UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF VITAMIN E-ENRICHED NANOEMULSION FOR WOUND HEALING

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

March 2020

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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March 2020

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Wound problem is a global health care issue that can burden the individuals and countries. Vitamin E is a potent natural antioxidant and tocopherols are the common form to be used in skin-care products. However, studies found that the antioxidant potency of tocotrienols is 60 times than tocopherols which believe can benefit for the wound problems. Red palm oil (RPO) rich in vitamin E (70-80% tocotrienols; 20-10% tocopherols) and carotenoids, is a favourable choice to be used as a natural source of tocotrienols. In our work, a tocotrienol-rich oil-in-water-nanoemulsion (NE) formulation was optimized using response surface methodology (RSM) and formulated using high-pressure homogenizer. Effect of the concentration of three independent variables [surfactant (5-15 wt%), co-solvent (10-30 wt%) and homogenization pressure (500-700 bar)] toward two response variables (droplet size, polydispersity index) was studied using central composite design (CCD) coupled to RSM. RSM analysis showed that the experimental data could be fitted into a second-order polynomial model and the coefficients of multiple determination (R^2) is 0.9115. The optimized formulation of NE consisted of 6.09 wt% mixed surfactant [Tween 80/Span 80 (63:37, wt)], 20 wt% glycerol as a co-solvent via homogenization pressure (500 bar). The optimized NE response values for droplet size and polydispersity index were 119.49nm and 0.286, respectively. The actual values of the formulated nanoemulsion were in good agreement with the predicted values obtained from RSM, thus the optimized compositions have the potential to be used as a nanoemulsion for cosmetic formulations.

Characteristics and stability studies were evaluated for 6 months at three different temperatures (4 ℃, 25 ℃ and 40 ℃), which included droplet size, polydispersity index, viscosity, antioxidant activity, active contents (carotenoids and vitamin E) and colour. It was found that optimized nanoemulsion has fewer changes over the time. No significant difference ($P>0.05$) was found in terms of droplet size, polydispersity index, viscosity, antioxidant activity and active contents at 4 ℃ storage condition over the time. These findings indicate that optimized nanoemulsion was more stable than the nanoemulsions

without co-solvent (glycerol) and emulsions without co-solvent and surfactant (Tween 80 and Span 80).

Keratinocytes migration and zebrafish tail regeneration experiments were used to evaluate the wound healing effect of NE. MTT assay provided a concentration range of 0.35-8.75 µg/ml of nanoemulsion that produced cell viability more than 100%. The wound closure of keratinocytes treated with 3.50 µg/ml and 1.75 µg/ml of NE was significantly faster than the blank (35.56%); they increased to 73.76% and 67.37%, respectively, after 24 hours of treatment. The lethal concentration at 50% (LC_{50} value) obtained from acute and prolonged toxicity was almost similar, which was 4.6 mg/ml and 5.0 mg/ml, respectively. Growth of zebrafish tail regeneration treated with NE at a concentration of 2.5 mg/ml was significantly faster than the untreated zebrafish, which regenerated to 40% on the fifth day, more than 60% on the tenth day of treatment and fully recovered at the 20^{th} day.

In conclusion, these results indicate that tocotrienols-rich nanoemulsion formulated was stable and showed potential in enhancing wound healing through accelerated wound closure.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PEMBANGUNAN NANOEMULSI YANG DIPERKAYA DENGAN VITAMIN E SEBAGAI RAWATAN PENYEMBUHAN LUKA

Oleh

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Masalah luka adalah isu penjagaan kesihatan global yang boleh membebankan individu dan negara. Vitamin E ialah antioksidan semula jadi yang bagus dan tokoferol merupakan bentuk biasa yang sering digunakan dalam produk penjagaan kulit. Walau bagaimanapun, kajian mendapati bahawa potensi antioksidan tokotrienol adalah 60 kali daripada tokoferol dan dipercayai dapat memberi manfaat kepada masalah luka. Minyak sawit merah (RPO) yang kaya dengan vitamin E (70-80% tokotrienol; 20-10% tokoferol) dan karotenoid adalah pilihan utama yang boleh digunakan sebagai sumber semula jadi tokotrienol. Formulasi minyak-dalam-air-nanoemulsi (NE) yang kaya dengan tokotrienol telah dioptimalkan dengan menggunakan kaedah response surface methodology (RSM) dan dirumuskan dengan penggunaan homogenizer tekanan tinggi. Kesan daripada tiga pemboleh ubah dimanipulasi [surfaktant (5-15 wt%), pelarut-bersama (10-30 wt%) dan tekanan homogenisasi (500-700 bar)] ke arah dua pemboleh ubah bergerak balas (saiz titisan, indeks polidispersiti) teleh diselidikkan dengan menggunakan central composite design (CCD) dalam RSM. Analisis RSM menunjukkan bahawa data eksperimen boleh dipasang pada model second-order polynomial dan coefficients of multiple determination (R^2) ialah 0.9115. Formulasi optimum NE terdiri daripada 6.09 wt% surfaktan campuran [Tween 80/Span 80 (63:37, wt)], 20 wt% gliserol sebagai pelarut-bersama melalui tekanan homogenisasi (500 bar). Saiz titisan dan indeks polidispersiti NE ialah 119.49nm dan 0.286, masing-masing. Nilai sebenar nanoemulsi yang dirumuskan ialah persetujuan dengan nilai yang telah diramalkan oleh RSM. Oleh itu, komposis optimum ini mempunyai potensi untuk digunakan sebagai nanoemulsi bagi formulasi kosmetik.

Kajian ciri dan kestabilan dinilai selama 6 bulan pada tiga suhu yang berbeza (4 ℃, 25 ℃ dan 40 ℃). Selain itu, saiz titisan, indeks polidispersiti, kelikatan, aktiviti antioksidan, kandungan aktif (karotenoid dan vitamin E) dan warna juga telah dinilaikan. Menurut kepada data kajian, perubahan dalam nanoemulsi optimum ini adalah kecil manakala perbezaan dari segi saiz titisan, indeks polistispersiti, kelikatan, aktiviti antioksidan dan

kandungan aktif dalam suhu penyimpanan 4 ℃ adalah tidak signifikan. Keputusan ini telah menunjukkan bahawa nanoemulsi adalah lebih stabil daripada nanoemulsi tanpa pelarut-bersama (gliserol), emulsi tanpa pelarut-bersama dan surfaktan (Tween 80 dan Span 80).

Eksperimen pertumbuhan semula sel keratinocytes dan ekor zebrafish telah dijalankan untuk menilai kesan NE terhadap penyembuhan luka. Ujian MTT menunjukkan kepekatan nanoemulsi pada 0.35-8.75 µg/ml menghasilkan keviabelan sel yang lebih daripada 100%. Penutupan luka sel keratinocytes yang dirawati dengan 3.50 µg/mL dan 1.75 µg/mL NE adalah lebih cepat daripada sel yang tidak dirawati dengan nanoemulsi (35.56%), kadar penutupan luka telah meningkat kepada 73.76% (3.50 µg/mL) dan 67.37% (1.75 µg/mL). Lethal concentration pada 50% (LC_{50}value) yang diperolehi daripada kajian ketoksikan akut dan ketoksikan berpanjangan adalah hampir sama, iaitu 4.6 mg/mL dan 5.0mg/mL, masing-masing. Pertumbuhan regenerasi ekor zebrafish yang dirawati dengan 2.5 mg/mL NE adalah lebih cepat daripada zebrafish yang tidak dirawati dengan NE, pertumbuhannya naik kepada 40% pada hari kelima. Akhirnya, pada hari ke-10, pertumbuhannya terus meningkat kepada 60% dan pulih sepenuhnya pada hari ke-20.

Kesimpulannya, keputusan ini menunjukkan bahawa nanoemulsi yang kaya dengan tokotrienol ini adalah stabil dan berpotensi dalam meningkatkan penyembuhan luka dengan mempercepat penutupan luka seperti yang telah ditunjukkan dalam penyelidikan ini.

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude and appreciation to my supervisor, Prof. Dr. Lai Oi Ming, who supervises, supports and leads me throughout my master's works and thesis. She is an intellectual lady who guides me and has always been concerned with my progress. Her patience and immense knowledge are very much appreciated. Besides, I would like to thank my co-supervisors, Prof. Dr. Tan Chin Ping and Prof. Ts. Dr. Cheah Yoke Kqueen, who help in providing me instruments and facilities for my works.

A special thanks to my family for supporting me financially and emotionally. Next, my sincere appreciation goes to my beloved friends, Khor Yih Phing, Chan Yong Lin, Goh Hong Lip, Lee Choon Min, Ng Siang Keat and Chen Gao Zheng. They have selflessly to share their knowledge, helps and times with me. I sincerely appreciate all the guidance and supports from those I mentioned above. Thank you.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AA	Ascorbic acid
Abs	Absorbance
ANOVA	Analysis of variance
AV	Actual value
C	Blank-control
CAR	Carotenoids
CCD	Central composition design
CH	Carbon-hydrogen bond
DMSO	Dimethyl sulfoxide
dpe	Days of post exposure
DPPH	2, 2 diphenyl-1-picryl hydrazyl
F	Full nanoemulsions
G	Nanoemulsions without glycerol
HLB	Hydrophilic-lipophilic balance
hpe	Hours of post exposure
HPH	High pressure homogeniser
HPLC	High-performance liquid chromatography
IACUC	Instituional Animal Care and Use Committee
LC50	Lethal concentration at 50%
MDA	Malondialdehyde
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromidefor
NE	Red palm oil-in-water nanoemulsions
NS	No separation

O	Oiling off
O/W	Oil-in-water
OECD	Organization for Economic Cooperation and Development
PBS	Phosphate-buffered saline
PDI	Polydispersity index
PIT	Phase inversion temperature
PV	Predicted value
RDB	Refined, bleached and deodrised
RPO	Red palm oil
RSM	Response methodology response
S	Separation
S80	Span 80
T80	Tween 80
TEM	Transmission electron microscope
Toc	Tocopherol
Toc-3	Tocotrienol

LIST OF NOTATIONS

n	Sample size
P	Statistical notation and symbol for p value
R °	Free radical
ROO °	Peroxyl radical
ROOH	Hydroperoxide
$\beta_0, \beta_i, \beta_{ii}$ and β_{ij}	Intercept, linear, quadratic and interaction terms in RSM equation
$X^{1,2,3}$ / $X_{i,j}$	Independent variables in RSM equation
Y	Dependent variables in RSM equation
R^2	Coefficients of multiple determination
ΔE	Total colour difference
L*-	Lightness
A*-	Redness
B*-	Yellowness

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Among vegetable oils, palm oil has the most massive production which contributed 45.5 million tonnes of palm oil in 2009 (Mahat, 2012). The oil palm tree was originated in West Africa but was introduced to Southeast Asia and South America. The oil palm tree was first brought in by the British in the 1870s (MPOC, 2015). The oil palm (*Elaeis guineensis*) tree is a tropical tree. Year-round rainfall and the stable temperatures are needed for optimal growth and production crop of the oil palm tree. With these optimal conditions, a total of 4.49 million hectares of land in Malaysia is used to grow the oil palm tree and made Malaysia become one of the largest exporters and producers of palm oil in the world (MPOC, 2014). The demand for palm oil is increasing as it is widely used in food, skin products, household products and fuel. Therefore, the Malaysian palm oil industry plays an essential role in contributing to Malaysia's economy, including providing employment and exports.

There are a few types of palm oil and they are different due to the various oils extracted from different parts of the palm fruit. Red palm oil and crude palm oil is extracted from the fruit of the oil palm tree while palm kernel oil is from the seed or the kernel. Therefore, they are distinct from their chemical composition and physical characteristics. Red palm oil is red in colour due to the high concentration of carotenoids. Red palm oil provides energy for daily life and nutrients. Fat of red palm oil is trans-fatty acid free which believe that will not cause adverse health effects such as heart disease (Stuijvenberg, Dhansay, Lombard, Faber and Benadé, 2001). Red palm oil is the most abundant source of carotenoids (500-700ppm) and vitamin E (500-1000ppm; tocotrienol and tocopherol) which act as antioxidant that against free radicals in the body (Edem, 2009; Mba, Dumont and Ngadi, 2015; Sundram, Sambanthamurthi and YewAi, 2003).

Wounds are defined as a damaged part of the body which occurred through cut, burn, scratch and/or breakdown of skin. In developed countries, around 2% of the general population was suffering from wound problem and estimate to rise 800 per 100000 people aged of 75 years every year (Guest et al., 2017; Heyer, Herberger, Protz,Glaeske and Augustin, 2016). The expenditure spends on wound healing poses not only a burden for an individual but also the countries, it can cost about 2-4% of the government's health budget (Gottrup, 2004; Gottrup, Holstein, Jørgensen, Lohmann and Karlsmar, 2001). For example, the England government spends £5.3 billion on wound management annually, which is 4% of the total cost on public health (Guest et al., 2015, 2017). Although there is no clear data on non-healing wounds in Malaysia, injury and inevitable other consequences of external causes were one of the top ten principal reasons of hospitalization and death in government and private hospitals in 2013 (MOH, 2014). Improve wound healing which can reduce the risk of contamination and infections is the main key goal of wound management. Therefore, the consequence of impaired and poorly healing wounds should not be underestimated and should be taken prudently as complication can arise in the future.

1.2 Problem statement

Wound problems remain a challenging growing health care issue in the world. Although there are many treatments and products available to treat wounds but people still suffering from wound problems, especially the high-risk populations (e.g. diabetic, obese, smokers or the aged) (Sen et al., 2009). The harm caused by wound problems cannot be underestimated and neglected. It can lead to people suffering from impaired wound healing, delayed healing of wounds, pain, stress and scar which can bring complications and affect the quality of life in the later of life. To overcome this significant hurdle, a more effective or alternative medication or product is needed to improve wound healing and lower risk of scar formation, complications, morbidity and mortality, as well as enhance the quality of life.

There are different wound healing agents that have been used to handle wounds. Honey, green tea, turmeric and aloe vera are the ancient and folk remedies for wound healing while saline, antiseptic solutions and topical antibiotics are the modern wound treatments (Kateel, Adhikari, Augustine and Ullal, 2016; Page, 2002; Teplicki et al., 2018). The advance of technology brings us artificial and synthetic ingredients but nowadays people more likely to choose natural ingredient products. Studies found that 54% of the new anti-cancer drugs (developed in the year between 1940-2002) and 73% of the pharmaceutical products were derived from natural ingredients (Wangchuk, 2018; Yuan, Ma, Ye and Piao, 2016). Studies provided evidence that naturally derived compounds, such as tannins, curcumin, vitamin C, vitamin E and so on, enhanced wound healing. All of these natural compounds were linked with significant anti-inflammatory, antioxidant and antimicrobial activities (Ibrahim et al., 2018).

It has been widely reported that vitamin E can be used as bioactive compounds in many cosmetics and dermatological products (Jiang, 2014; Meganathan and Fu, 2016). Vitamin E is well-known as a powerful lipophilic antioxidant. It is scientifically proven to be effective in treating dermatological problems such as melasma and skin inflammation (Gensler and Magdaleno, 1991; Jiang, 2014; Kosmadaki and Gilchrest, 2004). Tocopheryl acetate is the common form of vitamin E used in industry as it is available and stable in different conditions (Dauqan, Sani, Abdullah, Muhamad and Top, 2011). However, synthetic vitamin E such as tocopheryl acetate and α-tocopherols can only provide antioxidant protection to the skin but not the formulation.

Natural additives are becoming more popular than synthetic additives due to their natural property and this makes the natural vitamin E resources more desirable. Although synthetic vitamin E possesses a high content of vitamin E but the purification process may cause an additional cost to the production cost. A solution to this issue (to keep low production cost and high antioxidant content) is to substitute the synthetic vitamin E with high tocotrienols ingredient. Tocopherols and tocotrienols are subfamilies of vitamin E but antioxidant potency of tocotrienols is 60 times more effective than tocopherols

(Serbinova, Kagan, Han and Packer,, 1991). The benefits and potent effects of tocotrienols lead to their wide application in many fields especially in dermatology (e.g., treating skin inflammation) (Jiang, 2014; Shibata, Nakagawa, Kawakami, Tsuzuki and Miyazawa, 2010; Yamada et al., 2008). Palm oil (940 mg/kg total tocotrienols), rice bran oil (464 mg/kg total tocotrienols) and annatto (*Bixa Orellana L.*) (1400-1470 mg/kg total tocotrienols) are the tocotrienols commercial sources (Aggarwal, Sundaram, Prasad and Kannappan, 2010; Frega, Mozzon and Bocci, 1998). Annatto is the richest source of tocotrienols among others but a few studies reported that annatto seed caused allergic reactions (Ebo, Ingelbrecht, Bridts and Stevens, 2009; Myles and Beakes, 2009; Young, Patel, Stoneham, Rona and Wilkinson, 1987). In this aspect, red palm oil which is rich vitamin E (70% tocotrienol and 30% tocopherols) and carotenoids, is a favourable choice as a natural source of tocotrienols (Mba et al., 2015; Nagendran et al., 2000). RPO is widely used as edible oil but research in dermatology, primarily through nanoemulsion, is lacking.

The use of red palm oil is limited due to its poor water solubility and this restricts its role in other fields. Low absorption rate caused by poor water solubility results in low bioavailability (McClements, 2011). Thereby, improving the solubility of red palm oil can widen its applications and the market values. Other than benefit to the public, diversification of the applications of red palm oil also contribute to the economy of Malaysia, as Malaysia is one of the biggest red palm oil exporters. An answer to this challenge is to improve the solubility of red palm oil by transforming it into oil-in-water nanoemulsions. We believed that nanoemulsions encapsulated red palm oil could effectively enhance their solubility and stability, while the effect of tocotrienols beneficial to wound healing can be achieved. Hence, this study aims to optimize the red palm oil-in-water nanoemulsions and investigate the potential of vitamin E enriched oil-in-water nanoemulsions from red palm oil on wound healing.

1.3 Objectives

1.3.1 General objectives

To optimize the red palm oil-in-water nanoemulsions and evaluate its effect on wound healing.

1.3.2 Specific objectives

1. To determine the optimum conditions for the formulation of red palm oil-in-water nanoemulsions using response surface methodology.
2. To determine the characteristics and storage stability of red palm oil-in-water nanoemulsions for six months at 4, 25 and 40 ℃.
3. To evaluate the wound healing activity of red palm oil-in-water nanoemulsion using *in-vitro* (migration of keratinocytes) and *in-vivo* (tail regeneration of zebrafish) models.

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BIODATA OF STUDENT

Chong Wai Ting was born on 7th February 1991, in Kuala Lumpur. She received her primary and secondary education in SJK (C) Batu 11 Cheras and SMJK Yu Hua from 2003-2010, respectively. She was an active and outgoing girl. She used to be the school head prefect and vice-president of Kadet Remaja Sekolah. Besides, she was physically active as well. She used to represent the school in netball competition and was the captain of the team. In 2010, she studied her degree, Bachelor of Science (Nutrition and Community Health) at Universiti Putra Malaysia (UPM). Her study was sponsor Jabatan Perkhidmatan awam Malaysia (JPA). Other than sports, she likes music and voluntary work. She used to be the president of the Chinese Orchestra UPM and volunteer of AIESEC Global Community Development Program in Taiwan (2013). During her final year of the degree, she worked as a research internship at the Malaysian Palm Oil Board for her internship. Her final year project studied on Modification of phosphorus-to-protein ratio in fresh chicken meat and chicken meat products through different cookings. In 2015, she graduated her bachelor degree with First-class honors and was awarded Dean List for three consecutive years (2011-2013) with Vice Chancellor's List in 2015. In 2016, Wai Ting continued her Master in Institute of Biosciences, UPM, under supervision of Prof Lai Oi Ming. Her research project is related to the development of red palm oil nanoemulsions which can be used for skincare. She was a scholarship holder of the Graduate Research Fellowship, UPM. She also awarded RM 25,000 research grant by Putra Grant (Putra Graduate Initiative), UPM.

PUBLICATION

Chong, W. T., Tan, C. P., Cheah, Y. K., Lajis, A. F. B., Dian, N. L. H. M., Kanagaratnam, S., & Lai, O. M. (2018). Optimization of process parameters in preparation of tocotrienol-rich red palm oil-based nanoemulsion stabilized by Tween80-Span 80 using response surface methodology. *PloS one*, *13*(8), e0202771. (Submited and published)

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