OPTIMIZATION AND CHARACTERIZATION OF CURCUMIN LOADED COCONUT OIL–HONEY NANOEMULSION FOR SKIN PERMEABILITY ENHANCEMENT

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ABSTRACT

Nanoemulsion which consists of particles in a nanometer range is one of the common carriers for dermal and transdermal drug delivery. This delivery system is suitable for encapsulates active compounds that are poorly soluble in water. Curcumin is a lipohilic bioactive compound with poor bioavailability, and therefore, nanoencapsulation was used to increase its stability and skin permeability. This study focused on the optimization and characterization of curcumin nanoemulsion composed of coconut oil, Tween 80 (surfactant) and polyethylene glycol (co–solvent), with honey and glycerol as additives. The formulation of nanoemulsion was optimized and systematically characterized for transdermal delivery. Response surface methodology (RSM) with Box Behnken design was used to optimize the base formulation based on the three independent variables that were honey (1–3 %), virgin coconut oil (1.0–1.5 %) and Tween 80 (5.0–9.0 %) which led to formation of formulation with low particle size 10.11 nm, polydispersity index 0.27 and turbidity 0.24–1.11 system. Subsequently, the optimization of curcumin nanoemulsion was carried out again after curcumin was loaded into the base formulation. Another three independent variables that were polyethelene glycol (0.8–1.5 %), curcumin (0.01–0.1 %) and honey (1.8–2.4 %) were used to produce the nano–range of particle size 14.32 nm, narrow polydispersity index 0.152, and high encapsulation efficiency 98.0 %. Slight acidic (pH 4.18) curcumin nanoemulsion was obtained without any chemical degradation based on the results of attenuated total reflection – Fourier transform infrared (ATR–FTIR). The incorporation of curcumin inside nanoglobuls improved curcumin stability and skin permeability. The curcumin loaded nanoemulsion was found to have high stability with only 8.5 % increment in particle size after it was stored for 3 months at 4 °C and 45 °C. The radical scavenging activity of encapsulated curcumin in nanoemulsion was slightly decreased (7.9 %) compared to free curcumin. Nanoemulsion appeared to increase the *in vitro* release rate of curcumin for about 42.3 %, especially for the first 2 hours in Franz diffusion cell using rat skin. Its high permeability can be seen from Nile dyed curcumin in different layers of skin through fluorescent imaging. The release kinetic of curcumin nanoemulsion followed the Higuchi model which explains a Fickian diffusion controlled skin permeation because the Korsmeyer constant was proven to be 0.3 (< 0.5). Curcumin nanoemulsion showed low cytotoxicity (EC_{50} 2.3652 µg/mL) to human skin fibroblasts. Cell death was noticed at high concentration (2.5000 µg/mL) of treatment. Curcumin was also found to promote wound closure at low concentration of 0.1563 µg/mL and its performance is comparable with the performance of ascorbic acid based on scratch assay. Therefore, this nutritious curcumin nanoemulsion is a promising transdermal delivery system for topical application.

ABSTRAK

Nanoemulsi yang mengandungi zarah–zarah bersaiz nanometer adalah salah satu pembawa umum untuk menyampaikan ubat dermal dan transdermal. Sistem penyampaian ini sesuai untuk merangkumi sebatian aktif yang kurang larut dalam air. Kurkumin adalah sebatian lipofilik bioaktif bersifat lipofilik yang mempunyai bioketersediaan rendah, oleh itu kaedah nanoenkapsulasi digunakan dalam kajian ini untuk meningkatkan kestabilan dan kebolehtelapan kulit. Kajian ini difokuskan pada pengoptimuman dan pencirian nanoemulsi muatan kurkumin yang terdiri dari minyak kelapa, Tween 80 (surfaktan) dan polietilena glikol (pelarut bersama) dengan madu dan gliserol sebagai bahan tambahan. Rumusan nanoemulsi dioptimumkan dan dicirikan secara sistematik untuk penyampaian transdermal. Kaedah tindak balas permukaan (RSM) dengan reka bentuk Box Behnken digunakan untuk mengoptimumkan formulasi asas berdasarkan tiga pemboleh ubah bebas iaitu madu (1–3 %), minyak kelapa dara (1.0–1.5 %) dan tween 80 (5.0–9.0 %) bagi mendapatkan formulasi asas zarah bersaiz kecil 10.11 nm, indeks poliserakan 0.27 dan sistem kekeruhan 0.24–1.11. Selepas itu, pengoptimuman kedua dilakukan setelah kurkumin dimasukkan ke dalam formulasi asas. Tiga lagi pemboleh ubah bebas iaitu polietilena glikol (0.8–1.5 %), kurkumin (0.01– 0.1 %) dan madu (1.8–2.4 %) digunakan untuk menghasilkan zarah bersaiz nano (14.32 nm), indeks poliserakan sempit (0.152), dan kecekapan enkapsulasi tinggi (98.0 %). Nanoemulsi kurkumin yang sedikit berasid (pH 4.18) diperolehi tanpa sebarang degradasi kimia berdasarkan hasil pantulan keseluruhan terkecil inframerah transformasi Fourier (ATR–FTIR). Penggabungan kurkumin di dalam nanoglobul meningkatkan kestabilan kurkumin dan kebolehtelapan kulit. Nanoemulsi yang mengandungi kurkumin didapati mempunyai kestabilan yang tinggi dengan hanya 8.5 % kenaikan pada ukuran zarah setelah disimpan selama 3 bulan pada suhu 4 °C dan 45 °C. Kegiatan penyingkiran radikal oleh kurkumin terkapsul dalam nanoemulsi sedikit menurun (7.9 %) berbanding kurkumin bebas. Nanoemulsi nampaknya meningkatkan kadar pelepasan kurkumin secara *in vitro* sekitar 42.3 %, terutama bagi dua jam pertama dalam sel penyebaran Franz menggunakan kulit tikus. Kebolehtelapannya yang tinggi dapat dilihat melalui kurkumin yang dicelup Nil merah pada lapisan kulit yang berlainan menggunakan pengimejan pendarfluor. Kinetik pelepasan kurkumin adalah berdasarkan model Higuchi yang menerangkan penyerapan kulit dikawal oleh resapan Fickian kerana pemalar Korsmeyer terbukti 0.3 (<0.5). Kurkumin nanoemulsi menunjukkan sitotoksisiti rendah (EC50 2.3552 μg / mL) kepada fibroblas kulit manusia. Kematian sel diperhatikan pada kepekatan tinggi (2.5 μg / mL) rawatan. Kurkumin juga didapati mendorong penutupan luka pada kepekatan rendah 0.1563 μg / mL dan prestasinya adalah setara dengan prestasi asid askorbik berdasarkan ujian calar. Oleh itu, nanoemulsi kurkumin berkhasiat ini adalah sistem penyampaian transdermal yang berpotensi untuk aplikasi topikal.

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LIST OF ABBREVIATIONS

ATR–FTIR	–	Attenuated total reflection–Fourier transforms infrared
ANOVA	–	Analysis of variance
BBD	–	Box–Behnken design
CoH–N	–	Coconut oil honey nanoemulsion
CCD	–	Central composite design
CMC	–	Critical micelles concentration
DLS	–	Dynamic light scattering
DNA	–	Deoxyribonucleic acid
DOE	–	Design of Experiment
DPPH	–	1,1–Diphenyl–2–picryl–hydrazyl
DNA	–	Deoxyribonucleic acid
DMEM	–	Dulbecco's Modified Eagle's Medium
DL	–	Drug loading
DLS	–	Dynamic light scattering
DMSO	–	Dimethyl sulfoxide
DKSH	–	Diethelm Keller Siber Hegner
EE	–	Entrapment efficiency
FRAP	–	Ferric reducing ability of plasma
FAMA	–	Federal Marketing Agriculture
FTIR	–	Fourier–transform infrared spectroscopy
FESEM	–	Field–emission scanning electron microscopy
GRAS	–	Generally recognized as safe
HIV	–	Human immunodeficiency virus

HDL – High–density lipoproteins

HLB – Hydrophilic lipophilic balance

HPLC – High Performance Liquid Chromatography

HPH – High pressure homogenization

HSF – Human fibroblast cell

IBD – Institute of Bioproduct Development

LCT – Long chain triacylglicerols

LDL – Low–density lipoprotein

MCT – Medium chain triglycerides

MTT – Tetrazolium

NNI – National Nanotechnology Initiative

O/w – Oil in water

OD – Optical density

PEG – Polyethylene glycol

PIC – Phase inversion composition method

PIT – Phase inversion temperature method

PDI – Polydispersity index

PEG – Polyethylene glycol

PCS – Photon correlation spectroscopy

PBS – Phosphate–buffered saline

RSM – Response surface methodology

SE – Spontaneous emulsification

SEM – Scanning electron microscopy

SSD – Somatic symptom disorder

SOR – Specific surfactant–to–oil

SC	–	Stratum Corneum
UAP	–	Unified Authentication Platform
UV	–	Ultraviolet
USA	–	United States of America
TEM	–	Transmission electron microscopy
USDA	–	United States Department of Agriculture
UK	–	United Kingdom
VCO	–	Virgin Coconut Oil
W/O	–	Water in Oil

LIST OF SYMBOLS

Ag	–	Argentum
Fe	–	Ferum
H	–	Hydrogen
H_2O_2	–	Hydrogen peroxide
G	–	Gram
Kg	–	Kilogram
m	–	Meter
Mg	–	Milligram
min	–	Minutes
ML	–	Milliliter
mm	–	Millimeter
nm	–	Nanometer
mAU	–	Milli–absorbance unit
Na_2CO_3	–	Sodium carbonate
Na+	–	Natrium
K+	–	Potassium
SE	–	Sucrose ester
Span 80	–	Polysorbate 80
Psi	–	Pound per square inch
pH	–	Potential of hydrogen
pt	–	Platinum
rpm	–	Revolutions per minute
Tween 80	–	Polysorbate 80

Tween 20	–	polyoxyethylene sorbitol ester
°C	–	Degree celcius
µM	–	Micrometer
%	–	Percentage
µL	–	Microliter
w/w	–	Weight per weight
OH	–	Hydroxide
wt %	–	Weight percent
λ_{max}	–	Lambda max
≥	–	Greater than or equal
Na_2CO_3	–	Sodium Carbonate
ppm	–	Parts per million
Kp	–	Permeability coefficient
Mg	–	Milligram
cm^2	–	Square centimeters
dQ	–	Differential of quanta
dt	–	Quantum mechanic description of the electrostatic model of crystalline
h	–	Hour
cm	–	Centimeter
mm	–	Millimeter
CO_2	–	Carbon Dioxide
IC50	–	The half maximal inhibitory concentration
Um	–	Measure of length
R^2	–	Coefficient of determination

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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Nanoemulsion is the most widely used delivery system in the cosmetics and pharmaceutical drug applications. Nanoemulsion system can enhance drug delivery due to its submicron size (20–200 nm). Takur et al. (2013) defined that the nano–size of particles was in the range of 20–200 nm in the presence of two immiscible liquids (oil and water) with a sufficient amount of surfactant(s). Nanoemulsion was created by incorporating the lipophilic active ingredient into aqueous with the help of surfactant (Bouchemal et al., 2004). This delivery system helps to increase the surface area of lipophilic substance like curcumin, in order to improve its solubility and skin permeability.

Curcumin is a bioactive compound found in the rhizomes of *Curcuma longa*, a member of the Zingiberaceae ginger family, that has a wide range of medicinal properties including antioxidant (Akbik et al., 2014) and anti–inflammatory (Jurenka, 2009), anti–cancer (Pongrakhananon et al., 2011), anti–microbial and antifungal (Martins et al., 2008), and wound healing (Akbik et al., 2014). In recent years, VCO has gained popularity because of its antioxidant (Mansor et al., 2012) and anti–inflammatory therapies (Seneviratne et al., 2008). Curcumin was added to the nanoemulsion system in which virgin coconut oil (VCO) was used as the oil phase. The medium chain fatty acids such as lauric acid, palmitic acid, and caprylic acid which are abundantly present in VCO have outstanding antibacterial capabilities (Varma et al., 2017). VCO has also high fluidity and self–emulsification ability, and thus making it an ideal oil for nanoemulsification. As a result, the combination of VCO with aqueous–based components are suitable for topical administration on human skin. The chosen aqueous–based component was honey containing monosaccharides and

could act as a natural nanoemulsion stabilizer. Honey is commonly utilized in transdermal administration (El–Kased et al., 2017), burn wound treatment (Zbuchea, 2014), and infected surgical wounds (Minden, 2018). Owing to the low bioavailability and poor solubility of curcumin in aqueous medium, nanoemulsion could improve its stability by incorporating curcumin into an effective carrier system into the human body. Therefore, encapsulation technology confines curcumin within nano–sized particles, are therefore vital in the drug delivery application.

The antioxidant property of nanoemulsion system was used to evaluate the quality of nanoemulsion in the past few years. Donsi et al. (2011) reported that the antioxidant activity of curcumin nanoemulsion (0.996 ± 0.07) in absorbance of solid lipid nanoparticles. The ferric reducing antioxidant power was lower than its free counterpart (2.504 ± 0.06). According to Sari et al. (2015), the antioxidant activity of curcumin nanoemulsion was slightly lower than that of non–nanocurcumin. Hence, nanoemulsion is very important to preserve curcumin from chemical degradation, the antioxidant activity and enhance the permeability of curcumin. The other physiochemical properties such as particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency (EE), morphology, and curcumin degradation were evaluated to ensure the quality of curcumin loaded nanoemulsion.

A stability study and controlled release kinetics were also determined accordingly. Skin permeability is one of the effective ways to evaluate the delivery of active ingredients or drugs. According to Han et al. (2015) and Brambilla et al. (2014), skin permeability is a process in which active chemicals or medications penetrate the stratum corneum of skin to travel through the deeper epidermis and dermis without accumulating in the dermal layer. When active substances or medications reach the dermal layer, dermal microcirculation makes them available for systemic absorption (Quinn and Donnelly, 2018). The penetration of stratum corneum is the important initial step, not only for the therapeutic action of applied active ingredients or drugs, but also for wound healing by externally applied antigenic substances.

The cytotoxicities of pure curcumin and curcumin nanoemulsion were tested and compared using human fibroblasts (HSF 1184). A wound–healing assay was also performed to determine its functionality. Wound healing is a dynamic and complex biological process that necessitates the coordination of several cellular activities in order to assist damaged skin in regaining its normal function and structure. (Eming et al., 2014). An adequate penetration must occur to give the optimum effectiveness level at the desired sites for skin permeability enhancement.

The purpose of this research was to improve the nanoemulsification of curcumin together with VCO and honey as a nutritious carrier and additive, respectively in the delivery system. Honey was mixed with glycerol to enhance its additive function in this study. Both honey and glycerol could stabilize curcumin nanoemulsion, while enhancing the viscosity of the aqueous phase (Borrin et al., 2016). Honey and glycerol would also aid in the creation of nanoemulsions. Polyols include honey and glycerol have higher density than water. Polyols could help to reduce the difference in phase density between the oil and aqueous phases, resulting in a more stable nanoemulsion (Zhang et al., 2017). Ingredients that are natural, nutritional, and nontoxic would be the first choice of product formulation and development, especially for human application. Therefore, VCO and honey was added as the oil and aqueous phases components in the curcumin loaded nanoemulsion, whereas Tween 80 was used as the emulsifier which is claimed to have no negative effects (Polychniatou and Tzia, 2013). To further improve the curcumin solubility in the nanoemulsion, polyethylene glycol 400 (PEG 400) was used as a co–solvent. Su et al. (2017) utilized PEG 400 to create and improve a nanoemulsion–based formulation containing ceramide IIIB for transdermal administration using a phase–inversion composition. The findings revealed that PEG 400 can aid in the optimization of nanoemulsion formulation. The optimized curcumin nanoemulsion was further confirmed its physiochemical characteristics and functionality including cytotoxicity.

1.2 Problem Statements

Curcumin is a less stable bioactive compound of the turmeric plant. This study was aimed to overcome the drawback of instability curcumin since it has remarkable pharmacological property. The instability problem of curcumin could be overcome by encapsulating curcumin. This could also improve its bioavailability and solubility. As a result, the active component can be absorbed into human skin for functionality. The stability, solubility, and permeability of curcumin could be improved by incorporating it into a nanoparticle system. The appropriate amount and type of surfactant(s) should be optimized to make nanoparticles into a stable phase (Capek et al., 2004). The phenomena of creaming, sedimentation, flocculation, and Ostwald ripening are always contributed to the instability of curcumin nanoemulsion. Curcumin nanoemulsion could be improved by mixing with suitable carriers, additives and emulsifiers such as glycerol, honey, PEG 400, and Tween 80. Therefore, a systematic optimization of each component is very important to produce a stable and better functionality of curcumin nanoemulsion in this study.

The other research problem which is always related to nanoemulsion system is the toxicity of the components at high concentration. Although nanoemulsion has been developed to overcome the drawbacks of drug delivery, it is important to evaluate the toxicity of curcumin loaded nanoemulsion. Christopher et al. (2006) detected the minimal toxicity up to 12 g in a single dose of standardized powder extract (C^3 *Complex*™, Sabinsa Corporation) from Alleppey finger turmeric. The acceptable range of daily intake was 3 mg/kg to 4–10 g. The low surfactant ratio (using Tween 80) was also utilized to decrease nanoemulsion toxicity. When applied topically, a high concentration of surfactants could cause skin irritation. Therefore, the cytotoxicity should be determined after optimization of each component in curcumin loaded nanoemulsion. The cytotoxicity of nanoemulsion could be performed by using the MTT assay (3 – (4, 5–dimethylthiazol–2–yl) 2, 5–diphenyl tetrazolium bromide). The assay is commonly used to analyse cytotoxicity before drug administration in the dermis and transdermal areas. The stability of curcumin increased when the encapsulation of curcumin into nanoemulsion for skin permeability.

1.3 Objectives

The objectives of this research were:

1. To optimize the base formulation based on the independent variables (PEG 400, curcumin, honey, VCO, and Tween 80) composition in the preparation of curcumin loaded nanoemulsion.
2. To characterize the physicochemical properties (particle size, zeta potential, stability and antioxidant) of curcumin in nanoemulsion.
3. To evaluate the cytotoxicity and controlled release kinetics of curcumin loaded nanoemulsion in skin permeability.
4. To determine the functionality of curcumin loaded nanoemulsion in wound healing by *in vitro* study.

1.4 Scopes of the Study

Box Behnken design (BBD) was used to optimize a curcumin–loaded nanoemulsion utilizing the statistical response surface approach (RSM). The concentration of independent variables such as polysorbate 80 (Tween 80), polyethelene glycol 400 (PEG 400), curcumin, virgin coconut oil (VCO), and honey were statistically optimized using BBD. The responses such as particle size, polydispersity index (PDI), turbidity, and entrapment efficiency (EE) were used in the optimization experiments.

The quality of curcumin nanoemulsion was determined by analyzing physical parameters such as particle size, polydispersity index, and zeta potential using a particle sizer Nano S. Transmission electron microscopy (TEM) was used to examine the morphology of curcumin–loaded nanoemulsion. The chemical degradation of curcumin was determined using attenuated total reflectance–Fourier transforms infrared spectroscopy (ATR–FTIR) based on the detection of peak disappearance from

the functional groups of curcumin. The storage stability of the nanoencapsulated curcumin was monitored at 4 °C and 45 °C for three months. The antioxidant capacity of free curcumin and curcumin loaded nanoemulsion was also compared using the colorimetric assay of radical scavenging activity.

A cytotoxicity employing the MTT test using human fibroblast cells was used to investigate the cytotoxicity of curcumin loaded nanoemulsion (HSF 1184). The cytotoxicity was conducted based on the viability of HSF 1184 cells at the concentration range of (2.50 to 0.1563 µg/ml). An *in vitro* Franz diffusion cell was used to analyze the controlled release kinetics of free curcumin and curcumin–loaded nanoemulsion in skin permeability study. The cumulative amount of curcumin permeated through rat skin was used to develop the controlled release profile. Ultimately, the functionality of curcumin nanoemulsion was determined based on the *in vitro* wound healing assay. The efficacy tests demonstrated that curcumin nanoemulsion could aid in wound healing.

1.5 Significance of the Study

A stable nanoemulsion system with a smaller particle size makes curcumin loaded nanoemulsion to be more stable under long and extreme storage temperature. It also helps to prevent the system from coalescence, Ostwald ripening and undergoing reversible destabilization such as flocculation and creaming. Hence, curcumin stability and skin permeability were improved by incorporating curcumin into nanoglobules. It is also protected curcumin from chemical degradation. The inclusion of VCO and honey in the proper proportions contributed to the stability of curcumin nanoemulsion. The thermodynamical stability of curcumin–loaded nanoemulsion solves the problem of sedimentation, flocculation, and as well as having a stable shelf–life nanoemulsion. The efficiency of curcumin–loaded nanoemulsion with reduced particle size for skin administration of lipophilic curcumin was established in skin permeability. Therefore, the curcumin nanoemulsion could be used for further product formulation on human skin application in the future.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **N. H. Md Saari,** L. S. Chua, R. Hasham, and Leny Y. (2020). Curcumin–Loaded Nanoemulsion for Better Cellular Permeation. *Journal Science Pharm, 88*(4), 1–12. doi:10.3390/scipharm88040044. (**Q2, IF: 3.43)**

2. **N. H. Md Saari,** L. S. Chua, R. Hasham. (2020). Process Optimization of Curcumin–Loaded Coconut Oil and Honey Nanoemulsion for Better Skin Permeation. *International Journal of Nanoscience,* 19 (6), 1–9. doi.org/10.1142/s0219581x20500064. (**Q3, IF: 0.68)**

Book chapter

1. **N. H. Md Saari,** L. S. Chua. (2020). Nanoengineering in the Beverage Industry. *Nano−Based Products in Beverage Industry, Academic Press,* 20, 405–436. Editors: Alenxandru, M. G. and Alina, M. H. doi:10.1016/b978–0–12–816677–2.00014–4.