IMPROVEMENT OF ANTI-INFLAMMATION OF *SWIETENIA MACROPHYLLA* SELF NANOEMULSION

AHMAD MUSTAFA MASOUD EID

UNIVERSITI TEKNOLOGI MALAYSIA

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AHMAD MUSTAFA MASOUD EID

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To my lovely wife Maha, my cute daughters Leen, Lana, and my beloved mother Rwaida, father Mustafa, my brothers, and sisters may ALLAH bless them.
Who have been constant sources of pride, support, encouragement, and love.

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ABSTRACT

Nowadays there is an intensely usage of natural bioactive materials as medicinal agent in pharmaceutical industries. *Swietenia macrophylla* (SM) has been reported to have biological activities such as anti-inflammatory, anti-mutagencity, anti-fungal and anti-tumor activities. Therefore, SM oil was used in the formulation of oral nanoemulsion as self-nanoemulsifying system and topical nanoemulsion as nanoemulgel. In this study, self-nanoemulsifying formulations were prepared for both SM and olive oils using different surfactants/co-surfactants nonionic surfactants (Labrasol, Tween 20, Capmul and Labrafil). For topical preparation, nanoemulgels of SM and olive oils were prepared, first by mixing the oil, glycerol with sucrose ester (Laureate, Oleate and Palmitate) to produce pre-nanoemulsion by heat inversion technique. Then nanoemulsion was formed upon the mixing with water by self-emulsification technique. After that Carbopol (934 and 940) was added to nanoemulsion to produce the nanoemulgel. Finally safety and pharmacology studies were conducted for the prepared formulations. The acute and sub-acute toxicity studies were conducted for SM oil self-nanoemulsifying system on rats. The biochemical parameters were evaluated by studying serum *alanine transferase* (ALT), *aspartate transferase* (AST) and *alkaline phosphatase* (ALP). The histopathology of the rats liver sections were studied under light microscope after staining with haematoxylin and eosin. On the other hand, the anti-inflammatory property for SM oil was screened using carrageenan induced rat paw edema method for SM oil for both oral (self-nanoemulsifying system) and topical (nanoemulgel) preparations. The optimal self-nanoemulsifying formulations were prepared using Tween20/Labrafil (2:1) and Capmul/Labrasol (1:2), producing small droplets size of <150 nm, low polydispersity index below 0.3 and relatively good stability with zeta potential lower than -30. It was found that 50% oil with sucrose laureate (20%) and glycerol (30%) was able to produce a very stable nanoemulsion when stored at 4 °C with droplets size less than 150 nm, with low size distribution below 0.2 and low zeta potential -40. The optimal nanoemulsion formulation was mixed with water and different grades of Carbopol (934 and 940) to produce nanoemulgel. It was found that 0.5% Carbopol 940 produces a stable nanoemulgel and it showed high stability when stored at different temperatures 4 °C, 25 °C and 40 °C for one year with no significant influence on the oil droplets size, size distribution and zeta potential. In addition, the anti-inflammatory properties of *Swietenia macrophylla* oil were greater in the form of self-nanoemulsifying system and nanoemulgel than in the oil solution. *Swietenia macrophylla* oil in the form of self-nanoemulsifying system possesses no toxicity effect on rats after acute and sub-acute studies. In conclusion, *Swietenia macrophylla* oil showed a safety profile with improvement in the anti-inflammatory activity with the help of nanoemulsion.

ABSTRAK

Pada masa kini terdapat peningkatan ketara penggunaan bahan bioaktif semula jadi sebagai agen ubatan dalam industri farmaseutikal. *Swietenia macrophylla* (SM) telah dilaporkan mempunyai aktiviti biologi seperti anti-radang, anti-mutagencity, anti-kulat dan anti-tumor. Oleh itu, minyak SM telah digunakan dalam formulasi nanoemulsi oral sebagai sistem nanoemulsi kendiri dan nanoemulsi topikal sebagai nanoemulgel. Formulasi nanoemulsi kendiri telah disediakan untuk kedua-dua minyak iaitu minyak SM dan zaitun menggunakan surfaktan/surfaktan bersama nonionik yang berbeza (*Labrasol*, *Tween* 20, *Capmul* dan *Labrafil*). Untuk penyediaan topikal, nanoemulgel telah disediakan menggunakan minyak SM dan minyak zaitun, dimulai dengan mencampurkan minyak, gliserol dengan sukrosa ester (laurat, oleat dan palmitat) untuk menghasilkan pra-nanoemulsi menggunakan teknik pembalikan haba. Kemudian nanoemulsi terbentuk apabila bercampur dengan air dengan teknik pengemulsian kendiri, selepas itu *Carbopol* (934 dan 940) telah ditambah kepada nanoemulsi untuk menghasilkan nanoemulgel. Akhir sekali kajian keselamatan dan farmakologi telah dijalankan bagi formulasi yang dihasilkan. Kajian ketoksikan akut dan sub-akut telah dijalankan untuk sistem nanoemulsi kendiri minyak SM ke atas tikus. Parameter biokimia dinilai dengan mengkaji *alanina transferase* (ALT), serum *aspartate transferase* (AST) dan *alkaline phosphatase* (ALP). Histopatologi bahagian hati tikus telah dikaji di bawah mikroskop cahaya selepas sampel diwarnakan dengan hematoksilin dan eosin. Sifat anti-radang minyak SM telah disaring menggunakan kaedah karagenan teraruh edema kaki tikus untuk penyediaan kedua-dua oral (sistem nanoemulsi kendiri) dan topikal (nanoemulgel). Formulasi optimum nanoemulsi kendiri telah disediakan dengan menggunakan *Tween*20/*Labrafil* (2:1) dan *Capmul*/Labrasol (1:2), menghasilkan saiz titisan kecil <150 nm, indeks kepoliserakan terendah di bawah 0.3 dan kestabilan relatif baik dengan zeta potensi yang lebih rendah daripada -30. Kajian ini mendapati bahawa minyak 50% dengan sukrosa laurate 20% dan 30% gliserol dapat menghasilkan nanoemulsi yang sangat stabil apabila disimpan pada 4 °C dengan saiz titisan kurang daripada 150 nm, taburan saiz rendah di bawah 0.2 dan potensi zeta kurang daripada -40. Formulasi nanoemulsi optimum telah dihasilkan dengan mencampurkan air dan *Carbopol* yang berbeza gred (934 dan 940) untuk menghasilkan nanoemulgel. Didapati bahawa 0.5% *Carbopol* 940 menghasilkan nanoemulgel yang stabil dan ia menunjukkan kestabilan yang tinggi apabila disimpan pada suhu yang berbeza selama satu tahun iaitu pada 4 °C, 25 °C dan 40 °C dengan tiada perbezaan yang signifikan pada saiz titisan minyak, taburan saiz dan potensi zeta. Di samping itu, ciri-ciri anti-radang minyak *Swietenia macrophylla* adalah lebih baik dalam bentuk sistem nanoemulsi kendiri dan nanoemulgel berbanding larutan minyak. Minyak *Swietenia macrophylla* dalam bentuk sistem nanoemulsi kendiri tedak mempunyai sebarang kesan toksik kepada tikus selepas kajian akut dan sub-akut. Kesimpulannya, minyak *Swietenia macrophylla* menunjukkan profil keselamatan dengan peningkatan dalam aktiviti anti-radang dengan bantuan nanoemulsi.

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LIST OF ABBREVIATIONS

ANOVA	-	Analysis of variance
ALP	-	Aspartate transferase
ALT	-	Alaninie transferase
ASA	-	Acetylsalicylic acids
AST	-	Aspartate transferase
CE	-	Coarse emulsion
cm	-	Centimeter
cm/mol	-	Centimeter per mole
cP	-	Centipoises
°C	-	Degree centigrade
HLB	-	Hydrophile-Lipophile Balance
et al	-	Elsewhere or add others
etc	-	Et cetera
g	-	Gram
hr	-	Hour
κ	-	Consistency coefficient
Kg	-	Kilogram
L	-	Laurate
ME	-	Microemulsion
mg	-	Milligram
µg	-	Microgram
min	-	Minute
mg/kg	-	Milligram per kilogram
mg/ml	-	Milligram per milliliter
ml/kg	-	Milliliter per kilogram
µm	-	Micrometer

mm	-	Millimeter
mV	-	Milivolt
n	-	Flow behaviour index in power law model
NE	-	Nanoemulsion
nm	-	Nano-meter
NSAIDs	-	Non-steroidal anti-inflammatory drugs
O	-	Oleate
OECD	-	Organization of economic co-operation and development
O/W	-	Oil-in-Water
O/W/O	-	Oil-in-Water-in-Oil
P	-	Palmitate
PDI	-	Polydispersity index
PIT	-	Phase inversion temperature
rpm	-	Rotation per minute
S	-	Second
SD	-	Standard deviation
SE	-	Separation of emulsion
SEDDS	-	Self-emulsifying drug delivery systems
SEDS	-	Self-emulsifying delivery systems
SEM	-	Standard error of mean
SLN	-	Solid lipid nanoparticles
SMEDDS	-	Self-microemulsifying drug delivery systems
SNEDDS	-	Self-nanoemulsifying drug delivery systems
SM	-	*Swietenia macrophylla*
SNES	-	Self-nanoemulsifying system
γ	-	Shear rate
τ	-	Shear stress
T20	-	Polyoxyethylene sorbitan mono-oleate (Tween 20)
W/O	-	Water-in-Oil
W/O/W	-	Water-in-Oil-in-Water
W/W		Weight over weight

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

The application of nanotechnology today is not solely to one science aspect but it is beyond expectation compared to the time when it was introduced years ago. With time, the knowledge in nanotechnology has made grow in many aspects; one of them is the desire to make remarkable changes in pharmaceutical dosage forms and their application with active ingredients. Due to the dynamics of the pharmaceutical products market, developments of new products using the latest and innovative technology are becoming a norm of many pharmaceutical companies in the recent years (Zhang *et al.*, 2008; Mei *et al.*, 2013; Mehravi *et al.*, 2014). To develop innovative and superior pharmaceutical dosage forms, it is necessary to depart from conventional technology. One of the key technologies which can lead to innovative product changes is nanotechnology. A key aspect of nanotechnology is that nanoscale materials offer different chemical and physical properties from bulk materials, and these properties could form the basis of new technology (Morigi *et al.*, 2012; Mei *et al.*, 2013).

Nanotechnology as encompasses science, engineering and technology is related to the understanding and control of matter. It also stressed importance on research and development of nanotechnology materials, devices and systems with novel properties and functions because of their nano-scale dimensions or components (NSTC, 2005). Nanotechnology is an exciting phenomenon in the recent history that applies to virtually all sectors of research, especially science, cosmetics industry, and

drug delivery fields with versatility in targeting tissues, accessing deep molecular targets and time controlled release of small molecular weight drugs (Sun *et al.*, 2008; Jain *et al.*, 2009; Andrade *et al.*, 2013). The ability to characterize, manipulate and organize materials at the nanoscale in promoting a scientific and technological revolution of proportions not yet identified (Lee, 2004; Azeem *et al.*, 2012). Today, the use of nanoparticles has transitioned from the prestigious market to the mass market and this trend is expected to continue as pharmaceutical manufacturers seek new idea to differentiate their products from competitors.

In the pharmaceutical area, nanometric systems are not widely characterized as the classic emulsions, liposomes and suspensions, but have great potential to be used as a sophisticated drug delivery (Lee, 2004; Azeem *et al.*, 2012). Nanosystems include various types of dosage form systems that are broadly grouped on the basis of size and ease delivery of active ingredients to the human body. Drug delivery is a direct beneficiary of the developments in nanotechnology, due to that development it is now possible to produce drug's nanoparticles that can be utilized in a variety of innovative ways. New methods of drug delivery can now be used to increase the effectiveness and safety of medication (Gupta and Kompella, 2006; Borhade *et al.*, 2012; Mehravi *et al.*, 2014). Improving drug absorption, controlling drug release and adequate stability are the main purposes of nanotechnology in the design of miniaturized drug carrier systems. However, several new drug carrier systems have been developed such as nano-emulsions (NE), self-emulsifying drug delivery systems (SEDDS), nano-suspensions (NS), liposomes, polymeric nanoparticles, nanostructured lipid carriers (NLC) and solid lipid nanoparticles (SLN) (Mehnert and Mader, 2001; Naik *et al.*, 2004; Muller *et al.*, 2007; Teeranachaideekul *et al.*, 2007; Zhou *et al.*, 2014).

Nanoemulsions are systems with unique characteristics such as with fine and narrow droplet size distribution that lead to a higher kinetic stability compared to conventional emulsion. Nanoemulsions are emulsions with droplet size in the nanometric scale usually in the range 20-200 nm (Maher *et al.*, 2014; Zhang *et al.*, 2013), it is also called miniemulsions, ultrafine emulsions or submicron emulsions (Abbas *et al.*, 2014). The term nanoemulsion is preferred because in addition to give

an idea of nanometer size range of the droplets it is concise and avoids misinterpretation with the term microemulsion. Due to their characteristics size, nanoemulsions appear transparent or translucent to the naked eye and possess stability against sedimentation or creaming. These properties make nanoemulsions of interest for fundamental studies and for practical applications (Jaworska *et al.*, 2014).

Most of the medicinal agents are originated from nature and considered as a rich source for producing drugs including modern drugs. Various types of medicines have been created since plants contain diverse range of bioactive molecules (Kang *et al.*, 2013; Marwan *et al.*, 2013). In pharmaceutical industry, more than 50% of the modern clinical drugs consist of active ingredients which are originated from natural products or synthesized based on clinically approved natural ingredients. The limited ability of synthetic pharmaceutical products in controlling diseases increase the demands of finding new molecular structure from natural origin and enhance interest in herbal medicines. Herbal medicines are acknowledged by national health care institutions and public because of safety and economic issues (Liu *et al.*, 2000; Kang *et al.*, 2013).

Inflammatory diseases are one of the most major health problems (Li *et al.*, 2003). The response of living tissues to an injury is called inflammation. Scientific researches have been focused on inflammation because of its inference with almost all human and animal diseases (Dharmasiri *et al.*, 2003; Tang *et al.*, 2012). Inflammation involves a complex group of enzyme activation, mediator release, extravasations of fluid, cell relocation, tissue breakdown and repair (Perianayagam *et al.*, 2006). Non-steroidal anti-inflammatory drugs (NSAIDs) are the main agents used in the treatment of inflammation. However, they have several adverse effects such as a gastric lesion which is caused by tolerance and dependence induced by opiates. Therefore, their use is not safe and suitable to treat all cases of inflammation (Dharmasiri *et al.*, 2003; Park *et al.*, 2004). Accordingly, researchers are still ongoing looking for safe new drugs or modified compounds of NSAIDs which have no adverse effect profile on the body (Kumara, 2001; Dharmasiri *et al.*, 2003).

Medicinal plants are believed to be an important source of new chemical compounds having potential therapeutic effects. According to the WHO records, about 80% of the world populations are still relying on herbal remedies (Kumara, 2001; Dharmasiri *et al.*, 2003; Li *et al.*, 2003). Accordingly, researchers attention have been oriented towards investigating efficacious plants used in the traditional medicine practice. These plants are cheap and may show better safety profile when compared with the synthetic medicines (Kang *et al.*, 2013).

1.2 Problem Statement

The major challenge in the pharmaceutical industry is to design the effective formulations for drugs. This is because the drug poor solubility or instability in the vehicle can lead or limit the drug efficacy. Low aqueous solubility of a large number of plant extracts and chemical entities will lead to poor dissolution in gastrointestinal tract. Poor aqueous solubility which exhibited in approximately 40% of the new chemical entities and plant extracts present a major challenge to the modern drug delivery system, Resulting in high intra- and inter-subject variability, poor oral bioavailability and lack of dose proportionality (Patel *et al.*, 2011).

Nanoemulsion drug delivery system is one of the most promising technologies, which known to increase water-soluble of poor water soluble drugs, improve the bioavailability and decrease the absorption variability of the drugs. Therefore, nanoemulsion is beneficial to the drugs having low therapeutic index. *In-vitro* as well as *In-vivo* studies of transdermal, dermal delivery properties and gastrointestinal absorption have been improved for nanoemulsion formulations, which is proved by many researchers (Date *et al.*, 2010; Villar *et al.*, 2012). Such properties increase the importance of this system for product innovation in many pharmaceutical and cosmetic companies.

It is the main concern of pharmaceutical industry to produce a drug delivery system that can deliver its carrying drug to the extent of maximum to achieve maximal drug therapeutic benefit, as well as to reduce drug's side effect (Ahmed *et al.*, 2012; Anandharamakrishnan, 2014). This can improve the effectiveness, the safety and the ease of administration of drug which will indirectly improve patient compliance. Therefore, it is important to formulate drug delivery system that can increase the delivery of the right quantity of drug to the right site of action within the right time to achieve therapeutic benefit of it.

Recently, in order to improve oral bioavailability of lipophilic drugs many attentions have been focused on lipid based formulations. In fact, to improve drugs bioavailability, the drug was incorporated into inert lipid vehicles such as oils,

surfactant dispersion, liposome, microemulsion, nanoemulsion were the most popular approach (Wang *et al.*, 2009).

In this study we hope to develop and optimize Self-nanoemulsifying formulations and nanoemulgel which contain *Swietenia* oil as well as study of the anti-inflammatory activity of the oil and formulations also conducting acute and sub-acute toxicity study. This study is an important tool for the development of drug delivery system which can contribute to better pharmaceutical products in the future.

1.3 Objectives of the Research

The principle aim of this work was to develop and evaluate internal and external nanoemulsion formulations of *Swietenia* oil that would improve the oral bioavailability and the penetration through the skin, also to study the toxicity and anti-inflammatory effect of *Swietenia* oil.

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

1. To apply and evaluate self-nanoemulsifying technology in the formulation and production of *Swietenia* oil nanoemulsion.
2. To prepare and evaluate nanoemulgel formulations containing *Swietenia* oil.
3. To study the acute and sub-acute toxicity of *Swietenia* oil.
4. To study the anti-inflammatory activity of *Swietenia* oil for oral and topical preparations.

1.4 Research Hypothesis

Self-nanoemulsifying system and nanoemulgel having nano-droplets size will provides a large interfacial surface area for drug absorption. The decrease in droplets size will help in improving the anti-inflammatory activity of *Swietenia* oil. This system will provide a promising approach to effectively tackle the problem of poorly soluble materials.

1.5 Scope of the Research

This study will be focusing on four major scopes in order to achieve the objectives of this research. The scopes of the research are:

1. Preparation and evaluation of internal nanoemulsion formulation containing *Swietenia* oil using different types of surfactants which can achieve the nano-size formulations. Self-nanoemulsifying system will be considered to achieve the nanoemulsion.

2. Preparation and evaluation of external nanoemulsion formulations containing *Swietenia* oil using different types of sucrose monoester as surfactants. In order to achieve the nano-size formulations nanoemulgel system was used.

3. Anti-inflammatory activity of *Swietenia* oil and its self-nanoemulsifying system and nanoemulgel formulations will be evaluated. Carrageenan anti-inflammatory module will be used to fulfill this objective.

4. Acute and sub-acute toxicity of *Swietenia* oil formulations will be studied. Rats will used to fulfill this objective.

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