
**UNIVERSITI PUTRA MALAYSIA**

***FORMATION OF PALM KERNEL OIL ESTERS NANOEMULSION SYSTEMS CONTAINING IBUPROFEN FOR TOPICAL DELIVERY***

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# FORMATION OF PALM KERNEL OIL ESTERS NANOEMULSION SYSTEMS CONTAINING IBUPROFEN FOR TOPICAL DELIVERY

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**DOCTOR OF PHILOSOPHY**
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# FORMATION OF PALM KERNEL OIL ESTERS NANOEMULSION SYSTEMS CONTAINING IBUPROFEN FOR TOPICAL DELIVERY

**By**

**NORAZLINALIZA BINTI SALIM**

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

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**July 2013**

**Chair : Professor Mahiran Basri, PhD**

**Faculty: Science**

The formation of palm kernel oil esters (PKOE) nanoemulsions containing ibuprofen as a model drug, suitable for topical delivery was studied in oil/non-ionic surfactant/water system. Initially, several ternary phase diagrams with different non-ionic surfactants and with/without ibuprofen were constructed. From these ternary phase diagrams, PKOE/Cremophor EL/water and PKOE/Tween 80/water systems, which exhibited large isotropic region were selected for nanoemulsion preparation. Nanoemulsions with 2% ibuprofen, 18% of oil phase (oil and surfactant) and 80% of water were prepared by using low energy emulsification method. Six formulations were studied; CEL1, CEL2 and CEL3 from the PKOE/Cremophor EL/water system and T801, T802 and T803 from the PKOE/Tween 80/water system with different oil:surfactant ratios (10:90, 20:80 and 30:70, respectively).

All formulations were characterized. The smallest droplet size was obtained at oil:surfactant ratio of 20:80 for CEL2 and T802 (20.48 nm and 16.52 nm, respectively). The largest droplet size was obtained at oil:surfactant ratio of 10:90 for CEL1 and T801 (32.87 nm and 84.51 nm, respectively). The polydispersity index indicated that formulations CEL2 and T802 had a narrow size distribution (<0.2) when compared to other samples (CEL1, CEL3, T801 and T803). The zeta potentials were between -1 and -19 mV, pH ranged from 3.53 to 3.93, the refractive index values were 1.347 to 1.361 and their viscosity values were between 3.00 and 5.00 cP for all the formulations.

In the rheological study, the flow characteristics of the nanoemulsions with and without ibuprofen were investigated. Shear thinning increased in the nanoemulsions after the addition of 2% of ibuprofen, which exhibited apparent plastic behaviour. The viscosity decreased with increase in shear rate and reached a constant value at high shear rates for all the formulations containing ibuprofen. No significant differences were observed in the flow characteristics when the ratio of oil:surfactant increased. The spherical shape of the nanoemulsions was confirmed by Transmission Electron Microscopy (TEM) analysis. The mean droplet size ranged between 16 to 20 nm and revealed a good size distribution. For the 6-month stability studies, samples CEL2, CEL3, T802 and T803 were found to be stable with respect to homogeneity after centrifugation and storage at temperatures 4°C and 25°C, but unstable at 45°C.

Due to the high kinetic stability of CEL2 and T802, their modification using different hydrocolloids (gellan gum, carrageenan and xanthan gum) namely T802G, CEL2G, T802C, CEL2C, T802X and CEL2X were investigated. No significant changes were observed in droplet size (~16-20 nm) but there was a significant difference in polydispersity indexes, zeta potentials, pH and their rheology after modification. For the 6-month study period, samples T802G, CEL2G, T802X and CEL2X were found to be stable, with no phase separation observed after centrifugation and storage at temperature 4°C and 25°C and unstable at 45°C. However T802C and CEL2C only stable when it stored at 4°C.

The permeation of ibuprofen from PKOE nanoemulsions through a cellulose acetate membrane was studied using Franz diffusion cells. It was found that the permeation of ibuprofen from CEL2 (303.05 $\mu g.cm^{-2}.h^{-1}$, with the permeability coefficient ($K_p$) value of 0.170 cm/h) ($p<0.05$) was 1.78 times higher than T802 (254.94 $\mu g.cm^{-2}.h^{-1}$, $K_p$ 0.140 cm/h). The addition of different hydrocolloids into CEL2 showed that carrageenan gave highest permeation of ibuprofen (79.2% release) at 8 h. However, when different penetration enhancers (terpenes) were added to CEL2, the permeation of ibuprofen through cellulose acetate membrane was hindered, decreasing to 22.3%. No significant differences ($p>0.05$) was observed when menthol, camphor and limonene were used as penetration enhancer.

The ability of the nanoemulsions before (T802 and CEL2) and after modification (T802G and CEL2G) to deliver ibuprofen through Wistar rat skin were evaluated in-vitro using Franz diffusion cells. The in-vitro permeation data showed that the sample T802G (49.32 ± 4.88 μg .$cm^{-2}h^{-1}$, $K_p$ 55.4 × $10^{-3}$ cm/h) increased the permeability of ibuprofen ($p<0.05$) 4.40 times over the sample T802 (25.25 ± 5.87 $\mu g.cm^{-2}h^{-1}$, $K_p$ 12.6 × $10^{-3}$ cm/h). The percentage of ibuprofen released versus time from T802G was slightly greater than T802 up until 24h of the study. While, CEL2G (49.32 ± 4.88 $\mu g.cm^{-2}h^{-1}$, $K_p$ 18.2 × $10^{-3}$ cm/h) decreased the permeability of ibuprofen when compared to the initial nanoemulsion, CEL2 (56.90 ± 17.90 $\mu g.cm^{-2}h^{-1}$, Kp 31.6× $10^{-3}$ cm/h). No significant differences were observed in percentage of release but there was a significant difference in permeability of ibuprofen up to 8h of the study.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**PEMBENTUKAN SISTEM NANOEMULSI BERASASKAN MINYAK ESTER ISIRONG KELAPA SAWIT YANG MENGANDUNGI IBUPROFEN BAGI PENGHANTARAN SECARA TOPIKAL**

Oleh

**NORAZLINALIZA BINTI SALIM**

**Julai 2013**

**Pengerusi: Profesor Mahiran Basri, PhD**

**Fakulti : Sains**

Pembentukan nanoemulsi berasaskan minyak ester isirong kelapa sawit (PKOE) yang mengandungi ibuprofen sebagai model drug, sesuai bagi penghantaran topikal telah dikaji dalam sistem minyak/surfaktan tanpa ion/air. Pada mulanya, beberapa gambarajah fasa ternari dengan surfaktan tanpa ion berbeza dengan/tanpa mengandungi ibuprofen telah dibina. Daripada gambarajah fasa ternari tersebut, sistem PKOE/Kremofor EL/air dan PKOE/Tween 80/air yang mempunyai rantau isotropi terbesar telah dipilih bagi penyediaan nanoemulsi. Nanoemulsi yang mengandungi 2% ibuprofen, 18% fasa minyak (PKOE dan surfaktan) dan 80% air telah disediakan dengan menggunakan kaedah pengemulsian tenaga rendah. Enam formulasi telah dikaji; CEL1, CEL2 dan CEL3 dari sistem PKOE/Kremofor EL/air dan T801, T802 dan T803 dari sistem PKOE/Twin 80/air dengan nisbah minyak:surfaktan yang berbeza (masing-masing 10:90, 20:80 dan 30:70).

Semua formulasi telah dicirikan. Titisan saiz terkecil telah diperolehi pada nisbah minyak:surfaktan 20:80 bagi sampel CEL2 dan T802 (masing-masing 20.48 nm dan 16.52 nm). Saiz titisan terbesar diperolehi pada nisbah minyak:surfaktan 10:90 bagi sampel CEL1 dan T801 (masing-masing 32.87 nm dan 84.51 nm). Indeks penyerakkan menunjukkan bahawa formulasi CEL2 dan T802 mempunyai saiz taburan yang sempit (<0.2) apabila dibandingkan dengan sampel-sampel lain (CEL1, CEL3, T801 dan T803). Potensi zeta adalah di antara -1 mV dan -19 mV, pH antara 3.53-3.93 dan nilai indeks biasan 1.347-1.361 serta kelikatan di antara 3.00 dan 5.00 cP bagi semua formulasi.

Dalam kajian reologi, ciri-ciri aliran untuk nanoemulsi dengan dan tanpa ibuprofen telah dikaji. Penipisan ricih meningkat dalam nanoemulsi selepas penambahan 2% ibuprofen, di mana ia mempamerkan kelakuan plastik. Kelikatan menurun dengan peningkatan kadar ricih dan mencapai nilai malar pada kadar ricih yang tinggi bagi semua formulasi yang mengandungi ibuprofen. Tiada perbezaan yang ketara dapat diperhatikan terhadap ciri-ciri aliran apabila nisbah minyak:surfaktan meningkat. Bentuk sfera daripada nanoemulsi telah disahkan oleh analisis Mikroskopi Transmisi Elektron (TEM). Saiz titisan min adalah di antara 16-20 nm dan menunjukkan taburan saiz yang baik. Bagi 6 bulan kajian kestabilan, sampel CEL2, CEL3, T802 dan T803 didapati stabil semasa proses pengemparan dan penyimpanan pada suhu 4°C dan 25°C dan tidak stabil pada suhu 45°C.

Disebabkan kestabilan kinetik sampel CEL2 dan T802 yang tinggi, pengubahsuaian nanoemulsi menggunakan hidrokoloid berbeza (gam *Gellan*, karagenan dan xanthan) yang dinamakan T802G, CEL2G, T802C, CEL2C, T802X dan CEL2X telah dikaji. Tiada perubahan ketara dapat diperhatikan terhadap saiz titisan (~ 16-20 nm) tetapi terdapat perbezaan yang ketara dalam indeks polidispersiti, potensi zeta, pH dan reologi selepas pengubahsuaian. Bagi tempoh 6 bulan kajian kestabilan, sampel T802G, CEL2G, T802X dan CEL2X didapati stabil di mana tiada pemisahan fasa dapat di lihat selepas proses pengemparan dan penyimpanan pada suhu 4°C dan 25°C dan tidak stabil pada suhu 45°C. Tetapi T802C and CEL2C hanya didapati stabil apabila ia disimpan pada suhu 4°C.

Penyerapan ibuprofen daripada nanoemulsi berasaskan PKOE melalui membran selulosa asetat telah dikaji menggunakan sel difusi Franz. Di dapati bahawa penyerapan ibuprofen daripada formulasi CEL2 (303.05 $\mu g.cm^{-2}.h^{-1}$ dengan nilai pekali kebolehtelapan ($K_p$) adalah 0.170 cm/h) ($p < 0.05$) adalah sebanyak 1.78 lebih tinggi daripada formulasi T802 (254.94 $\mu g.cm^{-2}.h^{-1}$ dengan nilai $K_p$ 0.140 cm/h). Penambahan pelbagai hidrokoloid ke atas formulasi CEL2 menunjukkan bahawa karagenan memberikan penyerapan ibuprofen tertinggi (79.2%) pada 8 jam kajian. Walau bagaimanapun apabila pelbagai terpena ditambah kepada formulasi CEL2, penyerapan ibuprofen melalui membran selulosa asetat terhalang, menjadikan ia penyerapan menurun kepada 22.3%. Tiada perbezaan yang signifikan ($p > 0.05$) dipehatikan apabila menthol, kamfor dan limonena digunakan sebagai peningkat penembusan.

Keupayaan nanoemulsi sebelum (T802 dan CEL2) dan selepas pengubahsuaian (T802G dan CEL2G) bagi penghantaran ibuprofen melalui kulit tikus *Wistar* juga dinilai secara in-vitro menggunakan sel difusi *Franz*. Data penyerapan in-vitro menunjukkan bahawa kebolehtelapan sampel T802G (49.32 ± 4.88 μg .$cm^{-2}h^{-1}$, $K_p$ 55.4 × $10^{-3}$ cm/h) meningkat ($p < 0.05$) 4.40 kali lebih tinggi berbanding sampel T802 (25.25 ± 5.87 μg.$cm^{-2}h^{-1}$, $K_p$ 12.6 × $10^{-3}$ cm/h). Peratusan ibuprofen terlepas daripada T802G terhadap masa adalah lebih tinggi berbanding T802 sehingga 24 jam kajian. Manakala, kebolehtelapan ibuprofen daripada CEL2G (49.32 ± 4.88 μg.$cm^{-2}h^{-1}$, $K_p$ 18.2 × $10^{-3}$ cm/h) menurun jika dibandingkan dengan CEL2 (56.90 ± 17.90 μg.$cm^{-2}h^{-1}$, $K_p$ 31.6× $10^{-3}$ cm/h). Tiada perbezaan yang signifikan diperhatikan dalam peratus lepasan tetapi terdapat perbezaan yang signifikan dalam kebolehtelapan ibuprofen sehingga 8 jam kajian.

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I certify that an examination committee met on 9 July 2013 to conduct the final examination of Norazlinaliza binti Salim on her Doctor of Philosophy thesis entitled "Formation Of Palm Kernel Oil Esters Nanoemulsion Systems Containing Ibuprofen For Topical Delivery" in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Examination Committee are as follows:

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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## DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently submitted for any other degree at Universiti Putra Malaysia or at any other institution.

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**NORAZLINALIZA BINTI SALIM**

Date: 9 JULY 2013

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| | |
|---|---|
| ANOVA | Analysis of variance |
| AUC | Area under the plasma–time curve value |
| CEL | Cremophor EL |
| CG | Carrageenan gum |
| $C_{max}$ | Maximum concentration |
| CMC | Carboxymethyl cellulose |
| cP | Centipoise |
| GG | Gellan gum |
| HLB | Hydrophilic-Lipophilic Balance |
| IPM | Isopropyl Myristate |
| kDa | Kilo Dalton |
| $K_p$ | Permeability coefficient |
| $L_1$ | Isotropic liquid region |
| $L_c$ | Liquid crystalline region |
| M | Multilayer region |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| O/W | Oil-in-Water |
| O:W | Oil:water Ratio |
| O:S | Oil:Surfactant ratio |
| P | Partition coefficient |

| | |
|---|---|
| Pa | Pascal |
| Pa.s | Pascal second |
| PBS | Phosphate buffer solution |
| PIC | Phase inversion composition |
| PIT | Phase inversion temperature |
| $pK_a$ | Logarithm of the acid dissociation constant |
| PKOE | Palm kernel oil esters |
| PTA | Phosphotungstic acid |
| rpm | Revolution per minute |
| SD | Standard deviation |
| $t_{1/2}$ | Half-life |
| T80 | Tween 80 |
| TEM | Transmission Electron Microscopy |
| $T_{max}$ | Time maximum |
| UV | Ultraviolet |
| w/w | Weight per weight |
| Wt % | Weight percent |
| XG | Xanthan gum |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of Research

Non-steroidal anti-inflammatory drugs (NSAIDs) have prominent antipyretic, anti-inflammatory and analgesic properties. Ibuprofen is an NSAID that is commonly used to reduce pain, stiffness, and inflammation condition and it has fewer side effects than other NSAIDs. It is effective for the treatment of osteoarthritis (Altman, 1984) and rheumatoid arthritis (Ward, 1984). Ibuprofen is a white powder or crystal, which is practically insoluble in water. Due to their low solubilities in water, these drugs have a correspondingly low degree of bioavailability. Ibuprofen has been formulated into many topical preparations in order to reduce adverse side effects associated with the hepatic first-pass metabolism. However it is difficult to maintain effective concentrations by topical delivery of ibuprofen due to its poor skin permeation ability. In order to enhance the permeation of ibuprofen, many formulations such as emulsions (Perumal, 2001) and gels (Rhee *et al*., 2008), have been explored.

Emulsions are defined as homogeneous mixtures of oil and water phases stabilized by the presence of surfactant. Emulsions which are an effective approach to many of the problems in drug delivery, often show distinct advantages over other dosage forms by way of improved bioavailability and reduced side effects. In emulsions, the drug can be solubilized in the dispersed lipophilic phase of oil-in-water (O/W)

emulsion and the surfactant in the system may act to reduce the diffusional barrier of the stratum corneum by acting as permeation enhancers (Delgado-Charro *et al*., 1997).

Nanoemulsions are isotropic, transparent (or translucent) systems consisting of oil, surfactant, and water having a droplet size of less than 100 nm (Solans *et al*., 2005). Low viscosity, high kinetic stability against creaming or sedimentation, and large interfacial area make nanoemulsions of increasing use in different applications (Tadros *et al*., 2004). In the pharmaceutical field, nanoemulsions have been increasingly developed for use as drug delivery systems for parenteral (Kelmann *et al*., 2007), oral (Ganta *et al*., 2010), ocular (Hagigit *et al*., 2012), and topical administration (Shrestha *al*., 2012). Specifically, in the case of topical delivery, nanoemulsions offer several significant advantages including powerful permeation ability, no skin irritation, and high drug-loading capacity (Mason *et al*., 2006).

Palm kernel oil esters (PKOE) are produced from the alcoholysis of triglycerides (consisting of glycerol and different fatty acids) from palm kernel oil through enzymatic transesterification process with oleyl alcohol using Lipozyme RM IM as a catalyst (Keng *et al*., 2009). PKOE is rich in oleyl laurate, C30:1 (54.1%), and it can be used as an oil phase due to its unique property of exhibiting excellent wetting behaviour without the oily feeling. PKOE has low viscosity and is colourless, which are desirable properties as ingredient in pharmaceutical products.

## 1.2 Problem Statements

As in literature, oral therapy of NSAIDs is very effective, but the clinical use is often limited because of their potential to cause adverse effects such as irritation and ulceration of the gastro-intestinal (GI) mucosa (Beetge *et al*., 2000). To reduce such effects, it would clearly be preferable to administer NSAIDs topically. The advantages of topically-applied pharmaceutical agents compared to oral drug administration are reduction in first pass metabolism by the liver, avoidance of the gastric route, improved owner compliance with drug administration, non-invasiveness and reducing the potential for both degradation of the drug and gastric irritation (Magnusson *et al*., 2001).

The major problem encountered by NSAIDs administered topically is that they are poorly water soluble drugs with log P around 3 and have a high molecular weight between 200 and 500 (Beetge *et al*., 2000). Poor skin permeability of NSAIDs by transdermal delivery will cause difficulties in maintaining effective blood concentrations of drug because they would form reservoirs in the stratum corneum and be exposed to enzymatic breakdown thus, reducing total bioavailability of the drug (Kawakami *et al*., 2002).

## 1.3 Scope of Study

This study focuses on the development of palm-based nanoemulsion as a carrier system of ibuprofen for topical delivery, whereby palm kernel oil esters (PKOE) was used as an oil phase. The phase behaviour of PKOE containing ibuprofen in the ternary phase diagram with different surfactants was first studied. The system with

the largest of isotropic liquid region was selected for the preparation of nanoemulsion. The nanoemulsion was prepared by low energy emulsification method and subsequently characterized with respect to different physicochemical properties. In vitro drug permeations of ibuprofen from nanoemulsions through cellulose acetate membrane and Wistar rat skin were also evaluated.

## 1.4 Objectives

The objectives of this research are:

1. To determine the phase behaviour of palm kernel oil esters (PKOE) system with and without ibuprofen by constructing the ternary phase diagrams.
2. To prepare the formulation of the PKOE nanoemulsions containing ibuprofen using low energy emulsification method and modify the formulations with different hydrocolloid gums (gellan gum, carrageenan gum, xanthan gum, carbopol 940 and carboxymethyl cellulose).
3. To characterize the physicochemical properties of the nanoemulsion containing ibuprofen before and after modification.
4. To determine the permeation of ibuprofen from PKOE nanoemulsion systems through cellulose acetate membrane and through Wistar rat skin.

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