FORMULATION OF *Andrographis paniculata*-LOADED NANOEMULGEL AND ITS *IN VIVO* WOUND HEALING ACTIVITY IN MICE

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ABSTRACT

Andrographis paniculata has been reported to contain several bioactive compounds proven to aid in wound healing mechanisms such as anti-inflammatory, anti-oxidant, analgesic, and anti-bacterial activities. However, there is no scientific study conducted to formulate this herb in the form of nanoemulgel for wound treatment. Hence, the objectives of this study were to optimise, characterise and evaluate a wound healing nanoemulgel containing *A. paniculata* extract for topical wound treatment application. In this study, virgin coconut oil nanoemulsion (VCO-NE) was optimised using quality by design (QbD) tools such as risk assessment and design of experiments (DoE) to choose the best formulation and processing parameters. The rheology and pharmacology studies were conducted for the prepared formulations. The *in vivo* wound healing assay was then conducted to evaluate the efficiency of the prepared formulations in mice. The QbD approach showed that the optimal VCO nanoemulsion could be formulated with Tween 20/Span 80 as surfactants, at hydrophilic-lipophilic balance (HLB) = 8, oil/surfactant = 2/1 and 85% water using a high-pressure homogeniser (HPH) at 800 bar for 5 cycles. The produced nanoemulsions had a droplet size of 151.5 ± 0.45 nm for blank VCO-NE, 141.17 ± 0.6 nm for S1 (1 mg/g *A. paniculata* extract) and 145.57 ± 0.74 for S2 (2 mg/g *A. paniculata* extract) as *A. paniculata* extract-loaded nanoemulsions (AP-NEs). Moreover, the developed nanoemulsions had a low polydispersity index (PDI) below 0.15 and relatively good stability with zeta potential -6.91 ± 0.64 for blank VCO-NE, -10.03 ± 1.36 for S1, and -16.40 ± 1.39 for S2. The prepared nanoemulsions were stable after 30 days when stored at 4 °C and 25 °C. Formulating nanoemulgel using the optimised nanoemulsions was found not to affect droplet size, PDI nor morphology. In addition, the rheology study showed that the prepared nanoemulgels could withstand segregation phenomena with preferred spreadability properties for long durations. Storage stability study also showed high stability for the nanoemulgels when stored at 4 °C and 25 °C for 90 days with no significant influence on the oil droplets size and PDI. Results from *in vivo* wound healing assay showed that, by day 11, wound treated with SG2 (1 mg/g *A. paniculata* extract-loaded nanoemulgel), which was developed from S2 nanoemulsion, exhibited 99.1% total wound recovery. The healing was found to be equivalent to 100% of the reference drug BETADINE®. In conclusion, results from this study indicated that nanoemulgel containing 1 mg/g *A. paniculata* extract could effectively promote wound healing process with less scar formation and no signs of irritation. Thus, *A. paniculata* extract nanoemulgel could be one of the potential ingredients for pharmaceutical and cosmeceutical applications, particularly for wound treatment.

ABSTRAK

Andrographis paniculata telah dilaporkan mengandungi sebatian bioaktif yang terbukti dapat membantu dalam mekanisma penyembuhan luka seperti anti-radang, anti-oksidan, analgesik, dan aktiviti anti-bakteria. Namun, tiada kajian saintifik telah dijalankan bagi memformulasi herba ini dalam bentuk gel nanoemulsi untuk perawatan luka. Justeru, kajian ini adalah bertujuan untuk mengoptimum, menciri dan menilai gel nanoemulsi yang mengandungi ekstrak *A. paniculata* untuk rawatan luka. Dalam kajian ini, nanoemulsi minyak kelapa dara (VCO-NE) telah dioptimumkan dengan menggunakan alat kualiti dengan reka bentuk (QbD) seperti penilaian risiko dan reka bentuk eksperimen (DoE) bagi memilih formulasi dan parameter pemprosesan terbaik. Kajian reologi dan farmakologi telah dijalankan ke atas formulasi yang dihasilkan. Kajian rawatan luka secara *in vivo* kemudiannya dijalankan untuk menilai kecekapan formulasi yang dihasilkan terhadap mencit. Kaedah QbD menunjukkan VCO optimum nanoemulsi dapat diformulasi dengan menggunakan Tween 20/Span 80 sebagai surfaktan, pada keseimbangan hidrofilik-lipofilik (HLB) = 8, minyak/surfaktan = 2/1 dan 85% air menggunakan penghomogen bertekanan tinggi (HPH) pada 800 bar sebanyak 5 kitaran. Nanoemulsi yang terhasil mempunyai saiz titisan 151.5 ± 0.45 nm untuk VCO-NE sahaja, 141.17 ± 0.6 nm untuk S1 (1 mg/g ekstrak *A. paniculata*) dan 145.57 ± 0.74 untuk S2 (2 mg/g ekstrak *A. paniculata*) sebagai nanoemulsi termuat ekstrak *A. paniculata* (AP-NEs). Selain itu, nanoemulsi yang terhasil mempunyai indeks polidispersi (PDI) yang rendah di bawah 0.15 dan secara relatifnya sangat stabil dengan potensi zeta -6.91 ± 0.64 untuk VCO-NE sahaja, -10.03 ± 1.36 untuk S1, and -16.40 ± 1.39 untuk S2. Nanoemulsi yang dihasilkan berkeadaan stabil lebih daripada 30 hari jika disimpan pada suhu 4 °C and 25 °C. Penghasilan gel nanoemulsi menggunakan nanoemulsi teroptimasi tidak memberikan kesan kepada saiz titisan, PDI dan juga morfologi. Tambahan pula, kajian reologi menunjukkan bahawa gel nanoemulsi yang dihasilkan mampu menahan fenomena pemisahan jangka panjang dengan ciri-ciri penyebaran yang baik. Kestabilan penyimpanan juga menunjukkan kestabilan nanopartikel yang tinggi ketika disimpan pada suhu 4 °C dan 25 °C selama 90 hari tanpa kesan signifikan terhadap saiz titisan minyak dan PDI. Keputusan daripada kajian rawatan luka *in vivo* menunjukkan bahawa, pada hari ke-11, luka yang dirawat dengan SG2 (1 mg/g gel nanoemulsi termuat ekstrak *A. paniculata*), yang dihasilkan daripada nanoemulsi S2, menunjukkan 99.1% penyembuhan luka. Penyembuhan ini adalah setanding dengan formulasi rujukan, BETADINE® yang menunjukkan penyembuhan luka 100%. Kesimpulannya, rawatan luka biopsi di mencit dengan menggunakan 1 mg/g gel nanoemulsi ekstrak *A. paniculata* mampu membantu proses penyembuhan luka secara efektif dengan kurang kesan parut dan tanpa tanda-tanda kerengsaan. Justeru, gel nanoemulsi ekstrak *A. paniculata* berpotensi menjadi salah satu bahan untuk aplikasi dalam farmasi dan kosmetik, khususnya bagi perawatan luka.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

3D	-	Three-dimensional
AN	-	Andrographolide
ANOVA	-	Analysis of Variance
AP	-	*Andrographis Paniculata*
AP-NE	-	*A.paniculata*-Loaded Nanoemulsions
AP-NG	-	*A.paniculata*-Loaded Nanoemulgel
API	-	Active Pharmaceutical Ingredient
ARU	-	Animal Resource Unit
BBD	-	Box–Behnken Designs
BPE	-	Propolis by-Product
CCD	-	Central Composite Design
CMAs	-	Critical Material Attributes
cP	-	Centipoise
CPPs	-	Critical Process Parameters
CQAs	-	Critical Quality Attributes
D	-	Detectability
DDAG	-	14-deoxy-11,12-didehydroandrographolide
DLS	-	Dynamic Light Scattering
DS	-	Design Space
DoE	-	Design of Experiment
ECM	-	Extracellular Matrix
EGF	-	Epidermal Growth Factor
EIP	-	Emulsion Inversion Point
EMC	-	Extracellular Matrix Components
FCCCD	-	Face-Centred Central Composite Design
FD	-	Franz Diffusion
FDA	-	Food and Drug Administration
EMA	-	European Medicines Agency
FGF	-	Fibroblast Growth Factors
FMEA	-	Failure Mode and Effect Analysis

FRIM	-	Forest Research Institute Malaysia
H-B	-	Herschel-Bulkley
H&E	-	Haematoxylin & Eosin
Hcl	-	Hydrochloric Acid
HDF	-	Human Dermal Fibroblast cells
HLB	-	Hydrophilic-lipophilic balance
HNC	-	HPH Number of Cycles
HNC	-	Homogenisation Number of Cycles
HPH	-	High Pressure Homogeniser
HLPC	-	High-Pressure Liquid Chromatography
HSF	-	Human skin fibroblast cells
HTN	-	Hydrogel-thickened nanoemulsion
IAEC	-	Animal Ethical Committee
ICH	-	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human
ICR	-	Imprinting Control Region
IGF-l	-	Insulin-Like Growth Factor-1
IL-6	-	Interleukin-6
KGF cDNA	-	Keratinocyte Growth Factor Complementary DNA
LNCs	-	Lipid nanocapsules
LPS/IFN- γ	-	Lipopolysaccharide Gamma interferon
LVE	-	Linear Viscosity Region
MAs	-	Material Attributes
MIP-2	-	Macrophage Inflammatory Protein-2
NAG	-	Neoandrographolide
NaOH	-	Sodium hydroxide
NCs	-	Nanocapsules
NEs	-	Nanoemulsions
nm	-	Nanometre
NEGs	-	Nanoemulgels
NLCs	-	Nanostructured Lipid Carriers
NO	-	Nitric Oxide
O	-	Occurrence

OFAT	-	One Factor at a Time
O:S	-	Oil/Surfactant
O/W	-	Oil-in-water
Pa	-	Pascal
PAT	-	Process Analytical Technology
PDGF	-	Platelet-Derived Growth Factor
PDI	-	Polydispersity Index
PE	-	Propolis extractive solution
PEG	-	Polyethylene Glycol
pH	-	Power of Hydrogen
PIT	-	Phase Inversion Temperature
PPs	-	Process Parameters
PU	-	Probe Ultrasonication
QbD	-	Quality by Design
QTPP	-	Quality Target Product Profile
RPM	-	Revolution per Minute
RPN	-	Risk Priority Number
RSM	-	Response Surface Methodology
S	-	Severity
S1	-	Nanoemulsion incorporating 1 mg/g *A. paniculata* extract
S2	-	Nanoemulsion incorporating 2 mg/g *A. paniculata* extract
SG1	-	Nanoemulgel incorporating 0.5 mg/g *A. paniculata* extract
SG2	-	Nanoemulgel incorporating 1 mg/g *A. paniculata* extract
S80	-	Span 80
SD	-	Standard Deviation
SLNs	-	Solid Lipid Nanoparticles
Span	-	Sorbitan esters
T20	-	Tween 20
T40	-	Tween 40
T80	-	Tween 80
TCM	-	Traditional Chinese Medicine
TEA	-	Triethanolamine
TEM	-	Transmission Electron Microscopy

TNF-R	-	Tumor Necrosis Factor Receptor
Tween	-	Polyethoxylated sorbitan esters
UK	-	United Kingdom
UN	-	Unloaded
UPM	-	University Putra Malaysia
USA	-	United State of America
VCO	-	Virgin Coconut Oil
VCO-NE	-	Virgin Coconut Oil Nanoemulsion
VEGF	-	Vascular Endothelial Growth Factor
VG	-	Van Gieson
W	-	Water
W/O	-	Water-in-oil
W/W	-	Weigh/Weight
ZSP	-	Zeta Sizer Nano

LIST OF SYMBOLS

°C	-	Celsius
K	-	Kelvin
s	-	Second
T	-	Temperature
μ	-	Micro-meter
ω	-	Frequency
η	-	Viscosity
G'	-	Storage modulus
G″	-	Loss Modulus
LD_{50}	-	Lethal Dose 50
γ	-	Gamma

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

The main protective shield of the human body, the skin, is vulnerable to several external factors that can cause various forms of skin damage and injuries due to its direct interaction with the environment. Cutaneous wounds arise when the integrity of the skin is compromised. When the body fails to effectively regain anatomic and functional integrity in a reasonable amount of time, chronic wounds occur. Late-healed wounds are regarded as one of the most significant clinical and economic problems in modern medicine (Schreml et al., 2010). On the other hand, traditional wound care treatments have been struggling to ensure effective healing, as long healing periods and high relapse rates persist (Wang et al., 2019). Therefore, it is critical to create a safe and efficient novel wound healing product that supplies wound therapeutics, especially natural active compounds, to the wound area.

Medicinal plants have been applied to treat diseases for thousands of years. *Andrographis paniculata* (*A. paniculata*) or 'Creat/King of bitters' is an annual herbaceous plant belonging to the family *Acanthaceae* (Valdiani et al., 2012). *A. paniculata* can act as an adaptogenic herb, and it has been used for centuries in Ayurvedic and Chinese medicine to treat fever, respiratory infections, diabetes, and non-infectious diarrhoea. Thus, *A. paniculata* is becoming a key alternative crop, and it is witnessing a rising market demand for its products (Jarukamjorn & Nemoto, 2008; Pawar et al., 2016). Previous studies showed that *A. paniculata* crude extract has potent wound healing activity, anti-oxidant activity, anti-inflammatory activity and can stimulate collagen synthesis (Al-Bayaty et al., 2012; Sheeja et al., 2006). Recent studies revealed that *A. paniculata* crude extracts contain various bioactive compounds, such as diterpene lactones, flavonoids, and polyphenols (Casamonti et al., 2019; Valdiani et al., 2012). However, formulating a product with the beneficial

attributes of bioactive substances is a challenging process. Poor water solubility, protection and skin permeation of the bioactive entities are the most faced challenges when developing biopharmaceuticals.

Drug encapsulation in novel delivery systems gained increased interest in pharmaceutical and cosmeceutical formulations to develop a better delivery mechanism and an advanced end-product. Emulsions are indeed among the most promising encapsulation-based delivery systems. By definition, an emulsion is a mechanically dispersed liquid phase in another immiscible liquid phase by the presence of a third compound: the surfactant. Nanoemulsion is a class of emulsion with tiny droplets ranging in diameter from 20 to 200 nm (Yukuyama et al., 2017). It has the highest drug encapsulation performance among its competitors and the capacity to improve solubility and bioavailability (Ahmed et al., 2018). Even though the nanoemulsion's small droplet size provides high kinetic stability against sedimentation and creaming, it is a thermodynamically unstable structure that needs certain emulsifiers on the oil-water interface to stabilize the colloidal system (Jinglei Li et al., 2016; McClements, 2012; Simões et al., 2018). Thickening the nanoemulsion with hydrogel produces a nanoemulgel that has gel characteristics with improved nanoemulsion properties. Nanoemulgel creates a dual-control release mechanism and features high viscosity, which reduces the instability that might occur in the nanoemulsion during storage (Ribeiro et al., 2015). Furthermore, nanoemulgel is easily spreadable, thixotropic, greaseless, non-staining, mucoadhesive and possesses high penetration ability (Choudhury et al., 2017; Mulia et al., 2018).

Pharmaceutical Quality by Design (QbD) is a scientific, systematic, comprehensive, and proactive approach to develop an "optimised" pharmaceutical product. The process begins with pre-defining objectives that emphasise the product, process understanding, and process control. Instead of testing the product at the end of every stage of the traditional testing method, the main objective of the QbD paradigm is to build quality within the product. QbD employs various tools, including prior knowledge, risk assessment, mechanistic models, Design of Experiments (DoE)/ data analysis, and Process Analytical Technology (PAT) (Raza et al., 2013; Yu et al., 2014)

to provide an alternative and sophisticated method for the development of quality pharmaceutical products.

QbD has the potential to implement the final pharmaceutical product quality criteria through a systematic and scientific approach that consider a broad range of aspects, such as clinical performance, variability prevention, process design improvement, manufacturing efficiency enhancement, and post-approval change management (Cunha et al., 2020). Additionally, QbD facilitates gathering the maximum amount of information from the collected data by establishing the influence of several factors and their ranges on the formulation, process development safety, and efficacy (Marto et al., 2016).

1.2 Problem Statement

The primary constituent responsible for the therapeutic properties of *A. paniculata* is andrographolide (AN), a diterpenoid with a γ-lactone moiety (Casamonti et al., 2019). However, it is agreed that andrographolide, along with two other diterpenic compounds (14-deoxy-11,12-didehydroandrographolide and neoandrographolide), are responsible for the pharmacological activities of *A. paniculata* (Thisoda et al., 2006; Valdiani et al., 2012). Formulating the low aqueous soluble active extract of *A. paniculata* in conventional drug delivery systems has been reported with limitations (Pawar et al., 2016). These drawbacks could be eliminated using novel drug carrier systems such as nanoemulgel, which have shown remarkable advantages for both herbal and chemical drugs (Baboota et al., 2007; X. Li et al., 2017; Ngan et al., 2014; Ruiz-montañez et al., 2017).

In recent decades, nanosystem-related research has sparked a technological revolution in pharmaceutical delivery systems. Concurrently, the conventional approach for nanosystem development is becoming obsolete (Yu, 2008). The product quality testing over multiple stages is complex, expensive, and could lead to variations that reduce the safety and quality of the final product. Thus, the QbD is a cost-effective science- and risk-oriented approach that improves the manufacturing processes and

ensures the quality and safety of the final nanosystem products (Cunha et al., 2020; Zhang & Mao, 2017). This study combined the cutting-edge technologies of nano-drug delivery systems and QbD to formulate and optimise *A. paniculata*-incorporated nanoemulgel (AP-NG) as a topical nano carrier to treat wounds.

1.3 Hypothesis

Encapsulation of *A. paniculata* extract in an optimised nanoemulsion for wound treatment has not been reported in any literature. Thus, this study was carried out by employing several QbD tools to define and identify the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQAs), the Critical Material Attributes (CMAs), and the Critical Process Parameters (CPPs) of an optimised Virgin Coconut Oil nanoemulsion (VCO-NE) as lipid-based nano carrier for *A. paniculata* extract. The optimised AP-NE/ AP-NG were expected to have higher biological efficacy than extract without any encapsulation.

1.4 Objectives of the Study

The principle aim of this work was to optimise, characterise and evaluate an *Andrographis paniculata*-loaded-nanoemulgel (AP-NG) for application on topical wound treatment.

The present study was conducted in various stages with the following objectives:

(a) To develop and optimise a Virgin Coconut Oil (VCO) nanoemulsion (VCO-NE) as a lipid-based nano carrier for *A. paniculata* active extract.

(b) To characterise the *A. paniculata*-incorporated nanoemulsion (AP-NE)/ *A. paniculata*-incorporated nanoemulgel (AP-NG) formulations based on physical and chemical bases.

(c) To evaluate the *in vivo* wound healing property of the AP-NG in mice.

1.5 Scope of the Study

To achieve the study objectives, the following scope was carried out:

Objective (1): Construct QbD approach step-by-step by employing several QbD tools to evaluate and optimise the appropriate formulation, procedures, and manufacturing processes involved in the development of VCO-NE for topical wound treatment; the included tools are:

(a) Preliminary screening (Formulation/ Process).

(b) Risk assessment (Ishikawa fishbone diagram/ Failure Mode and Effect Analysis).

(c) DoE studies for Formulation (Water (75-85%), HLB (8-10), Oil:Surfactant (2-4)) and Process (HPH Pressure (700-900 bar), HPH Number of Cycles (3-7)) by employing Full Factorial Design/ Face-Centred Central Composite Design.

Objective (2): Characterise AP-NE/AP-NG formulations by:

(d) High-Performance Liquid Chromatography (HPLC) analyse of *A. paniculata* active extract.

(e) Characterising AP-NE formulations based on droplet size, zeta potential, polydispersity index (PDI), pH, viscosity, and stability.

(f) Developing and characterising AP-NG formulation based on droplet size, polydispersity index (PDI), pH, rheology, and stability.

Objective (3): Evaluate the *in vivo* wound healing property of the AP-NG in the Imprinting Control Region (ICR) mice by:

(g) Primary skin adhesiveness and irritation assessment.

(h) Circular excision wound model study.

(i) Histopathological (Tissue morphology and collagen estimation) and biochemical studies (Hexosamine estimation).

1.6 Significances of Study

The wound care market across the globe is witnessing growth due to factors such as rising incidences of diabetes, rising ageing population, increasing venture capitalist funding from governments, rapid technological innovations, and rising awareness regarding new natural-based techniques of wound care. Therefore, it is a potentially high demand to employ the new lipid-based nanocarrier drug delivery technology to produce a natural-based product to treat chronic wounds and scares.

A. paniculata is widely used in traditional medicine and has been reported to have wound healing capacity. However, topical delivery system products that contain this active plant extract is yet to be further studied. The importance of this study is to overcome the limitation in the topical application of the plant extract, which mostly has the characteristic of hydrophobic compounds. Nanoemulsion as a lipid-based nanocarrier has potential applications in delivering hydrophilic and hydrophobic drugs (Sonneville-aubrun et al., 2018; Thakur et al., 2013). Thus, incorporating the *A. paniculata* extract into the nanoemulsion then developing a nanoemulgel can overcome topical wound healing product limitations.

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LIST OF PUBLICATIONS

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