised version of SLN which offers more stable nanoparticle and high performance of drug-controlled release. The lipid nanoparticle, NLC has nano-size range and its formulation is suitable candidate to encapsulate active ingredients and assists in drug delivery to target site. The preparation method of NLC significantly influence the physical properties of NLC. The NLC must possess good loading capacity and long-term stability to ensure no premature release of drug before reaching the target tissue. In another aspect, a smaller size of NLC ensure close contact, specifically skin, and therefore increase the amount of drug penetrated.

1.2 Problem Statement

There are plenty of products on the shelf claimed to have anti-adiposity effect or in a simple word, slimming effect (Stickel, 2007; Phattanawasin *et al*., 2012). The products contain active ingredients such as essential oil and herbs extracts which potentially have anti-adiposity influence on human body. However, slimming requires reduction in unwanted adipose in subcutaneous tissue under the skin layer. The

efficacy studies of topical application for slimming or anti-adiposity product rarely focus on the delivery mode of active ingredient into the targeted layer. The data only considers the reduction of adipose tissue in subcutaneous layer and theoretically assumed that the active ingredient induced lipolysis in fat layer (Kennedy *et al*., 2015; Grosskreutz *et al*., 2017). The mechanism of carrier penetrating the subcutaneous skin layer for lipolysis needs further explanation and scientific proof as many topical slimming products claimed possibility to reduce adiposities (Sparavigna *et al*., 2012). The delivery of substance into subcutaneous layer of skin itself is challenging enough (Anissimov *et al*., 2013). The skin is an ultimate barrier against external mechanical, chemical, microbial and physical effects. Nevertheless, the large surface area and easy accessibility is the main reason for potential application in topical drug delivery. In order for a substance to reach into subcutaneous layer of skin, suitable carrier must be developed with desirable properties specifically to enhance deeper skin delivery.

NLC has been established since 2000 in encapsulation of active ingredients for various applications (Pardeike *et al*., 2009). The nano-scale size, stability, and high bioavailability as drug delivery system have made NLC are among preferred carrier especially in carrying lipophilic/hydrophobic type of active ingredient (O'Driscoll and Griffin, 2008; Das *et al*., 2012; Khan *et al*., 2013; Ranpise *et al*., 2014). Common size for nanoparticle for transdermal delivery system is in the range of 50-500 nm. Penetration through the skin depends on the particle size of nanoparticles, in which larger nanoparticles (>300 nm) will stay on stratum corneum, while smaller nanoparticles (<300 nm) will penetrate epidermis and dermis layer of the skin (Iannuccelli *et al*., 2014). However, smaller particle size (20 nm) possessed toxicity to the skin compared to larger particle size (Park *et al*., 2013). Additionally, it may cause interaction of nanoparticle with cells, body fluids, and protein. The interaction causes biological changes and ability to distribute throughout the body, hence generate complexes that are more mobile and can enter tissue sites that normally inaccessible (Nel *et al*., 2006). For instance, smaller particle allows penetration up to the dermis layer and causes particle trafficking to regional lymph nodes. Such trafficking can deliver particles to paracortical areas in the lymph nodes where macrophage and dendritic cells specialized in the uptake of particulate matter. This could lead to the effects on the immune system. Although the reticuloendothelial system is able to clear

or sequester nanoparticles, self-protein interactions with particles may change their antigenicity and initiate autoimmune responses. Therefore, the NLC must be able to penetrate into skin by having size of less than 300 nm and must not impose toxicity towards cells and tissue.

In the search for novel anti-obesity strategies via transdermal penetration for ZO and ZZ, the present study was designed to establish the formulation of NLC with better skin targeting efficiency, high stability, prolonged release to achieve maximum efficacy. The penetration of NLC encapsulated ZO and ZZ into subcutaneous layer was further enlightened through several series of experiments mimicking real skin condition.

1.3 Objective of the Research

The objective of this research is to formulate *Zingiber officinale* and *Zingiber zerumbet* oil loaded NLC system which having desirable physical characteristics and good stability to penetrate subcutaneous layer of skin hence activate lipolysis in adipose tissue.

1.4 Scopes of the Research

In order to achieve the objective, studies have been narrowed down and identified in this research. The scopes of this research listed as below:

1) Development of an optimized formulation of NLC encapsulated ZO and ZZ using hot homogenization and ultrasonication.

2) Characterization of NLC encapsulated ZO and ZZ by morphology, crystalline behavior, functional group, and skin penetration analysis, and storage stability study. Particle characteristics were measured including particle size, zeta potential, and polydispersity index analysis.

3) Determination of kinetic mechanism of active ingredients release from NLC using dialysis method.

4) Investigation of the efficacy of NLC encapsulated ZO and ZZ into subcutaneous layer of skin to induce lipolysis in adipose tissue, utilizing *in vitro* and *in vivo* analysis. *In vitro* study was conducted using 3T3-L1 cells to measure lipolysis activity. *In vivo* studies included *in vivo* skin deposition and penetration study as well as lipolysis marker measurement after treatment with NLC.

1.5 Significance and Original Contributions of the Research

This investigation offers several contributions in the area of essential oil encapsulation using NLC and its application in transdermal drug delivery which focused on subcutaneous skin layer. The contributions are as follows:

1) Transdermal delivery of active ingredients can circumvent first pass metabolism and maintains the concentration of drug at site of action for longer periods. Therefore, an investigation on permeation and release of active ingredients onto the targeted side may give useful insight into the understanding of NLC's mechanism of action *in vitro* and *in vivo*. *In vitro* study

focuses on the extent of active ingredient diffusion across the skin and the ability of lipolytic activity induction on adipocyte cell. The release mechanism of active ingredient from nanoparticle is identified according to kinetic release profile in the designated experimental condition. *In vivo* study highlights the extent of NLC penetration across rat skin in different treatment duration and lipolysis activity detected in plasma level.

2) ZO and ZZ belonged to Zingiberaceae family. It has a wide spectrum of traditional uses, as well as biological and pharmacological properties. New emerging *in vitro* data suggest both ZO and ZZ have demonstrated potential anti-obesity activity through various mechanisms *in vitro* and *in vivo*. NLC has been a good candidate for encapsulation ZO and ZZ due to the lipophilicity properties and capability to permeate challenging physiological barriers such as human and animal skins.

1.6 Thesis Structure and Organization

This thesis is divided into five chapters. Chapter 1 covers a brief overview of the research background, problems statement, a central objective, scopes of analyses, originality and significant contributions of the study.

Chapter 2 offer an overview of obesity and topical formulation for fat reduction. The literature also highlights the current drug delivery technology available for transdermal administration as well as current methodologies for nanoparticles characterization.

Chapter 3 covers the overall methodologies used for optimization of NLC encapsulated *Zingiber officinale* and *Zingiber zerumbet*, the physical characterization

of NLC and *in vitro* release study of active ingredients. The methodologies of *in vitro* and *in vivo* penetration of NLC through skin were described in this chapter.

Chapter 4 presents the comprehensive results and discussions on the optimization of NLC formulation using D-optimal mixture design and the characterization including particle size measurement, zeta potential, morphology, thermal properties, functional group analysis, *in vitro* permeation and kinetic of active ingredient release from NLC. The *in vitro* and *in vivo* analysis were also presented.

Chapter 5 provides the overall summary of the research findings and specific future recommendations for the upcoming works.

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