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Formulation and stability of Prasaplai microemulsions

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ABSTRACT

Prasaplai is a Thai herbal remedy used in obstetrics and gynecology. In this study, Prasaplai microemulsions (MEs) were developed for topical use, using two types of oil: isopropyl myristate (IPM) and tea tree oil, with polysorbate 80 and butanol as the surfactant and co-surfactant, respectively. The stability of Prasaplai MEs under accelerated conditions was studied. Prasaplai MEs from both oil types had a clear yellow color, with a diameter between 236 and 257 nm. The pH values of all ME were between 5.14 and 5.45, and the viscosities were between 19 and 26 centipoises, with Newtonian flow behavior. After storage under accelerated conditions, the tea tree oil-based MEs showed phase separation, whereas the IPM-based MEs were homogeneous. The size of the tea tree oil-based MEs increased, while pH decreased after storage. The decrease in pH indicated the presence of degradation products in the formulations. The IPM-based Prasaplai MEs reduced in size, and the pH value increased. The amount of remaining curcumin was 73.80% in the tea tree oil-based MEs and 92.20 % in the IPM-based MEs. In conclusion, oil types and ingredients in Prasaplai affects the stability of the MEs. IPM-based Prasaplai MEs might be better for use as topically applied remedies.

Keywords: Prasaplai; microemulsions; isopropyl myristate; tea-tree oil; stability

1. INTRODUCTION

Prasaplai is one of the herbal medicines on the Thailand National List of Essential Medicine. It is used in obstetrics and gynecology syndromes for treating dysmenorrhea and regulating the menstruation cycle (National Drug Information, 2016). Prasaplai refers to the preparation of 50% *Zingiber cassumunar* with 10 medicinal plants and two chemical compounds. Table 1 shows the ingredients of Prasaplai. The active ingredients of plai are (E)-3(-1,4,dimethoxyphenyl) butadiene (DMPBD), (E)-2(-4,4,-5,trimethoxyphenyl)but-1,-3dien(TMPBD) and cassumunaquinones, which are potent anti-inflammatory agents. Curcumin in khamin-oi has been reported as an anti-inflammatory agent that inhibits COX-II enzymes, thereby reducing inflammation and pain (Temsiririrkkul, 2016). When taken orally, Prasaplai helps to relieve primary dysmenorrhea as effectively as mefenamic acid (a non-steroidal anti-inflammatory drug, NSAID) (Sriyakul et al., 2012). However, one of the side effects of orally-consumed Prasaplai is heartburn (Wisai et al., 2019). Forms of Prasaplai include capsules, powder, tablets, and pills (National Drug Information, 2016). To date, Prasaplai has not been used in topical form, even though hot compressed plai oil for relieving muscle pain is available on the market. Topical Prasaplai for menstrual pain relief is a viable alternative for those who do not want to take herbal medicine or are sensitive to NSAIDs.

Microemulsions (MEs) are isotropic, thermodynamically

stable transparent systems comprised of oil, water, surfactant, and cosurfactant, with droplet sizes in the range of 20-200 nm. MEs are promising systems for topical drug delivery because of their ability to incorporate both hydrophilic and lipophilic drugs, while also enhancing their permeation (Azeem et al., 2009). It has also been reported that MEs could enhance the permeability of herbal topical medication (Pakpayak et al., 2011). This research focused on the development of a Prasaplai ME for topical use. Prasaplai MEs were formulated and their physical and chemical stability were determined.

Table 1. Medicinal plants and chemical compounds in Prasaplai (Adapted from Tangyuenyongwatana and Grisanapan, 2016)

Medicinal Plants and Chemical Compounds	Common name	Part of the plants	%w/w
Zingiber cassumunar	Plai	Rhizome powder	50
Citrus hystrix DC	Kaffir lime	pericarp	
Acorus calamus L.	Wan-nam	Root	
Allium sativum L.	Garlic	Bulb	
Eleutherine Americana Merr.	Hom-dang	Bulb	
Piper nigrum L.	Pepper	Fruit	
Piper retrofractum Vahl	Indian Long Pepper	Fruit	
Zingiber officinale Roscoe	Ginger	Rhizomes	50
Curcuma zedoaria Roscoe	Khamin-oi	Rhizomes	
Nigella sativa L.	Tien-Dum	Seed	
Camphor			
Sodium			

2. MATERIALS AND METHODS

2.1 Materials

Prasaplai was obtained from Bang Krathum hospital, Phitsanulok. IPM and polysorbate 80 were purchased from Namsiang Co. (Bangkok, Thailand). Tea tree oils were purchased from Honghuat Co. (Bangkok, Thailand). Butanol was purchased from Fisher Scientific (UK).

2.2 Preparation of Prasaplai extract

Prasaplai extraction was carried out at Naresuan University, Thailand. The ethanol extraction of Prasaplai was prepared using the percolation method. Three rounds of extractions were performed (three times each round) using 95% ethanol. The extract was collected in a flask receiver and then evaporated into syrup-like solutions. The yield was 11.5%.

2.3 Preparation of blank and Prasaplai MEs

MEs of Prasaplai (0.1% by weight) were prepared using a simple titration method. IPM or tea tree oil was mixed with water at a range of ratios (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 or 1:9, v/v), then the surfactant and co-surfactant mixture of polysorbate 80 and butanol, at a ratio of 1:1 (v/v), was added until a clear transparent solution was obtained, referred to as blank MEs. Prasaplai extract (10 µL) was then mixed with the clear solution to obtain Prasaplai MEs. Table 2 shows the oil: water: surfactant ratio (by weight) of Prasaplai MEs. All these formulations were transparent solutions.

2.4 Physical stability study of blank and Prasaplai MEs

Blank and Prasaplai MEs, obtained from IPM or tea tree oil, were characterized by droplet size distribution, pH value, and viscosity (cycle 0). MEs were then kept under accelerated stability testing for six cycles (one cycle of 45°C for 48 h and 4°C for 48 h). After six cycles, the droplet size distribution, pH value, and viscosity of the Prasaplai and blank ME were measured and compared to those in cycle 0.

2.5 Size distribution

Droplet size distribution of blank and Prasaplai MEs were measured using a Zetasizer Nano-ZS (Malvern Instruments, Worcestershire, UK). The formulations were diluted 100-fold with water and vortexed for 30 s before measuring. All measurements were performed in triplicate. The diluted MEs were clear, and the count rate was within the sufficient intensity of signal, according to the manufacturer's recommendations.

Table 2. Composition by weight of transparent IPM-based Prasaplai ME (M) and tea tree oil-based Prasaplai ME (T)

Formulation	Composition				
	Isopropyl myristate (g)	Tree tree oil (g)	Water (g)	Polysorbate80 : Butanol 1:1 (%v/v)	Prasaplai extract (g)
M2	63	-	8	29	0.10
M3	48	-	14	38	0.10
M4	39	-	20	41	0.10
M5	33	-	26	41	0.10
M6	29	-	34	37	0.10
M7	22	-	38	40	0.10
M8	17	-	47	36	0.10
M9	11	-	53	36	0.10
T2	-	41	5	54	0.10
T4	-	35	17	48	0.10
T5	-	28	22	50	0.10
T6	-	25	30	45	0.10
T7	-	20	35	45	0.10

2.6 Transmission electron microscopy

The morphology of M6 and T6, both undiluted and diluted 50-fold with water, were examined using transmission electron microscope (TEM) (HT7700, Hitachi, Japan). A drop of ME was deposited on to a grid and left for one minute. The excess fluid was removed with the filter paper. The grids were stained with 1% uranyl acetate and left for one minute. The image was taken after drying.

2.7 pH value

The pH values of the ME were measured in triplicate using a calibrated pH meter (Mettler Toledo, Switzerland).

2.8 Viscosity

Viscosity was measured by a control stress rheometer at 25°C (Hakke Rheostress, Malvern, Germany). Plate and plate geometry were used. Shear stress was measured by a stepwise increased shear rate from 0 to 200 s^{-1}. Viscosity was calculated from the shear stress.

2.9 Chemical stability

To examine the chemical stability of Prasaplai MEs, curcumin was assayed, as it is a main component in plai. To prepare the standard curve, 20 mg of curcumin was weighed and dissolved in methanol to obtain 100 mL stock solution. A series of five volumes of curcumin methanolic solution (250-1000 µL) was then pipetted and transferred into volumetric flasks. To each flask a 9:1 (v/v) mixture of acetonitrile and phosphoric acid solution was added until the target concentrations were obtained. The solutions were filtered through 0.45 µm polytetrafluoroethylene membranes before analysis by high performance liquid chromatography (HPLC) using a C18 column (ACE 250 mm × 4.60 mm, 5 µm). The mobile phase was a mixture of acetonitrile and 0.1% (w/w) phosphoric acid (45:55, v/v). The flow rate was maintained at 1.0 mL/min with an injection volume of 20 µL. The amount of curcumin was eluted and quantified at 423 nm. The standard curve, with a correlation coefficient of at least 0.999, was used. The chemical stability of two formulations of Prasaplai MEs, M6 and T6, were chosen for study because of the similarity in the concentration of the components (Table 2). These two formulations were assayed for curcumin content immediately after preparation (cycle 0) and after six heating-cooling cycles. To examine the curcumin content, 3 mL of the ME sample was pipetted and transferred into a test tube. Subsequently, 25 mL of methanol was added and the mixture was centrifuged for 5 min to produce a homogeneous solution. The sample solution was filtered through a 0.45 µm polyamide membrane prior to quantification using HPLC, with similar conditions to the standard curve preparation for curcumin. The remaining percentage of curcumin was calculated using the following equation (equation 1):

$$\text{Remained curcumin (\%)} = 100 - \left[\left(\frac{CW_{day0} - CW_{6\,cycles}}{CW_{day0}}\right) \times 100\right], \quad (1)$$

where CW_{day0} is the weight of curcumin assayed on the day of preparation and $CW_{6\,cycles}$ cycles is the weight of curcumin assayed after storage under heating-cooling conditions for six cycles.

2.10 Statistical analysis

The aforementioned parameters measured at cycle 0 and cycle 6 were statistically analyzed using the Student's t-test. A p-value less than 0.05 was considered significant.

3. RESULTS AND DISCUSSION

3.1 Preparation of blank and Prasaplai MEs

Prasaplai MEs (0.1% by weight) were prepared by varying the ratio of oil (IPM or tea tree oil), water, surfactant, and cosurfactant (polysorbate 80 and butanol, 1:1 v/v) as described above. Ternary phase diagrams of Prasaplai MEs were plotted using XLSTAT®. Figure 1 shows the ternary phase diagrams of Prasaplai MEs, for which the oil phases were IPM and tea tree oil. The ingredients of all transparent formulas are shown in Table 1.

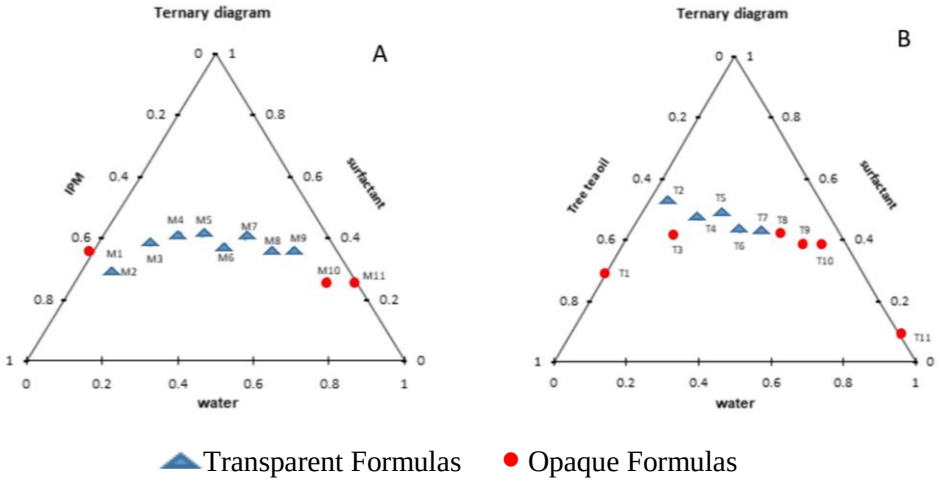

Figure 1. Ternary phase diagram of Prasaplai ME; IPM-based ME and tea-tree oil based ME

The appearance of IPM-based MEs and tea tree oil-based MEs at Day 0 are shown in Figure 2. The MEs obtained from IPM were more stable than those from tea tree oil. M2-M9 remained clear and homogeneous after six heating-cooling cycles. On the other hand, tea tree oil MEs (T4-T7) were opaque and showed phase separation in

cycle six. Only T2 was clear and homogeneous after cycle six (data not shown). This can be explained by the higher amount of surfactant and co-surfactant (54%) among tea tree oil-based ME formulations (Table 2).

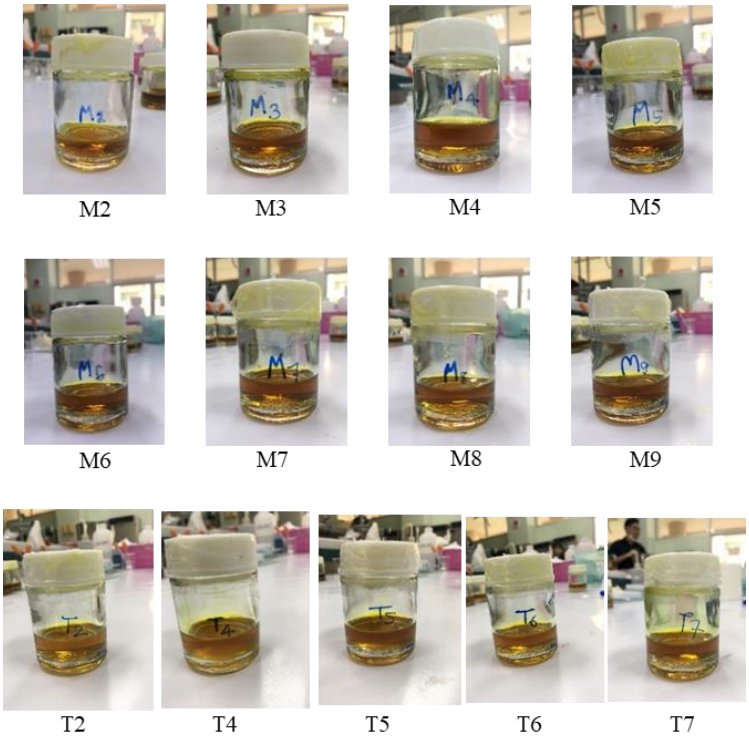

Figure 2. Appearance of IPM-based MEs (M) and tea tree oi-based MEs (T) (Day 0)

3.2 Physical stability of IPM-based MEs and tea tree oil-based MEs

3.2.1 Size distribution

Table 3 shows the physical properties (average value of M formulas and T formulas) of IPM-based MEs and tea tree oil-based MEs on cycle 0 and cycle six of heating-cooling. Figure 3 shows the mean diameter (nm) of IPM-based ME (blank ME; A, and Prasaplai ME; B), and tea tree oil-based ME (blank ME; C, and Prasaplai ME; D) at cycle 0 and cycle six.

After storing under six heating-cooling cycles, the size of the IPM-based MEs tended to decrease (from 257.50 nm to 188.27 nm in blank and from 223.95 nm to 190.99 nm in Prasaplai) (Table 3). This might be due to the degradation products of IPM: IPM is a long-chain hydrophobic ester mostly used to formulate MEs for carrying hydrophobic drugs (Roohpour et al., 2009). The chemical structure of IPM is shown in Figure 4. IPM was found to degrade to myristic and stearic acids, due to hydrolysis of the ester compound (Iskandarsyah and Rahman, 2018). Myristic and stearic acids lower the surface tension between two miscible liquids, which facilitates the formation of micelles, thereby decreasing the size of oil droplets. Moreover, critical micelle concentration of fatty acids is markedly affected by temperature and the presence of other ions (Rustan and Devon, 2005).

After storing under six heating-cooling cycles, the size of most tea tree oil-based blank ME did not significantly change (Figure 3C), whereas most of the tea tree oil-based Prasaplai ME were larger (Figure 3D). These results were in agreement with the physical appearance of tea tree oil-based Prasaplai ME, which showed phase separation. The presence of Prasaplai in formulations catalyze the degradation of the ME, since Prasaplai contains various types of herbs, especially curcumin, which will be discussed later. Moreover, ingredients of ME were also found to be degraded. Under high temperature conditions, polysorbate 80 degradation occurs via auto-oxidation and hydrolysis (Kishore et al., 2011), decreasing its ability as a surfactant. The evaporation of butanol can also affect ME formations (Asia Pacific Petrochemical, 2018). Moreover, the degradation of tea tree oil is one of the factors effecting tea tree oil-based Prasaplai ME stability, which will be discussed later.

TEM micrographs of M6 and T6 are shown in Figure 5. TEM imaging revealed globules of almost spherical shape, with an average size of 300-400 nm, which were bigger than those obtained from the particle size analyzer. This was due to the staining in TEM process. However, the size range of the droplets was maintained even after dilution with water, demonstrating that dilution did not disturb the microemulsion system.

3.2.2 pH value

The average pH values of blank IPM-based and tea tree oil-based ME were 7.22 and 6.52, respectively (Table 3). After adding Prasaplai, the average pH of both IPM and tea tree oil-based MEs decreased to 5.14 and 5.45, respectively, which could be due to the ingredients in the Prasaplai extract. Prasaplai consists of 50% plai, of which curcumin is the major ingredient. The phenolic acid group at the terminal of curcumin structure was responsible for the decreasing of pH of formulations. Figure 6 shows the pH values of IPM-based ME (blank ME; A and Prasaplai ME; B), and tea tree oil-based ME (blank ME; C, and Prasaplai ME; D)

at cycle 0 and cycle six of heating-cooling.

After storage under accelerated conditions, the pH of IPM-based blank MEs also decreased (Figure 6A). This could be attributed to stearic and myristic acids, degradation products of IPM, which lowers the pH of the formulations. Hydrolysis of ester groups of polysorbate 80 and surfactants of the ME could also lower the pH of the ME. The structure of polysorbate 80 is given in Figure 7. The pH of the IPM-based Prasaplai ME increased after storage under accelerated conditions (Figure 6B). Myristic, stearic, and fatty acids may have interacted with the sodium chloride in Prasaplai to form soap, thereby increasing the pH. Rustin and Dervon (2005) reported an increase in pH from the interaction between fatty acids and alkali metal salts, resulting in soap formation.

After storage under accelerated conditions, the pH of tea tree oil-based ME decreased (Figure 6C, D), which could be attributed to their degradation products. Tea tree oils, like other natural oils, are sensitive to light, moisture, heat, and oxygen (Carson et al., 2006). Heat could decrease the amount of α- and γ-terpinene, whereas it will increase the amount of *p*-cymene and peroxides in tea tree oil, thereby resulting in physical changes and decreasing the pH. As previously mentioned, curcumin could decrease the pH of formulations, not only because of its structure, but also because curcumin can rapidly degrade by alkaline hydrolysis, experiencing molecular fragmentation and splitting into vanillin, acetone, feruloylmethane, and ferulic acid (Mondal et al., 2016) which affects the pH of the ME.

Table 3. Physical properties (average value) of IPM-based MEs (M) and tea tree oil-based MEs (T) at cycle 0 and cycle 6 of heating-cooling

ME Type	Cycle 0				Cycle 6			
	Size (nm)	pH	PDI	Viscosity (cP)	Size (nm)	pH	PDI	Viscosity (cP)
Blank M	257.50	7.22	0.21	24.01	188.27	7.09	0.19	24.67
Prasaplai M	223.95	5.14	0.26	26.89	190.99	5.33	0.32	27.96
Blank T	236.01	6.52	0.22	17.58	257.76	5.11	0.27	22.79
Prasaplai T	234.06	5.45	0.26	19.87	247.14	5.36	0.29	17.47

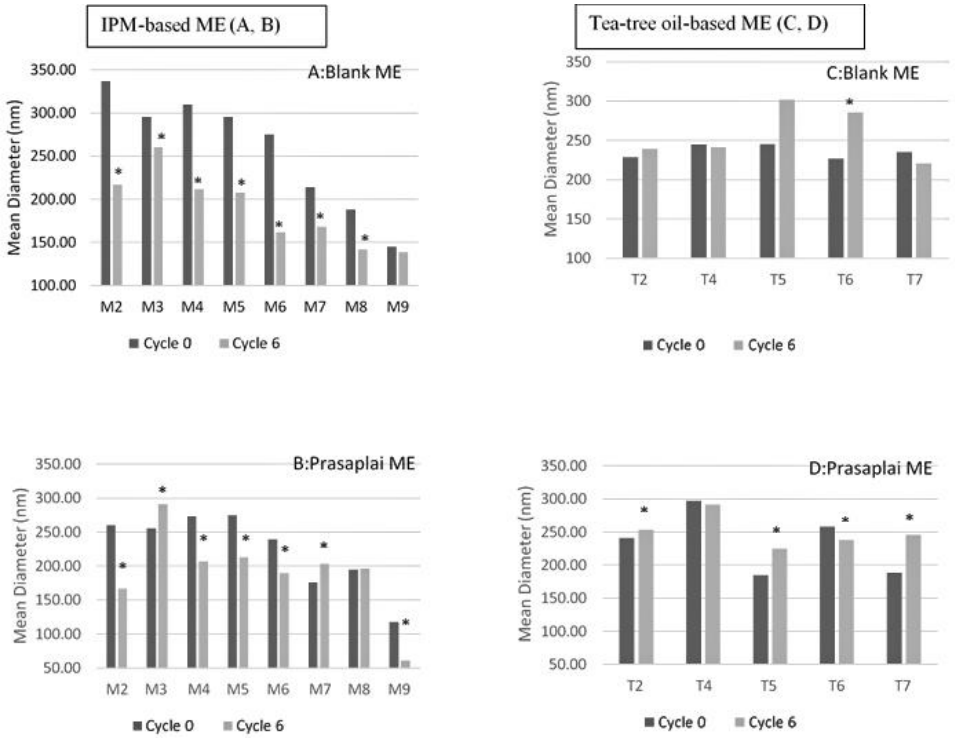

Figure 3. Mean diameter of IPM-based ME (blank ME; A and Prasaplai ME; B), and tea-tree oil-based ME (blank ME; C and Prasaplai ME; D) at cycle 0 and cycle 6 of heating-cooling
Note: *Significant difference (*p*-value<0.05)

3.2.3 Viscosity

The viscosities of IPM-based MEs were higher than those of the tea tree oil-based MEs (24.01 cP vs 17.58 cP). When the MEs were mixed with Prasaplai the viscosity did not change (Table 3). Figure 8 shows the viscosity of IPM-based MEs (blank ME; A, and Prasaplai ME; B), and tea tree oil-based ME (blank ME; C, and Prasaplai ME; D) at cycle 0 and cycle six of heating-cooling. After storage under accelerated conditions, the viscosity of most MEs was not significantly different from those of the IPM-based and tea tree oil-based MEs even though the viscosity of blank tea tree oil-based ME (T5, T6, T7) was significantly increased. Both the blank and

Prasaplai ME exhibited Newtonian flow, with stable viscosity at increasing shear rates (Figure 9). It has been reported that oil in water MEs exhibit Newtonian behavior (Kumar et al., 2014). This characteristic was found to be suitable for MEs (Thakkar, 2014). The rheological behavior of MEs is related to their structure: bicontinuous ME exhibits a Newtonian behavior (constant viscosity) at low to medium shear rates, but shear thinning is observed at high shear. Discontinuous ME, however, shows Newtonian behavior over a wide range of shear rates (Acharya and Hartley, 2012). The addition of polymers into ME affects its structure, which leads to rheological changes (Kumar et al., 2014). Valenta and Shultz (2004) reported that the rheological properties of carrageenan gelled ME can be adjusted by varying the polymer concentration, without affecting the permeability of the model compound sodium fluorescein.

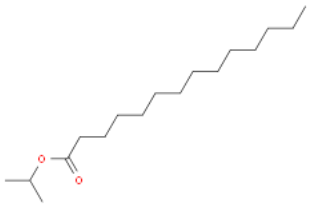

Figure 4. Structure of isopropyl myristate (Pubchem, 2020)

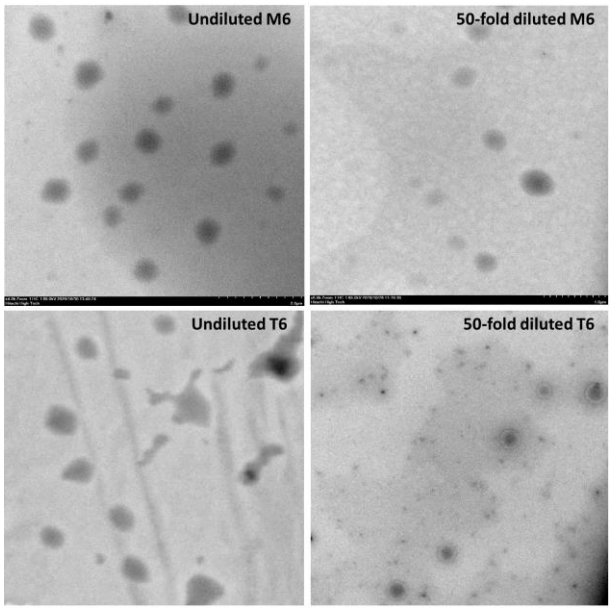

Figure 5. TEM micrographs of M6 and T6 (undiluted and 50-fold diluted with water)

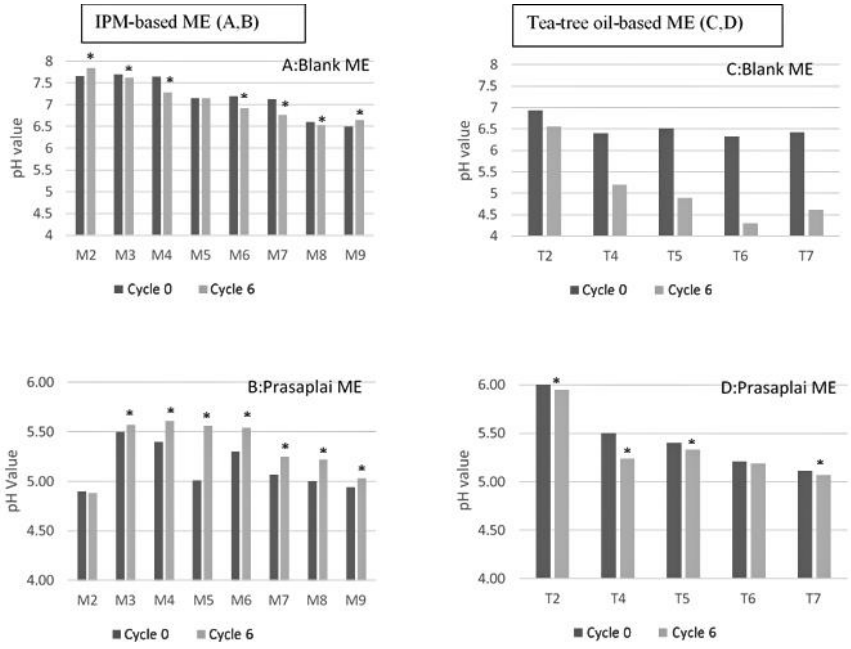

Figure 6. pH value of IPM-based ME (blank ME; A and Prasaplai ME; B), and tea-tree oil-based ME (blank ME; C and Prasaplai ME; D) at cycle 0 and cycle 6 of heating-cooling
Note: *Significant difference (p-value<0.05)

3.2.4 Chemical stability of Prasaplai MEs

As shown in Table 4, curcumin, the main component of Prasaplai in formulations M6 and T6 significantly decreased after storage with six heating-cooling cycles (100% to 92.20% (M6) and 73.80% (T6), $p<0.05$). These results suggested that the chemical stability of Prasaplai ME was influenced by the change in temperature. However, the curcumin remaining in tea tree oil-based Prasaplai ME was 73.80%, while it was 92.20% in IPM-based Prasaplai ME. The percentage of curcumin remaining in M6 was significantly greater than of T6 (92.20% vs 73.80%, $p<0.05$). The main difference between these two formulations was the oil type, while the proportions of each ingredient were comparable. This suggested that oil type significantly affects the stability of Prasaplai ME. The instability of T6 can be attributed to the volatile nature of tea tree oil, which was influenced by the temperature change during the heating-cooling cycles. The effects of oil type on the chemical stability of curcumin in ME have also been reported (Calligaris et al., 2017). Several studies have reported improved solubility and stability of curcumin by preparation in surfactant micelles and emulsion-based delivery systems (Mondal et al., 2016; Kharat et al., 2017; Bergonzi et al., 2014). This is in agreement with our assumption that the degradation of IPM to fatty acids can form micelles, which enhance the stability of curcumin in IPM-based MEs, compared to those in tea tree oil-based MEs. In addition, the pharmacological effects of the degradation products of curcumin (Shen and Ji, 2012) and the stability of curcumin in emulsion-based preparations have been reported (Kharat et al., 2017; Kharat et al., 2018; Bergonzi et al., 2014).

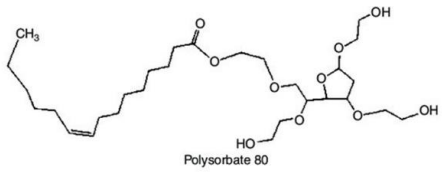

Figure 7. Structure of polysorbate 80 (Fratter and Semenzato, 2011)

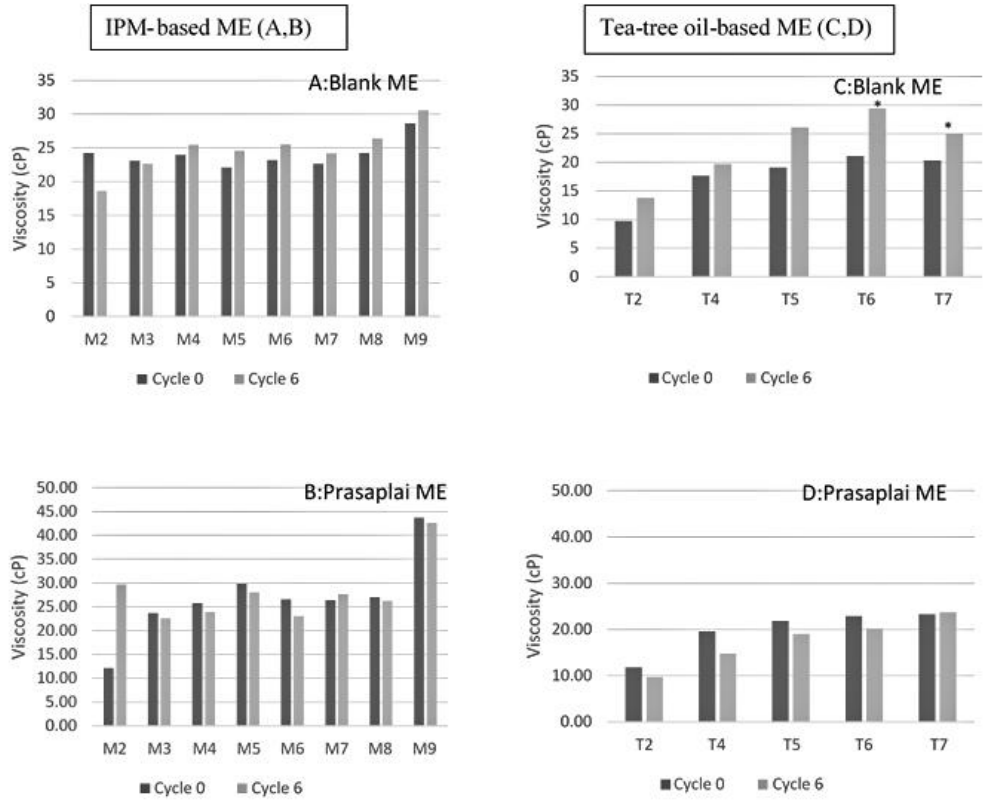

Figure 8. Viscosity of IPM-based ME (blank ME; A and Prasaplai ME; B), and Tea-tree oil-based ME (blank ME; C and Prasaplai ME; D) at cycle 0 and cycle 6 of heating-cooling
Note: *Significant difference (p-value<0.05)

4. CONCLUSION

The type of oil, as well as the other ingredients in ME or Prasaplai, affected their stability. IPM is also a skin penetration enhancer used in cosmetic products. Moreover, degradation products of IPM, myristic and stearic acids, can decrease ME size by micelle formation, which protects the curcumin in Prasaplai. For these reasons, IPM has the potential for developing ME for topical application. Tea tree oil, on the other hand, is a natural oil often used in cosmetic products. According to the chemical stability study, tea tree oil MEs did not protect curcumin from degradation. Skin permeation of IPM-based and tea tree oil-based MEs could be investigated further to ensure the MEs is suitable for topical remedies.

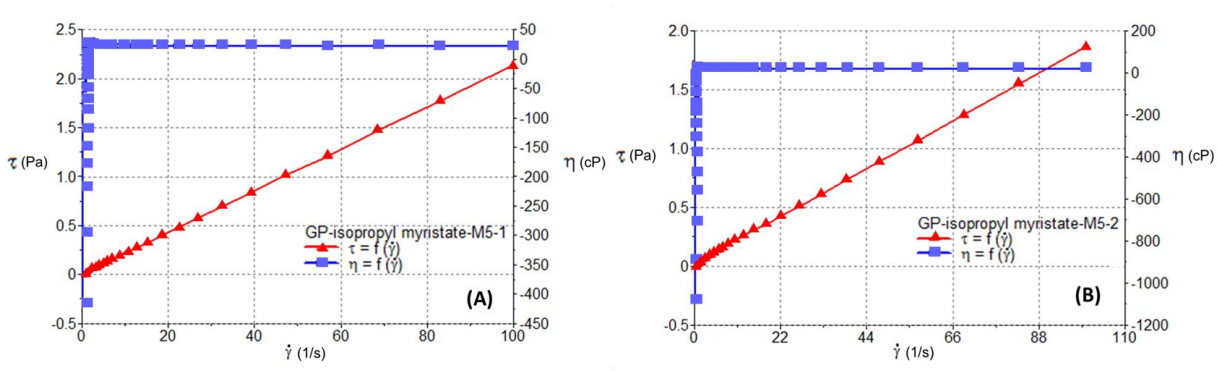

Figure 9. Rheological behavior of Prasaplai microemulsions at cycle 0 (A) and cycle 6 (B) of heating-cooling

Table 4. Chemical stability of Prasaplai MEs (M6 and T6) at cycle 0 and cycle 6 of heating-cooling

Formula	Concentration (μg/mL)		Weight (mg)		% Remaining
	Cycle 0	Cycle 6th	Cycle 0	Cycle 6th	
M6	13.67 ± 0.07	12.60 ± 0.10*	2.05 ± 0.01	1.89 ± 0.01*	92.20
T6	18.05 ± 0.06	13.34 ± 0.06*	2.71 ± 0.01	2.00 ± 0.01*	73.80

Note: Curcumin, as the main component in Prasaplai, was quantified by concentration and weight. Data in this table represent the mean ± S.D. (n = 3)

*Significant decrease (p-value<0.05)

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