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Phase Behaviour, Formation and Characterization of Palm-Based Esters Nanoemulsion Formulation containing Ibuprofen

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Abstract

Palm-based esters, synthesized through enzymatic transesterification of palm oil fractions with oleyl alcohol have potential application in pharmaceutical formulations. The phase behaviour of palm-based esters containing ibuprofen with surfactant of different HLB values was investigated for topical delivery system. The surfactants were Tween 85, Tween 60 and Tween 80, and the palm-based esters were palm oil esters (POEs) and palm kernel oil esters (PKOEs). Ternary phase diagrams of palm-based esters: Ibuprofen/surfactant/water systems were constructed. Three distinct regions were observed in the phase diagrams; isotropic liquid region, L_1, liquid crystalline region, L_c and multiphase region, M. Nanoemulsions were prepared spontaneously by the addition of water to oil:ibuprofen/surfactant mixtures based on the ternary phase diagrams constructed. Formulations from the PKOEs:Ibuprofen/Tween 80/water systems were selected due to the presence of large isotropic liquid region, which suggested that this region was suitable to be used in producing nanoemulsions. Particle size analysis showed that the mean particle sizes of these formulations ranged from 10 nm to 70 nm. Zeta potential analysis for all formulations showed negative values from -4 to -8 mV. Stability studies showed that, after 4 h of stirring at room temperature (25°C), the formulations were stable under centrifugation test at 4000 rpm for 15 min. Stability under different storage temperature showed that at 25°C, the four formulations, F1, F2, F3 and F4 were stable with no phase separation for the duration of 1 month. However, when these formulations were stored at 45°C and 4°C, respectively, only F3 and F4 were observed to be stable. These two formulations have the potential to be used for topical delivery of ibuprofen.

Keywords: Palm oil esters; Palm kernel oil esters; Topical delivery; Ibuprofen; NSAIDs

Introduction

The term 'nanoemulsions' has been widely used to describe the complex systems consisting of oil phase, surfactant and water, which are optically isotropic and kinetically stable colloidal solution with droplet size in the range of 20-200 nm [1]. Currently, nanoemulsions are becoming the subject of many studies due to their wide range of particle sizes in nanoscale, and this has contributed to more branches of potential uses and applications [2]. The nanoemulsion particles have given them the characteristic property of being easily absorbed by the skin which is sought after in the pharmaceutical industry.

Many initial pharmaceutical studies in the formation of nanoemulsions dealt with ternary phase diagrams studies. The ternary phase diagrams of several water–surfactant–oil mixtures have exhibited a variety of complex phases. In the single phase of isotropic region, the full determination of the phase boundaries requires many replicates experimental measurements due to the continuity among pure micellar solutions, swollen micelles, microemulsions and nanoemulsions [3-5]. In practice, nanoemulsion systems containing oil phase, surfactant and water are optically clear to the eye and have been identified as the 'isotropic liquid region', L_1 [6].

Palm oil esters (POEs) and palm kernel oil esters (PKOEs) are palm-based esters, which were synthesized from palm oil and palm kernel oil through the enzymatic process of transesterification [6]. POEs are rich with oleyl palmitate, C34:1 (42.1%) and oleyl oleate, C36:2 (31.7%), while PKOEs are rich with oleyl laurate, C30:1 (54.1%) [7]. The palm-based esters can be used as an oil phase due to its unique property of having excellent wetting behaviour without the oily feeling [8,9]. Palm kernel oil esters have lower viscosity and are colourless which have good properties in cosmetic and pharmaceutical products. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), which is often used for long-term treatment of rheumatoid arthritis, osteoarthritis and gout [10,11]. Oral therapy of ibuprofen can cause gastric mucosal damage, which may result in ulceration and bleeding [12-14], so transdermal therapy application can be an alternative route.

There are many methods available from low to high energy emulsification methods for the formation of nanoemulsions [15,16]. Spontaneous emulsification is a low energy method [17,18], whereby nanoemulsions with the particle size ranged from 100 to 600 nm could be obtained. The spontaneity of this emulsification process is dependent on three parameters, oil viscosity, surfactant HLB and solvent miscibility in water [17]. In this study, nanoemulsion system using palm-based esters containing a poorly water-soluble drug, ibuprofen, having compositions obtained from the ternary phase diagrams was developed via the spontaneous emulsification method and were then characterized.

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Materials and Methods

Palm-based esters of POEs and PKOEs were prepared in our laboratory using the method of Gunawan et al. [9]. Fatty acids composition in POEs are 0.4% oleyl laurate (C30:1), 2.6% oleyl myristate (C32:1), 42.1% oleyl palmitate (C34:1), 5.3% oleyl stearate (C36.1), 31.7% oleyl oleate (C36:2) and 10.2% oleyl linoleate (C36:3). Fatty acids composition in PKOEs are 0.5% oleyl caproate (C24:1), 5.6% oleyl caprate (C26:1), 5.9% oleyl caprylate (C28:1), 54.1% oleyl laurate (C30:1), 13.9% oleyl myristate (C32:1), 6.2% oleyl palmitate (C34:1), 1.2% oleyl stearate (C36.1), 6.4% oleyl oleate (C36:2) and 1.7% oleyl linoleate (C36:3). Ibuprofen [2-(4-isobutylphenyl)-propionic acid], 99.8% was purchased from Eurochem (China). The non-ionic surfactants, Tween 85 (polyoxyethylene (20) sorbitan trioleate), Tween 60 (polyoxyethylene (20) sorbitan monostearate) and Tween 80 (polyoxyethylene (20) sorbitan monooleate) were purchased from Merck (Germany). Deionized water was used.

Construction of phase diagram

Ibuprofen (8.0 g, 9wt.%) was added into 50 ml of PKOEs. The mixture was stirred until homogenization using magnetic stirrer for 1 h, at room temperature (25 ± 0.5°C). The oil phase (PKOEs and Ibuprofen) and Tween 80 were weighed at various weight ratios ranging from 0:100 to 100:0. Then, the mixture with a total weight of 0.5 g was placed into a 10 ml screw-cap glass tube (total 11 tubes), and was vortexed using a vortex mixer (VM-300, Gemmy Industrial CORP-Taiwan). Water (5 wt.%) was then added each time into the samples and were vortexed for 5 min. The samples were then centrifuged at 4000 rpm for 15 min and observed using polarized light. The steps were repeated with addition of 10, 20, 30, 40, until 90 wt.% of water was added. Ternary phase diagrams were constructed by using the Chemix School v3.50 software (Arne Standnes, Norway). The experiment was repeated using different surfactants (Tween 60 and Tween 80) and oil phase (POEs).

Selection and preparation of nanoemulsions loaded ibuprofen

A ternary phase diagram, which exhibited a large L_1 region, was selected for the preparation of nanoemulsion formulation. Table 1 shows the composition of the selected formulations. These formulations were prepared through spontaneous emulsification method where water was added dropwise into a beaker containing the surfactant-oil-ibuprofen mixture, using a stirrer (RW16 basic, IKA-Werke, Germany). The mixture was stirred at 300 rpm for 4 h at 25°C.

Characterization of the selected formulations

Particle size: The mean particle size of the prepared nanoemulsions was measured at 25°C by a high performance particle sizer (HPPS) from Malvern Instrument (UK) equipped with a Ne–He laser. For the measurement, the samples were diluted with deionized water (1µL/10mL).

Formulations	Composition (wt. %)			
	Oil	Ibuprofen	Tween 80	Water
F1	4.55	0.45	45	50
F2	4.55	0.45	40	55
F3	4.55	0.45	35	60
F4	4.55	0.45	30	65
F5	4.55	0.45	25	70
F6	4.55	0.45	20	75

*Nanoemulsions were produced by addition of water into the mixture of oil/ibuprofen/Tween 80

Table 1: Composition of palm-based esters nanoemulsion formulations prepared by spontaneous emulsification method.

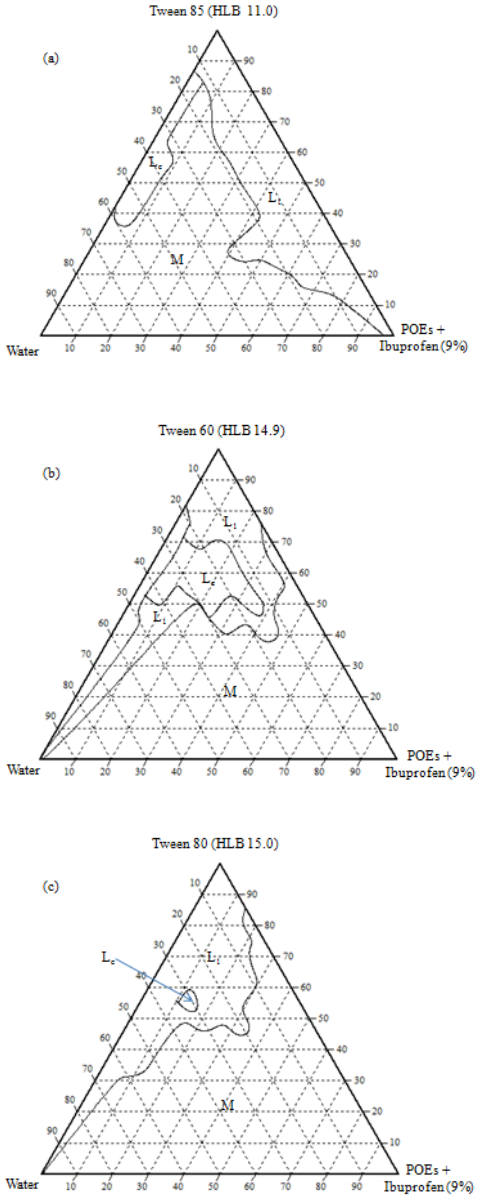

Figure1: (a-c) Phase diagrams of POEs systems containing ibuprofen at 25±1°C; where L_1 = isotropic liquid region, L_c = Liquid crystalline region and M = Multiphase region.

Zeta potential: The nanoemulsion formulations were diluted with deionized water (1µL/10mL) and were injected into the sample cell. Zeta potential was determined by measuring the electrophoretic mobility of the dispersed particles in a charged field. Measurements were carried out at their sample P^H, at 25°C with Zetasizer Nano Series from Malvern Instrument, UK. The zeta potential of each individual sample was calculated from the average of three measurements.

Stability study: Nanoemulsions are kinetically stable systems and are formed from a particular concentration of oil phase, surfactant and water, with no phase separation, creaming or coalescence at room temperature. All the selected formulations underwent a centrifugation

test at 4000 rpm for 15 min once after the preparation. The samples which did not show phase separation after the centrifugation test were kept for stability test under different storage temperature (4, 25 and 45°C).

Morphology

The morphology of the particles in the nanoemulsion formulations was visualized with the Transmission Electron Microscope (TEM). The samples were dropped to a 200 mesh formvar-coated copper grids and were negatively stained with 50µl of 2% (w/v) phosphotungstic acid (PTA) for 5 min, at room temperature. Excess liquid was removed with a piece of Whatman filter paper and dried at room temperature. The samples were observed with Hitachi H-7100 Transmission Electron Microscope (Japan). The acquired digital images were processed with Adobe Photoshop® software.

Results and Discussion

Phase behaviour analysis

Figure 1 and Figure 2 shows the ternary phase diagrams system of POEs: ibuprofen/ surfactant/water and PKOEs: ibuprofen/surfactant/water with increasing HLB values of the surfactant, respectively. The phases observed were: Isotropic liquid phase (L_1), liquid crystalline phase (L_c) and multiphase region (M).

Figure 1 shows the phase diagram of POEs system containing ibuprofen at different non-ionic surfactant (Tween 85, Tween 60 and Tween 80) with increasing values of HLB (11.0, 14.9 and 15.0), respectively. Result from Figure 1(a) (Tween 85, HLB 11.0) showed that when Tween 85 was used, large amount of water (32 wt.%) could be solubilized until up to 25 wt.% of Tween 85. As the concentration of Tween 85 was increased, solubilization of water was decreased. The HLB value of 11.0 could be the reason for the formation of large L_1 region, which extended from the surfactant vertex towards the oil vertex, where they likely to be formed towards the oil rich apex. L_c region was found towards water-rich apex and Tween 85 rich apex. The maximum amount of oil that could be solubilized was 9 wt.% by using 55 wt.% of Tween 85.

Results from Figure 1(b) (Tween 60, HLB 14.9) showed that the formation of L_1 region was found towards the water rich apex of the phase diagram. The maximum amount of oil that could be solubilized in the phase diagram was 45 wt.% at a high concentration of Tween 60 (39 wt.%). Large L_c region was found in the phase diagram which overlapped with L_1 region and the maximum amount of oil that could be solubilized was 40 wt.% using 45wt.% of Tween 60. When the HLB of the surfactant was further increased to 15.0 (Tween 80) (Figure 1(c)), the L_1 and L_c regions were decreased as compared to when Tween 60 (Figure 1(b)) was used. The maximum concentration of oil solubilized was 30 wt.% at a high concentration of Tween 80 (45 wt.%).

Figure 2 shows the phase diagram of PKOEs system containing ibuprofen at different non-ionic surfactant (Tween 85, Tween 60 and Tween 80) with increasing values of HLB (11.0, 14.9 and 15.0), respectively. Figure 2(a) (Tween 85, HLB 11.0) shows that a large amount of water (50 wt.%) could be solubilized in L_1 region using 30 wt.% of Tween 85 at oil rich apex. The L_c region was found towards the water rich apex and Tween 85 rich apex and the maximum concentration of oil that could be solubilized was 9 wt.% using 50 wt.% of Tween 85.

Figure 2(b) (Tween 60, HLB 14.9) showed that the L_1 region in phase diagram increased towards the water rich apex. The L_c region was found to increase and the maximum amount of oil that could be solubilized was 55 wt.% at Tween 60 concentration of 30 wt.%. Figure 2(c) (Tween 80) showed that when the HLB value was further increased from 14.9 to 15.0, L_1 region further increased up to 58 wt.% concentration of oil, using 35 wt.% of Tween 80. The higher HLB value may lead to greater penetration of oil phase in the hydrophobic region of the surfactant monomers. This seemed to be due to the reduction of interfacial tension, which will increase the fluidity of the interface, thus increasing the entropy of the system [19,20].

Formation of nanoemulsions

From the phase diagrams constructed, the highest concentration of oil could be solubilized was selected for further study. The system containing Tween 80 (Figure 2(c)) was selected as it exhibited large

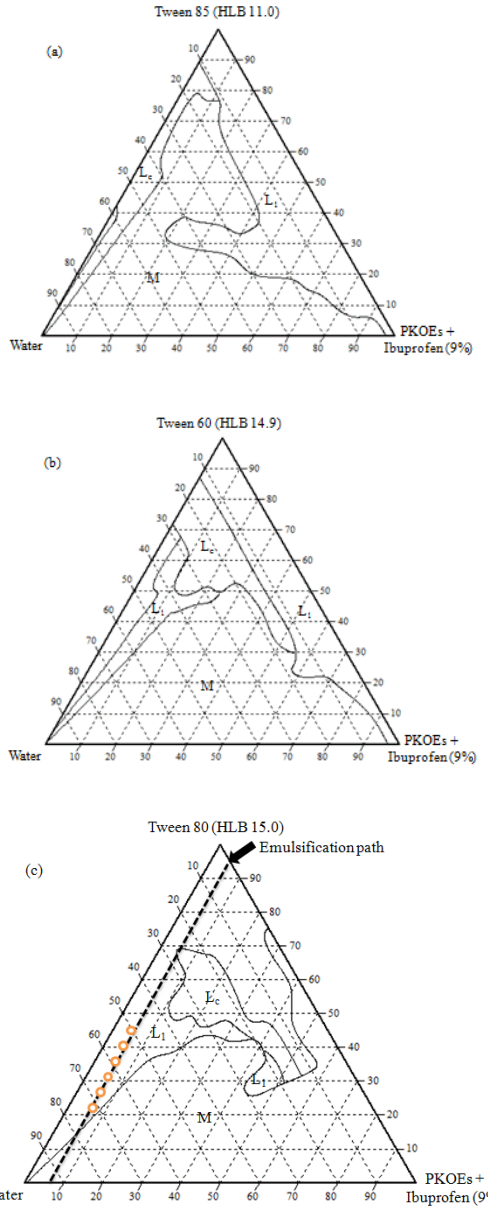

Figure 2: (a-c) Phase diagrams of the PKOEs systems containing ibuprofen at 25±1°C; where L_1 = isotropic liquid region, L_c = Liquid crystalline region and M = Multiphase region.

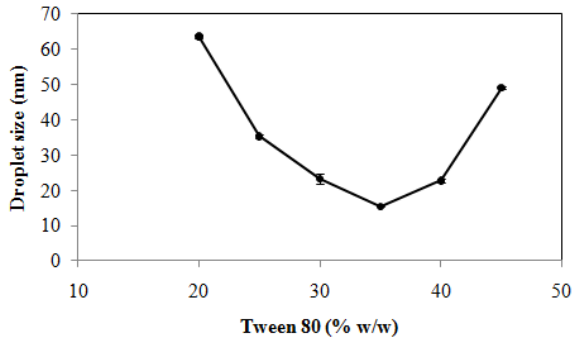

Figure 3: Average droplet size of nanoemulsions with increasing concentration of Tween 80 (nm±SD, n=3).

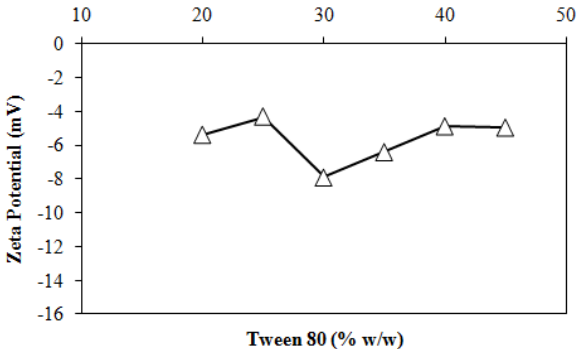

Figure 4: Zeta potential of nanoemulsions with increasing concentration of Tween 80 (mV±SD, n=3).

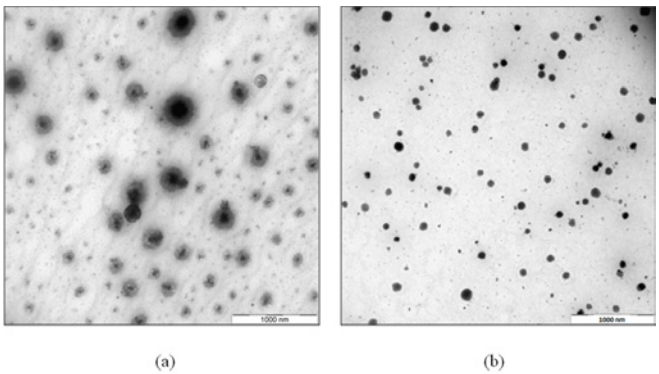

Figure 5: Transmission Electron Micrograph of (a) Oil containing Ibuprofen, and (b) Formulation F4 nanoemulsion at 25°C.

amount of oil that could be solubilized (up to 58 wt.%) using as low as 38 wt.% of surfactant. Therefore, from this phase diagram, six formulations at different concentration of oil in L_1 region, were selected (refer to the emulsification path in Figure 3(c)) for further study. The composition of the formulations is shown in Table 1.

Characterization of selected formulations

Droplet size and zeta potential analysis: Figure 3 shows the droplet size of the selected formulations as a function of Tween 80 concentration. Significant decrease in droplet size was observed with increase in Tween 80 up to 35 wt.%, which gave the smallest droplet size of 15.31nm. This observation could be explained as being the result of increase surfactant absorption around oil-water interface of a droplet, and decrease interfacial tension in the system, which favours the formation of nanoemulsions with smaller droplets [21].

When the concentration of Tween 80 was increased beyond 35 wt.%, an increase in droplet size was observed. This could be due to the formation of highly viscous formulation observed near to the formation of liquid crystalline phase in the phase diagram (Figure 2(c)). The appearance of liquid crystalline phase was reported to result in higher droplet size of nanoemulsions due to the high rigidity of the interface, which appeared to retard self-emulsification, where more energy was required to produce a fine dispersion [22,23]. Therefore, the droplet sizes of nanoemulsions increased with Tween 80 concentration above 35 wt.%.

Figure 4 shows the zeta potential values of the selected formulations at different concentration of Tween 80. The zeta potentials were in negative values between -4 to -8 mV. There is no significant difference for zeta potential values when the concentration of Tween 80 was increased. These values of <−25 mV indicated that low degree of physical stability was obtained. However, investigation by Roland et al. [24] revealed that the zeta potential values sometimes do not fit with the visual stability, where the most visually stable emulsions exhibit the lowest zeta potential absolute values. This means that the electrostatic stabilization is not the main mechanism for the stability of these formulations.

Stability study: Table 2 shows the stability of the selected formulations after centrifugation test and at different storage conditions for a month. All formulations were physically stable after being subjected to centrifugation test. Latreille and Paquin [25] reported that by using centrifugation test, the stability of the emulsion is directly proportional to the gravitational force, by observing the separation of the dispersed phase either by creaming or coalescence. When these formulations were stored at 4°C for a month, creaming was observed for formulations F1 and F2. Formulations; F3, F4, F5 and F6 were found to be stable. At 25°C, formulations F1, F2, F3 and F4 were found to be stable, but F5 and F6 were not. At 45°C, only F1, F3 and F4 were stable. The instability of formulations F1 and F4 in 4°C after a month could be due to the relatively higher composition of Tween 80 which had contributed to the higher viscosity of the formulation with low interfacial tension and thus easy formation of crystallization phase as reported in the case of formulations containing higher surfactants [23]. F5 and F6 were not stable when stored for a month at 25°C and 45°C due to the decreasing concentration of Tween 80 which lead to the lower viscosity of the formulation. This condition could affect the Brownian motion, low gravitational separation force, and thus creaming observed at high temperature [25].

Morphology

Figure 5(a-b) shows the TEM chromatogram of oil containing

Formulations	Centrifugation Test	Storage Condition (1 month)		
		4°C	25°C	45°C
F1	✓	×	✓	✓
F2	✓	×	✓	×
F3	✓	✓	✓	✓
F4	✓	✓	✓	✓
F5	✓	✓	×	×
F6	✓	✓	×	×

✓ No phase separation; × unstable system with phase separation or creaming.

Table 2: Stability of Palm-Based Esters Nanoemulsion Formulations.

ibuprofen and Formulation F4. Mixture of oil and ibuprofen exhibited irregular spherical shape (Figure 5(a)), where ibuprofen particles appeared in dark colour surrounded by oil particles. However, when nanoemulsion system, F4 was observed by TEM, the sphere became regular smaller droplets (Figure 5(b)), whereby the droplet size correlated well with the results obtained from droplet size analysis using HPPS (~25 nm).

Conclusions

Phase behaviour study of palm-based esters showed that the formation of isotropic liquid region, L_1 depended on the surfactant HLB value and oil viscosity. As the surfactant HLB value was increased, or the less viscous of the oil was used, larger L_1 region was formed. The ternary phase diagram system of PKOEs: ibuprofen/Tween 80/water exhibited large amount of oil solubilized (58wt.%) using 38wt.% of surfactant thus was used in the selection of the nanoemulsion system. The selected nanoemulsion exhibited droplet size between 10 nm to 70 nm. Formulations F3 and F4 were the most stable after being subjected to centrifugation test and different storage conditions. The droplets sizes of F4 observed by TEM correlated well with the results obtained from HPPS. The nanoemulsion formulation could be used for topical delivery of ibuprofen.

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