UNIVERSITI PUTRA MALAYSIA

DESIGN AND DEVELOPMENT OF NANOCOSMECEUTICAL CONTAINING NATURAL ANTIOXIDANT FROM Manilkara zapota (L.) P. ROYEN FRUIT EXTRACT

ZITI AKHTAR BINTI SHAFII

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By

ZITI AKHTAR BINTI SHAFII

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

February 2017

DEDICATION

This thesis is lovingly dedicated to

My great parents,

Mr. Shafii Haji Ali and Mrs. Salihah binti Mat

My beloved husband,

Mohd Shahril Amran Mat Noor

My dearest kids,

Putri Shaza Qistina and Putri Zara Qhadeja

My Kindness siblings,

Mohd Fairuz, Fauzani, Mohd Fadhli, Zaitul Akmam and Zaitul Aflah

Who lead me with the light of their endless love, support and encourage me throughout my life

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Doctor of Philosophy

DESIGN AND DEVELOPMENT OF NANOCOSMECEUTICAL CONTAINING NATURAL ANTIOXIDANT FROM *Manilkara zapota* (L.) P. ROYEN FRUIT EXTRACT

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Chairman : Professor Mahiran binti Basri, PhD
Faculty : Science

Plant-based extract is gaining interest as natural antioxidant in cosmetic industry. However, the primary challenges are incorporation of plant-based extract due to its poor bioavailability, low solubility and difficulties in formulating a stable carrier system. A newly developed nanoemulsion with extremely small particle size system was designed and formulated for transdermal application. To date, there are no reports on the uses of natural antioxidants from *Manilkara zapota* (L.) P Royen for topical applications in cosmeceuticals. Polyphenolic compounds (phenolic acid, flavonoid and tannin) are the major contributor to the antioxidant properties of *M.zapota* fruits.

Polyphenolic compounds in *M.zapota* fruit were extracted and evaluated. In-vitro antioxidants activity were evaluated using 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging, ß-carotene bleaching assay and oxygen radical absorbance capacity (ORAC). The highest antioxidant properties was observed in ethanol pulp (EtPE), ethyl acetate pulp (EaPE) and ethyl acetate seed (EaSE) extracts of *M.zapota*. The bioactive compounds were analyzed by Liquid Chromatography Mass Spectroscopy (LCMS) and Gas Chromatography Mass Spectroscopy (GCMS). The results demonstrated the presence of gallic acid, protocatachuic acid, ferullic acid, resorcinol, vanillic acid, epicatechin, quercetin linoleic acid and oleic acid in EtPE, EaPE and EaSE extracts.

Palm kernel oil esters (PKOEs), date seed oil (DSO) with addition of sorbitan monooleate (Span 80) and polyoxyethelene sorbitan monooleate (Tween 80) were chosen to be used as the oil phase due to high solubility of *M.zapota* fruit extract. In order to determine the suitable ratio of mixed surfactant, ternary phase diagram was constructed. Ternary phase diagrams were constructed to observe the incorporation of mixed palm kernel oil esters (PKOEs) and date seed oil (DSO), non-ionic surfactants, active compound and water. A composition of surfactant/oil/water (20/20/60) in ternary phase diagram was chosen and the particle size was measured. The results showed that the ratio of Span 80 to Tween 80 (3:7) exhibited the lowest particle size and polydispersity index.

The formulations were optimized using a multivariate statistical techniques by D-optimal experimental mixture design with oil, surfactant, xanthan gum, glycerol, water as the variables and particles size as the response. The nanoemulsions were prepared using high energy emulsification followed by low energy emulsification method. The optimum compositions were 14.03% (w/w) of oils, 7.86% (w/w) of surfactants, 0.64% (w/w) of xanthan gum, 7.35% (w/w) of glycerol, and 70.12% (w/w) of water. The particle size, zeta potential, and polydispersity index (PDI) obtained were 112.24 nm, -42.11 mV, and 0.3254, respectively. The surfactant amount gave the largest effect on the particle size of the system. In order to prepare a good texture which fits for cosmetic purpose, modifications was carried out. The modification made did not show any significant changes on the particle size and zeta potential readings.

The final formulations contained 0.0%, 0.1% and 0.5% of M.zapota fruit extract were labeled as BNE, MZNE1 and MZNE2. The particle sizes obtained were 110.0, 121.7 and 123.9 nm, respectively. The results showed that final nanoemulsions were stable up to 90 days in storage (room temperature (25°C, 45°C and 5°C). There were no bacterial growths in the storage. In-vitro safety evaluation of nanoemulsions showed no acute toxicity on fibroblast cells (3T3) up to 48 hours.

Rheological behavior of nanoemulsion was evaluated using viscometry test. From the results, nanoemulsion exhibited shear thinning (pseudoplasic) behavior which obeys the power law model. The results from oscillatory strain sweep test showed that the wide linear viscoelastic region (LVR) was directly correlated to high rigidity of the system. The morphological property of the nanoemulsion analysed using Transmission Electron Microscope (TEM) showed that the particle size was in agreement with the sample measured size using Zeta Sizer Analyzer. In the physical and thermal stability studies, the nanoemulsion was stable under high centrifugal force, storage at room temperature and 45°C for 90 days while maintaining its nano-size and zeta potential values. The developed nanoemulsion was also able to withstand freeze-thaw cycles and having low rate of Ostwald ripening.

The permeation of phenolic compounds through cellulose acetate membrane was studied using Franz diffusion cells. The result showed that 39.44% of total phenolic compounds were released from MZNE2. The antioxidant activity released was evaluated by DPPH scavenging assay. The activity were 29.94%, 27.81%, 48.25% and 68.64% of MZFE, BNE, MZNE1 and MZNE2, respectively. The nanoemulsions system provided a good protection for bioactive polyphenol compounds against degradation as there was significant antioxidant activity even after being encapsulated in the system.

The biophysical evaluations of MZNE2 on skin hydration showed significantly increased for 6h treatment. However the collagen content showed significant increase after 28d of application compared to 6h application. Transepidermal water loss was reduced in both treatments of 6h and 28d of applications. In addition, MZNE2 was classified as dermally non-irritant with a Human Irritancy Equivalent (HIE) score below 0.19 and this has been verified by the ultrasound skin imaging after application. No visible skin reactions caused by dermal irritation, contact sensitization or rash were experienced by the subjects during the application. The in vivo study has demonstrated that the increase of collagen content eventually led to higher skin hydration. This work conclude that a stable *M.zapota* nanoemulsion was successfully designed and developed, and showed potential collagen regeneration and delay intrinsic and extrinsic skin aging on human skin.

Abstrak tesis yang dikemukakan kepada Senat Unversiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

REKABENTUK DAN PEMBANGUNAN NANOKOSMESEUTIKAL YANG MENGANDUNGI ANTIOKSIDAN SEMULAJADI DARIPADA EXTRAK *Manilkara zapota* (L.) P. ROYEN

Oleh

ZITI AKHTAR BINTI SHAFII

Febuari 2017

Pengerusi : Profesor Mahiran binti Basri, PhD
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Ekstrak berasaskan tumbuhan semakin mendapat faedah sebagai antioksidan semulajadi dalam industri kosmetik. Walaubagaimanapun, cabaran utama penggabungan ekstrak berasaskan tumbuhan ialah disebabkan oleh bioavailability yang lemah, keterlarutan yang rendah dan kesukaran dalam memformulasikan sistem pembawa yang stabil. Nanoemulsi baru dihasilkan dengan saiz partikel yang sangat kecil telah direka dan diformulasikan untuk aplikasi transdermal. Sehingga kini, tiada laporan tentang penggunaan antioksidan semulajadi daripada *Manilkara zapota* (L.) P Royen untuk aplikasi topikal dalam kosmesiutikal. Sebatian polifenolik (asid fenolik, flavonoid dan tannin) adalah penyumbang utama kepada sifat antioksidan bagi buah *M.zapota*.

Sebatian-sebatian polifenolik dalam buah M.zapota telah diekstrak dan dikenalpasti. Aktiviti antioksidan in-vitro telah dikenalpasti menggunakan 1, 1-difenil-2-pikrilhidrazil (DPPH) pemerangkap radikal bebas, assai peluncur ß-carotina dan kapasiti penyerapan radikal oksigen (ORAC). Sifat-sifat antioksidan yang tinggi telah diperhatikan dalam ekstrak pulpa etanol (EtPE), ekstrak pulpa etil acetat (EaPE) dan ekstrak biji etil acetat (EaSE) bagi M.zapota. Sebatian-sebatian bioaktif telah dianalisa menggunakan spektroskopi jisim kromatografi cecair (LCMS) dan spektroskopi jisim kromatografi gas (GCMS). Keputusan menunjukan terdapat asid gallik, asid protokatachuik, asid ferulik, resorsinol, asid vanilik, epikatechin, quersetin, asid linoleik dan asid oleik dalam ekstrak EtPE, EaPE dan EaSE.

Ester minyak isirong sawit (PKOEs), minyak biji kurma (DSO) dengan penambahan sorbitan monooleat (Span 80) dan polietilina sorbitan monooleate (Tween 80) telah dipilih untuk digunakan sebagai fasa minyak disebabkan oleh keterlarutan yang tinggi bagi ekstrak buah M.zapota. Untuk menentukan nisbah surfaktan yang sesuai, rajah tiga fasa telah di bina. Rajah tiga fasa telah dibina untuk memerhati penggabungan bagi campuran ester minyak isirong (PKOEs), minyak biji kurma (DSO), surfaktan bukan ion, bioaktif dan air. Satu komposisi surfaktan/minyak/air (20/20/60) daripada rajah tiga fasa telah dipilih dan saiz partikel telah diukur. Keputusan menunjukan, nisbah Span 80 kepada Tween 80 (3:7) mempamerkan saiz partikel dan indeks polidispersiti indeks yang paling rendah.

Formulasi-formulasi telah dioptimumkan menggunakan teknik satistikal multivariasi oleh rekabentuk campuran eksperimen D-optimal dengan minyak, surfaktant, xanthan gum, glycerol dan air sebagai pembolehubah dan saiz partikel sebagai respon. Nanoemulsi telah disediakan menggunakan emulsifikasi tenaga tinggi diikuti emulsifikasi dengan tenaga rendah. Komposisi optimum ialah 14.03% (w/w) bagi minyak, 7.86% (w/w) bagi surfaktan, 0.64% (w/w) bagi xanthan gum, 7.35% (w/w) bagi glycerol dan 70.12% (w/w) bagi air. Saiz partikel, potensi zeta dan indeks polidispersiti (PDI) yang diperolehi masing-masing ialah 112.24 nm, -42.11 mV, and 0.3254. Kandungan surfaktan memberikan kesan yang paling besar terhadap saiz partikel bagi sistem. Untuk menyediakan tekstur yang bagus, sesuai untuk tujuan kosmetik, pengubahsuaian telah dilakukan. Pengubahsuaian yang dilakukan tidak menunjukan sebarang perubahan yang ketara terhadap saiz partikel dan bacan potensi zeta.

Formulasi terakhir mengandungi 0.0%, 0.1% dan 0.5% ekstrak buah M.zapota telah dilabelkan sebagai BNE, MZNE1 dan MZNE2. Saiz partikel yang diperolehi masing-masing ialah 110.0, 121.7 dan 123.9 nm. Keputusan menunjukan nanoemulsi akhir adalah stabil sehingga 90 hari dalam simpanan (suhu bilik (25°C, 45°C and 5°C). Tiada pertumbuhan bakteria dalam simpanan. Penentuan keselamatan in-vitro bagi nanoemulsi menunjukan tiada kesan toksiksiti akut pada sel fibroblas (3T3) sehingga 48 jam.

Ciri reologi bagi nanoemulsi telah ditentukan menggunakan ujian viskometri. Keputusan nanoemulsi mempamerkan sifat ricih penipisan (pseudoplastik) yang mematuhi model undang-undang kuasa. Hasil daripada ujian ketegangan ayunan menunjukan bahawa luas bahagian viskoelastik linear adalah berkadar terus dengan sistem ketegangan yang tinggi. Morfologi nanoemulsi dianalisis menggunakan mikroskop electron transmisi (TEM). Saiz partikel telah dipersetujui dengan saiz sampel yang ditentukan menggunakan pengsaiz Zeta. Dalam kajian fizik dan kestabilan terma, nanoemulsi adalah stabil di bawah tekanan empar yang tinggi, peyimpanan pada suhu bilik dan 45°C selama 90 hari. Sementara itu, saiz partikel adalah kekal. Nanoemulsi yang dibina juga mampu menahan kitaran beku cair dan mempunyai kadar pematangan Ostwald yang rendah.

Penyerapan sebatian fenolik melalui membran selulosa acetat telah dipelajari menngunakan alat sel penyebaran Franz. Hasil menunjukan bahawa 39.44% daripada jumlah sebatian fenolik telah dibebaskan daripada MZNE2. Aktiviti antioksidan yang dibebaskan juga ditentukan oleh assai DPPH analisis. Aktiviti masing-masing ialah 29.94%, 27.81%, 48.25% dan 68.64% bagi MZFE, BNE, MZNE1 dan MZNE2. Sistem nanoemulsi menyediakan penjagaan yang baik bagi sebatian bioaktif polifenolik terhadap kesan degradasi seperti aktiviti antioksidan masih ada walaupun dikapsulkan di dalam sistem.

Penentuan biofizikal MZNE2 terhadap hidrasi kulit manusia menunjukan peningkatan yang penting selepas 6 hari penggunaan. Kandungan kolagen menunjukan kesan selepas 28 hari rawatan. Kehilangan air transepidermal telah berkurang dalam kedua-dua rawatan bagi 6 jam dan 28 hari penggunaan. Tambahan pula MZNE2 telah diklasifikasikan sebagai dermal tidak merengsa dengan skor Persamaan iritasi manusia (HIE) di bawah 0.19 dan ini telah ditentukan oleh pengimejan kulit ultrabunyi selepas penggunaan. Tidak kelihatan tindak balas kulit yang disebabkan oleh iritasi dermal, kepekaan sentuhan dan ruam yang dihadapi oleh subjek semasa tempoh penggunaan. Pembelajaran in-vivo telah menunjukan bahawa peningkatan kandungan kolagen membawa kepada penghidrasi kulit yang tinggi. Kajian ini, menyimpulkan bahawa nanoemulsi M.zapota adalah stabil dan telah berjaya direka dan dibina juga menunjukan potensi pertumbuhan semula kolagen dan melambatkan kesan penuaan pada kulit manusia secara intrinsic dan ekstrinsik

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Thank you so much

I certify that a Thesis Examination Committee has met on 20 February 2017 to conduct the final examination of Ziti Akhtar binti Shafii on her thesis entitled "Design and Development of Nanocosmeceutical Containing Natural Antioxidant from *Manilkara zapota* (L.) P.Royen Fruit Extract" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of the 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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Declaration by graduate student

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Name of Member of Supervisory Committee: Professor Dr. Maznah binti Ismail

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LIST OF ABBREVIATIONS

ROS	Reactive oxygen species
UV	Ultraviolet
SC	Stratum corneum
SPF	Sun protection factor
DNA	deoxyribonucleic acid
AgNPs	Silver nanoparticles
H-ORAC	Hydrophilic
O/W	Oil in water
W/O	Water in oil
O/W/O	Oil in water in oil
W/O/W	Water in oil in water
PIC	Phase inversion concentration
PIT	Phase inversion temperature
GRAS	generally regarded as safe
PKOEs	Palm kernel oil esters
DSO	Date seed oil
HLB	hydrophilic-lipophilic balance
FDA	Food and Drug Administration
HPE	hexane pulp extract
EaPE	ethyl acetate pulp extract
EtPE	ethanol pulp extract

HLE	hexane peel extract
EaLE	ethyl acetate peel extract
EtLE	ethanol peel extract
HSE	hexane seed extract
EaSE	ethyl acetate seed extract
BHA	butylated hydroxynisole
BHT	butylated hydroxytoluene
EDTA	Ethylenediaminetetraacetic acid
MMP-9	Matrix metallopeptidase 9
TPA	12-O-tetradecanoylphorbol-13-acetate
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
AP-1	Protein 1
cAMP	cAMP-dependent pathway
TIMP-1	TIMP metallopeptidase inhibitor 1
DPPH	1, 1-diphenyl-2-picrylhydrazyl
Na2CO3	sodium carbonate
PVPP	polyvinylpoly pirrolidone
AlCl3	aluminium chloride
Span 80	sorbitan monooleate
Tween 80	polyoxyethylene sorbitan monooleate
(w/v)	Weight over volume
(w/w)	Weight over weight

(v/v)	Volume over volume
HPE	Hexane pulp extract
EaPE	Ethyl acetate pulp extract
EtPE	Ethanol pulp extract
HLE	Hexane peel extract
EaLE	Ethyl acetate peel extract
EtLE	Ethanol pulp extract
HSE	Hexane seed extract
EaSE	Ethyl acetate seed extract
EtSE	Ethanol seed extract
TPC	Total phenolic
TT	tannin content
TFC	flavonoid content
GAE/g	Gallic acid equivalent over gram
DW	Dried weight
GA	Gallic acid
mg/mL	Milligram over milliliter
mL	milliliter
µL	microliter
mM	millimolar
UV-Vis	Ultraviolet visible
AAPH	2, 2′-azobis (2-amidino-propane) dihydrochloride
DPPH	1, 1-diphenyl-2-picrylhydrazyl

PCA	Protocatechuic acid
PG	propyl gallate
TBHQ	tert-butylhydroquinone
ORAC	Oxygen radical absorbance capacity
TE/kg	Trolox equivalent over kilogram
SQD	Single Quadrupole Detector
HPLC	High performance liquid chromatography
LCMS	Liquid Chromatography Mass Spectrometry
GCMS	Gas Chromatography Mass Spectroscopy
POEs	Palm oil esters
SFO	sun flower oil
OO	olive oil
SBO	soy bean oil
MZFE	M.zapota fruit extract
BNE	Base nanoemulsion
MZNE1	Nanoemulsion containing 0.1% M.zapota fruit extract
MZNE2	Nanoemulsion containing 0.5% M.zapota fruit extract
TGA	Thermogravimetric
TEM	Transmission electron microscopy
η	viscosity
k	Consistency index
n	Flow behavior index
PBS	phosphate buffer solution

DAD	photo diode array detector
rpm	Rotation per minute
OD	Optical density
HIE	Human Irritancy Equivalent
MTT	3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
CO2	Carbon dioxide
DMEM	Dulbecco's modified Eagle's medium
DMSO	Dimethyl sulfoxide
TEWL	Transepidermal Water Loss
c.u.	corneometric units
WMA	World Medical Association
HO•	hydroxyl
O2•-	superoxide
ROO•	proxy
R2	Linear regressions
IC50	inhibitory concentration at 50%
BCB	ß-carotene bleaching
HAT	hydrogen atom transfer
SET	single electron transfer
LC-PUFAs	Long chain polyunsaturated fatty acid
EFAs	essential fatty acid
PUFAs	polyunsaturated fatty acids

PG	propyl gallate
TBHQ	tert-butylhydroquinone
ST80	Span 80: Tween 80
L1	Isotropic liquid phase
H	homogeneous phase
2P	two phases
p	Laplace pressure
RSE	Residual standard error
PDI	Polydispersity index
LVR	Linear viscoelastic region
G′	Storage modulus
G″	loss modulus
δ	phase angle
OH	hydroxyl group
C=O	carbonyl group
AAI	Antioxidant activity index

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Cosmeceuticals are multifunctional cosmetics and are believed to be the future generation skin care products. The term "Cosmeceuticals" was coined by Raymond Reed but the concept was further popularized by Dr. Albert Kligman in the late 1984's (Wanjari and Waghmare, 2015). The huge advantage of cosmeceuticals compared to conventional cosmetics is due to the presence of biological active ingredient which provided the therapeutic or medicinal benefits. A report, "Cosmeceuticals market to 2018," forecasted that the global cosmeceuticals market will reach $42.4 billion by 2018 and spurs to reach of $ 61 billion by 2020 (Lohani *et al.*, 2016). The cosmeceutical products include skin care to body care and hair products. The increasing demand of skin care products for topical cosmeceutical treatments such as photoaging, hyperpigmentation and wrinkles are due to the rising desire for consumers to seek beauty, youthful appearance as well as to enhance skin health.

Moreover, the hectic lifestyles with exposure to the environmental aggressions such as ultraviolet radiation, smoke and pollution have increase concerns about premature skin aging. There are three main factors that affect aging process; genetic, internal and external factors. Genetic factors depend on individual cell division and function, while internal factors are related to the endocrine system such as sex hormone. Meanwhile, the external factors involve exposure to sunlight, humidity, polluted air, infections and treatment on the skin. It is well known that the UV-induced skin damages including skin aging, cancer, and other skin diseases are associated to the harmful effect of free radical such as Reactive oxygen species (ROS) from sun light. Furthermore, skin is the largest organ and is constantly exposed to the harmful effect.

The human skin has an important function in providing a barrier between the internal and the external physical, chemical, and biological environment (Al-Edresi and Baie, 2010). The skin barrier provided a good protection against hazardous microorganisms, toxic chemicals, ultraviolet radiation and water loss. Ultraviolet radiation can penetrate deep into the skin layers and break down the skin structure. Collagen is one of the important component of skin structure that influence the firmness and elasticity of the skin (Fujii *et al.*, 2008). The normal sign of premature skin aging include wrinkles, sagging, pigmented spots and dryness. Several approaches have been done to prevent and repair the skin damage through oral intake or transdermal delivery.

Natural antioxidants from fruits are safe, novel, low cost with less side effect and environment friendly. Previous studies have reported that the bioactive compounds of *M.zapota* extracts contained high antioxidant potential evaluated by different measurement systems (Gomathy *et al*., 2013; Ma *et al*., 2003; Leong and Shui, 2002). Due to these valuables properties, these researchers suggested the use of *M.zapota* fruit extract as a cosmeceutical functional skin care products. The good effects of phenolic bioactive compounds on the skin have been widely investigated. However, to date research and publications of *Manilkara zapota* (L.) P Royen fruit extract in the area of nanocosmeceutical are still limited. The utilization of bioactive compound could be an asset which is sustainable to the environment. Delivery of bioactive compounds through the skin contributed by extremely smaller particles, are easily adsorbed and thus more efficient in repairing damage (Lohani *et al.,* 2016).

Nanoemulsions have uniform and extremely small droplet size, typically in the range of 20 to 200 nm (Solan *et al.,* 2012). Nanoemulsions are attractive systems for the use in the cosmetics, pharmaceutical, food and other industries due to their low amount of surfactant, higher stability against coalescence, lack of toxicity or irritant characteristics, low viscosity, good appearance, and versatility of formulation as foams, creams, liquids and sprays. Nanoemulsions, due to the extremely small size has closer contact with the stratum corneum (SC) and thus increasing the amount of active compound reaching the desired site of action. Nanoemulsions have also been developed for water insoluble active compounds such as Vitamin E (Teo *et al.,* 2010), tocotrienol (Ng *et al*., 2013) and kojic acid dipalmitate (Al-Edresi and Baie, 2010) as topical delivery system. Furthermore, nanoemulsions can be used to deliver bioactive compounds of plant extract such as *Opuntia ficus-indica* (L.) Mill extract (Ribeiro *et al.,* 2015), *Vellozia squamata* (Quintão *et al.,* 2013) and swiftlet nest (Mohd Taib *et al*., 2015). Nanoemulsions are also reported to be used in the formulation for the treatments of meningitis (Musa *et al.,* 2013), Parkinson's disease (Zainol *et al.,* 2012), rheumatoid arthritis (Salim *et al*., 2012).

1.2 Problem Statements

The human skin is an impermeable barrier that provides a strong protection against external substances, including bacteria, fungi, viruses, dust and large molecules. The major challenge of transdermal drug or cosmeceutical actives delivery is to overcome the strong barrier function of the skin to deliver the active ingredient to the target site with sufficient concentration. Therefore, using science and technology, nanosystem due to its extremely small size can be designed to enhance the permeation of active ingredient across the skin.

Often the bioactive compounds used in cosmeceutical products are synthetic in nature. The trend now is towards using plant-based natural compounds such as plant extracts as the bioactive components. In order to deliver the bioactive compounds through the stratum corneum, there are some challenges. The bioactive compounds are easily degradable and highly sensitive to light and temperature (Gadkari and Balaraman, 2015). Moreover, certain plant based extracts often exudes unpleasant smell which needs to be controlled without interfering with the phytochemical properties of the bioactive compounds. The advances in developing innovative and responsive colloidal delivery system such as nanoemulsion could overcome the problems.

Nanoemulsions are thermodynamically unstable, thus may have physical instabilities such as aggregation, flocculation, coalescence and Ostwald ripening. The greatest challenge is to maintain the required particle size. Stability of the nanoemulsion is also a critical factor to be analysed. The achievement of developing long time stability of cosmetic products (3 years shelf life) is often difficult and costly during the development of nanocosmeceutical products.

Solubility of bioactive compounds is often a problem in formulating cosmeceutical products, thus affecting the bioavailability of the compounds to the target site. Nanoemulsions have good potential in enhancing the bioavailability, stability against chemical degradation, and the pharmacological effects of bioactive compounds as compared to the conventional delivery systems (Ribeiro *et al.,* 2015).

To date, there is no publications on the contribution of *M.zapota* fruit extract as a natural active compound in topical application using nanotechnology. There is also no report on optimization of *M.zapota* nanoemulsion using a multivariate statistical methods using D-optimal mixture experimental design. This method is able to predict more accurate value to the actual response which is suitable to be used in formulation.

1.3 Objectives

The main objective of this research was to design and develop nanocosmeceutical containing *Manilkara zapota* (L.) P. Royen fruit extract. Therefore, the following specific objectives were pursued:

1. To isolate and identify the natural antioxidant compounds from *Manilkara zapota* fruit extracts.
2. To design palm kernel oil esters nanoemulsion systems incorporated with *Manilkara zapota* fruit extract.
3. To optimize stable palm kernel oil esters nanoemulsion system containing *Manilkara zapota* fruit extract.
4. To characterize the physicochemical properties of the palm kernel oil esters nanocosmeceutical with respect to particle size, zeta potential, thermogravimetric analysis, pH value, conductivity, the morphological and rheological study.
5. To study the efficacy test on antioxidant activity, skin hydration, water content, collagen regeneration, microbiology test and irritancy test of the product on the skin.

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