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Preparation, Characterization and Evaluation of Octyl Methoxycinnamate (OMC)-Loaded Solid Lipid Nanoparticles (SLNs) by Using a Microemulsion Technique

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Abstract

This research prepared the solid lipid nanoparticles (SLNs) based on microemulsion to load octyl methoxycinnamate (OMC) as a UV absorber for instability protection. The optimal microemulsion formulation was selected by visual assessment according to a transparent and thermodynamically system form. The optimal microemulsion obtained from the experiment composed of 10% w/w glyceryl monostearate (GMS, solid lipid), 10% w/w Tween 80 (surfactant), 15% w/w PEG-40 hydrogenated castor oil (surfactant) and 20% w/w ethanol (co-surfactant). Various processing parameters for the preparation of SLN was carried out using three factors including, 1) warm microemulsion (mL) and iced water ratio (mL), 2) homogenization speed (rpm) and 3) homogenization time (min) and two responses assessed were particle size and polydispersity index (PDI) to obtain a SLNs batch with smaller particle size and optimum PDI. The OMC-loaded SLN had 693.07± 0.05 nm mean particle size and 0.56±0.04 PDI, prepared by optimal processing parameters. The surface morphology of the SLNs was assessed by transmission electron microscopy (TEM), the result found that OMC-loaded SLN showed a smooth surface and spherical shape. Entrapment efficiency of OMC-loaded SLN was found to be 99.89±0.020% . The stability testing of the prepared SLN was studied. Result found that OMC-loaded SLN showed slightly lower stable compared with the initial condition. All obtained results indicated that this method and processing parameters can prepare the SLNs which was suitable for cosmetic application.

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Introduction

UV light is divided into UVA (320-400 nm), which can penetrate to reach the dermis, causing damage of the skin such as immediate and delayed tanning reactions, loss of collagen and skin photosensitization, UVB (280-320 nm) in the cause of sunburn (erythema) and skin cancer and UVC (100-280 nm), which is totally absorbed by the ozone layer (Gromkowska-Kępka et al., 2021). Thus, UV protection is very important to avoid harmful effects to the skin. The parameter for evaluation of the UV protection degree is the sun protection factor (SPF) rating. The substances with SPF have been widely used as a photoprotective agents which are known as sunscreens (Young et al., 2017).

Sunscreens have been divided into chemical absorbers and physical blockers on the basis of their mechanism of action, namely absorbance and reflection. Octyl methoxycinnamate (OMC) or 2-ethylhexyl 4-methoxycinnamate is currently the most popular chemical sunscreen, with good UVB absorption, solubility in oils and insolubility in water, so that it is suitable for use in most waterproof sunscreen formulations. Although this compound can be easily formulated in the lipid phase of cosmetic products, the concentrations of use as a cosmetic ingredient recommended by US and European Union (EU) was 7.5-10% because exposure of OMC to UV radiation generates reactive chemical species including free radicals which can give rise to adverse skin effects as well as to limit the UV-protected molecules to penetrate to the skin layer especially viable layer and presence on stratum corneum which are the two most important properties (Butt & Christensen, 2001; Andreani et al., 2020). That is why OMC is a good candidate for loading into nanoparticles by using a novel carrier since it can both reduce the adverse effects of sunlight and enhance UV protection (Xia et al., 2007).

Nowadays, the nanocarrier systems represent a mild way in order to enhance the penetration degree and increase the performance of a cosmetic product. Solid lipid nanoparticle (SLNs) is a novel drug delivery system for cosmetics and dermatologic formulations (Sastri et al., 2020). SLNs systems present some advantages including, improved stability of a chemical molecule which act as an active ingredient. It is able to provide a carrier system with controlled release and shows occlusive properties which created a film on the skin (Farboud et al., 2011). The use of SLNs as a carrier system for UV absorbers has been introduced because it showed that lipid nanoparticles present a high potential to inhibit the UV radiation and act as a physical UV sunscreen by scattering or reflection of light, thus able to improve the sun protection effect (Andreani et al., 2020). Chemical sunscreens incorporated into the solid lipid matrix of the SLNs can prevent penetration of the skin and resulting side effects (Andréo-Filho et al., 2018).

Therefore, this investigation is focused on the preparation of SLNs using a microemulsion. The microemulsion method is simple, contains no toxic organic solvents, reproducible and can be scaled up. For large-scale production, the microemulsion can be prepared in a large temperature-controlled tank and pumped into another tank containing cold water for lipid precipitation (Gasco, 1993). In order to optimize microemulsion for OMC-loaded SLN preparation, different formulation variables; types of solid lipid, quantity of selected solid lipid and type and concentration of surfactants were evaluated. The concept of this method is the optimal microemulsion dispersed in a cold water under homogenizer mixing and time for mixing. SLNs with reduced mean particle size and narrow size distribution can be obtained after dilution in cool water of the hot microemulsion (Gasco, 1993; Gasco, 1997). For this research, the optimization of processing parameters for the SLNs preparation was investigated. The smaller particle size and optimum polydispersity index (PDI) which were two responses from each SLN batch and were assessed for selection of the optimal parameter. This is the first study that examined the various parameters (type of solid lipid, quantity of lipid, type and concentration of surfactant and co-surfactant concentrations) for the preparation of the first oil in water microemulsion to select microemulsion formulations to prepare solid lipid nanoparticle evaluated by visual appearance in terms of a transparent and thermodynamically system form. Further, we studied the various processing parameters for the preparation using three factors; 1) warm microemulsion (mL) and iced water ratio (mL), 2) homogenization speed (rpm) and 3) homogenization time (min) and two responses assessed were particle size and polydispersity index (PDI) to obtain a SLNs batch with smaller particle size and optimum PDI. The characterization of OMC-loaded SLN; particle size, polydispersity index (PDI), entrapment efficiency and morphology were studied. The physicochemical stability of OMC-loaded SLN was evaluated.

Materials and methods

1. Raw materials

Glyceryl monostearate (GMS), Tween 80, PEG-40 hydrogenated castor oil, Palmitic acid, Stearic acid were purchased from Namsiang (Thailand). Ethanol (AR grade) was purchased from Labscan (Thailand). Octyl methoxycinnamate was purchased from Chemico group (Thailand).

2. Preparation of oil in water microemulsion components

The microemulsions are transparent, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. Preparing the first hot microemulsion, the solid lipid was melted as oil phase, and the water phase was prepared by a mixture of water, surfactant and co-surfactant(s) and heated at the same temperature as the solid lipid. The water phase was then added under mild stirring to the oil phase. After that, a transparent, thermodynamically stable system was formed since the component were mixed in the correct ratio. Finally, obtained SLNs was made by dilution of the hot microemulsion in cold water under constant stirring. The volume ratios of the hot microemulsion to cold water were in the range of 1:25 to 1:50 (Gasco, 1997). In this study, the selection of the optimal microemulsion formula, the parameters; solid lipids, surfactants and co-surfactants were examined for SLN preparation.

2.1 Types of solid lipid

Three solid lipids; stearic acid, palmitic acid and glyceryl monosterate (GMS) were used for formation of microemulsion. Solid lipids were melted at 60-70°C. The concentration of each solid lipid was 10% w/w for microemulsion preparation. The solid lipid was selected from a transparent form of microemulsion (Ramteke et al., 2012; Ratcharin et al., 2012).

2.2 Type and concentration of surfactant

This, two surfactants; Tween 80 and PEG-40 hydrogenated castor oil were used for microemulsion preparation. The concentration of surfactant was optimized; Tween 80 (10% w/w, 15% w/w and 20% w/w) and PEG-40 hydrogenated castor oil (10% w/w, 15% w/w and 20% w/w). The concentration of the surfactant was selected based on the transparent of the microemulsion form after 24 h storage (Ramteke et al., 2012; Ratcharin et al., 2012).

2.3 Co-surfactant concentrations

The concentration of ethanol used for the microemulsion formation were 10% w/w, 15% w/w and 20% w/w. The suitable of ethanol concentration was performed based on the transparent of the microemulsion form after 24 h (Ramteke et al., 2012; Ratcharin et al., 2012).

3. Optimization processing parameters for OMC-loaded SLN

The SLN for loading the OMC (10% w/w) was prepared by using microemulsion technique. The optimal microemulsion was then dispersed into cold water (2-4°C) under homogenizer mixing by using a high-speed homogenizer (Silverson L5M, England). Optimized processing parameters for the SLNs preparation was carried out using three factors; (i) microemulsion (mL) and iced water ratio (mL), (ii) homogenization speed (rpm) and (iii) homogenization time (min) and two responses assessed were particle size and polydispersity index (PDI) to obtain a SLN batch with lesser particle size and optimum PDI (Ratcharin et al., 2012).

(i) different ratio of microemulsion (mL) and iced water (mL) were 1:20, 1:25, 1:30 and 1:35,

(ii) homogenizer speeds were performed at 4000, 6000, 8000 and 10000 rpm,

(iii) homogenization time were done for 5, 10, 15 and 20 min.

4. Characterization of SLN

4.1 Particle size and size distribution

The mean particle size and size distribution of SLNs were assessed by dynamic light scattering (DLS) method using Zetasizer (Malvern, ZEN 3600, England).

4.2 Morphology

The surface morphology of SLN was characterized with scanning electron microscope (SEM) (Hitachi, S-3400N, Japan). The air-dried SLN were then coated with conducting materials using gold sputter and visualized under SEM. The morphology of SLN were observed under transmission electron microscopy (TEM) (Jeol, JEM-2100, Japan). SLNs were diluted with water and placed on a carbon-coated copper grid and the excess water was wiped off with filter paper. Then, 20 µL of 2% w/v uranyl acetate in water was placed on SLN and wiped off by another filter paper. The grid was dried at room temperature and assessed by TEM.

4.3 Entrapment efficiency (EE)

The entrapment efficiency (% EE) was determined by measuring the concentration of entrapped OMC. Briefly, 2.0 g of OMC-loaded SLN was dispersed in ethanol 1.0 mL and then placed into a centrifuge tube which was centrifuged at 8000 rpm for 10 min at 25°C (Gemmy, PLC-05, Taiwan) (Prombutara et al., 2012).

The supernatant was analyzed for encapsulated OMC at 348 nm using a UV-Vis spectrophotometer (Shimadzu, UV-2401PC, Japan). Then, the percent of entrapment efficiency in SLN was calculated according to the following equations:

$$\text{Entrapment efficiency (\% EE)} = (W_{\text{intial drug}} - W_{\text{free drug}} / W_{\text{intial drug}}) \times 100 \quad [1]$$

where $W_{\text{initial drug}}$ is the amount of OMC, $W_{\text{free drug}}$ is the amount of free OMC detected in the aqueous phase after isolation of the dispersion

5. Storage stability of SLNs

The stability of OMC-loaded SLN were evaluated at different stability conditions including room temperature (RT, ≈30±5°C), 4°C and 40°C for 30 d. Evaluating parameters included any change in physical appearance, particle size, PDI and entrapment efficiency (% EE) that were assessed compared with initial condition.

6. Statistical analysis

Data were reported as mean ± SD values of three different experiments. Statistical comparisons were analyzed by a one-way analysis of variance (ANOVA) using Microsoft Excel 2010. $P<0.05$ was considered statistically significant.

Results and discussion

1. Oil in water microemulsion preparation

As shown in Table 1, formulations with different solid lipids (stearic acid, GMS, palmitic acid) and a fixed amount of surfactant and co-surfactant. The result indicated that GMS gave a transparent microemulsion whereas stearic acid and palmitic acid showed slightly turbid microemulsion. Furthermore, we examined the effect of GMS at 5, 10 and 15% w/w on microemulsion form. The result clearly showed that GMS at 10% w/w gave a transparent microemulsion, whereas at concentration lower than 10% w/w could not formed a microemulsion and at concentration higher than 10% w/w could not be achieved due to highly viscous lipid phase (Yingngam et al., 2007). This investigation was in agreement with the results obtained by previously reported which found that GMS increased the solubility of drugs, therefore the concentration of 10% w/w of GMS was chosen for the preparation of solid lipid nanoparticles and concentration of GMS was not more than at 10% w/w showed a good SLNs (Mulla et al., 2009; Shah et al., 2009). The effect of type and concentrations of surfactant on the formation of microemulsion were investigated using 10, 15 and 20% w/w of Tween 80 and 10, 15 and 20% w/w of PEG-40 hydrogenated castor oil. This study was in good agreement with results previously reported which found that the amount of surfactant used to prepare o/w microemulsions should be between 8 and 30% w/v however, in this range, a concentration of 12–20% was the best (Gasco, 1997). From our preliminary study it was found that the mixture of nonionic surfactants, Tween 80 and PEG-40 hydrogenated castor oil, could give a transparent microemulsion which are more stability than single surfactant (data not shown), so that, in this research we examined the effect of surfactants mixtures on the formation of microemulsion. The results showed that Tween 80 at all concentration gave a transparent microemulsion, whereas PEG-40 hydrogenated castor oil at concentration of 15 and 20% w/w showed a transparent microemulsion. The mixture of surfactants can reduce surface tension and facilitate the particle partition. This result obtained from the experiment was similar to previous reports (Olbrich, & Muller, 1999). Thus, the lower concentration of Tween 80 and PEG-40 hydrogenated castor oil were chosen to use as a mixture surfactant in microemulsion formulation. The hydrophilic co-surfactant of the microemulsion could distribute very rapidly into the aqueous phase and have a critical role in the formation of lipid nanoparticles (Caboi et al., 2005). Ethanol was chosen as co-surfactant in this study.

Table 1 Various formulation parameters for the preparation of the first oil in water microemulsion

Formulations	Variables	Quantity (% w/w)	Visual appearance of O/W microemulsion
Type of solid lipid			
F1	Stearic acid	10	Slightly turbid
F2	GMS	10	Transparent
F3	Palmitic acid	10	Slightly turbid
Quantity of solid lipid			
F4	GMS	5	Slightly turbid
F5	GMS	10	Transparent
F6	GMS	15	Turbid
Type and concentration of surfactant			
F7	Tween 80	10	Transparent
F8	Tween 80	15	Transparent
F9	Tween 80	20	Transparent
F10	PEG-40 hydrogenated castor oil	10	Slightly turbid
F11	PEG-40 hydrogenated castor oil	15	Transparent
F12	PEG-40 hydrogenated castor oil	20	Transparent
Co-surfactant concentrations			
F13	Ethanol	10	Turbid
F14	Ethanol	15	Slightly turbid
F15	Ethanol	20	Transparent

Obtained result found that ethanol at a concentration of 20% w/w gave a transparent solution. This finding was in agreement with the previous work (Caboi et al., 2005).

According to Table 1, the optimal microemulsion composed of 10% w/w glyceryl monostearate (solid lipid), 10% w/w Tween 80 (surfactant), 15% w/w PEG-40 hydrogenated castor oil (surfactant) and 20% w/w ethanol (co-surfactant). The result was transparent and thermodynamically stable and this optimal formulation is visually represented in Fig 1. This optimal microemulsion was used for the preparation of SLNs for loading OMC.

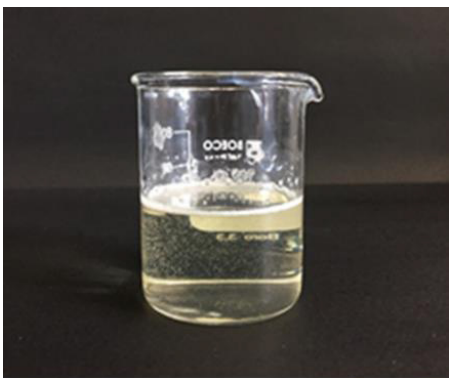

Fig. 1 Visual appearance of the optimal microemulsion (oil in water, O/W) formulation

2. Optimization processing parameters for OMC-loaded SLN

The results of various process variables for preparation SLNs are shown in Table 2. According to Table 2, we investigated the ratio of warm microemulsion (mL) and iced water (mL) using 1:20, 1:25, 1:30 and 1:35 which was modified from previous research (Ratcharin et al., 2012) and nowadays, few research have reported on this design. The size of the ratio of warm microemulsion (mL) and iced water (mL) using 1:25 significantly ($p<0.05$) decreased a mean particle size of 840.90±4.20 nm with the polydispersity index of 0.66±0.05 compared with each formulation in the same variables. Afterward, the homogenizer speeds (rpm) were examined using 4000, 6000, 8000 and 10000 rpm which was modified from previous research (Ratcharin et al., 2012). The homogenizing speed and time for mixing at 8000 rpm and 15 min, respectively, could significantly ($p<0.05$) reduce the particle size which was 219.77±1.82 nm with the polydispersity index of 0.51±0.04 compared with each formulation in the same variables. This might be due to the amount of surfactant and co-surfactants affect to SLNs particle size. Additionally, the use of proper homogenizing speed can reduce the free energy at the interfacial surface between the internal and external phase, thus making the particles smaller than lower speed.

Table 2 Various process variables for preparation solid lipid nanoparticles (SLNs)

Formulations	Variables	Particle diameter (nm)	Polydispersity index (PDI)
Microemulsion (mL):Iced water (mL)			
F16	1:20	1973.00±26.67^a	0.30±0.14^a
F17	1:25	840.90±4.20^b	0.66±0.05^a
F18	1:30	1028.67±24.9^c	0.52±0.07^a
F19	1:35	1239.33±7.37^d	0.39±0.01^a
Homogenizer speeds (rpm)			
F20	4000	840.90±4.20^a	0.66±0.05^a
F21	6000	878.50±9.66^a	0.50±0.04^a
F22	8000	219.77±1.82^b	0.51±0.04^a
F23	10000	333.77±1.89^c	0.54±0.03^a
Homogenization time (min)			
F24	5	414.53±5.50^a	0.64±0.03^a
F25	10	322.17±4.04^b	0.49±0.03^a
F26	15	219.77±1.82^c	0.51±0.04^a
F27	20	233.73±1.87^d	0.49±0.04^a

Remark: Values are given as mean ± S.D of triplicate. The different superscript letter in the same column represents significant differences when compared with each formulation in variables at $p<0.05$

Table 2 presents a summary of the optimum process for the preparation of SLNs that were mixed by glyceryl monostearate (GMS), Tween 80, PEG-40 hydrogenated castor oil and ethanol (10:10:15:20% w/w), respectively, then, the warm microemulsions were dispersed into a cold water at 2 to 4°C at the ratio of 1:25 (warm microemulsion, mL: iced water, mL), after that, the mixture was blended with a high-speed homogenizer at 8000 rpm for 15 min. After freezing, the obtained SLN showed a white fine powder as shown in Fig 2.

Fig. 2 The appearance of SLN loaded OMC

3. The characterization of SLNs

The characterization of prepared SLNs were investigated. Particle mean diameter of SLNs and polydispersity index (PDI) were determined by DLS. Obtained results showed the empty SLNs had the particle size of 219.77±1.82 nm with a minimum polydispersity index (PDI) of 0.51±0.04 (Fig.3A). OMC-loaded SLN was significant ($p<0.05$) resulting in larger particle size than empty SLNs which was 693.07±0.05 nm with a minimum polydispersity index of 0.56±0.04 (Fig.3B). This is possibly due to the presence of OMC inside of the solid lipid core of SLNs. However, mean diameters of OMC-loaded SLN showed particle in nanosize range without aggregation.

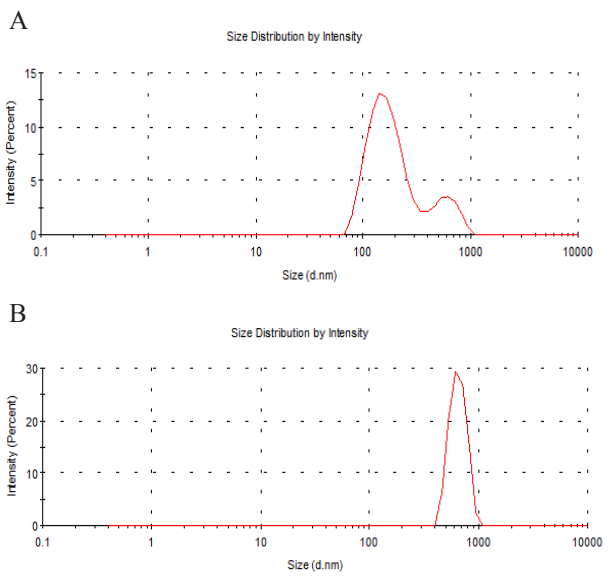

Fig. 3 The particle size and distribution of empty solid lipid nanoparticles (SLNs) (A) and solid lipid nanoparticles (SLNs) loaded octyl methoxycinnamate (10% w/w) (B)

The SEM and TEM analysis of OMC-loaded SLN are shown in Fig. 4. SEM micrograph showed a surface smooth and TEM image seen to be spherical in shape. The particle size as given by SEM and TEM were in line with that found using DLS. The result of entrapment efficiency (% EE) of OMC-loaded SLN was 99.89±0.02%. Obtained result was higher than previously report (Liu et a., 2015; Xu et al., 2021). This might be the sufficiently high solubility of the OMC in the lipid melt. High encapsulation of lipophilic agents is usually recorded for poorly water-soluble in lipid nanoparticles (Andreani et al., 2020).

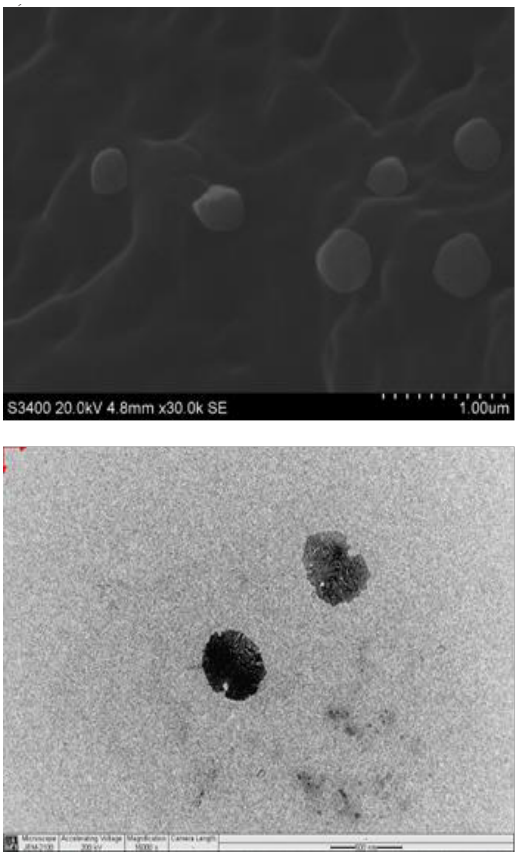

Fig. 4 Images of octyl methoxycinnamate (OMC)-loaded solid lipid nanoparticles (SLNs); scanning electron microscope (SEM) at x30000 magnification (A) and transmission electron microscopy (TEM) at x15000 magnification (B)

4. The physicochemical stability of OMC-loaded SLN

The physicochemical stability of OMC-loaded SLN were determined under three storage conditions; RT, 4°C and 40°C for 30 d. Results showed that the physical appearance of SLN remained as white powder under all conditions of testing. The particle size of OMC-loaded SLN under storage were found to be larger than initial condition ($p<0.05$). The PDI of OMC-loaded SLN under 4°C and 40°C showed no significant differences ($p>0.05$) when compared with the initial condition. Entrapment efficiency (% EE) of OMC-loaded SLN at all conditions tested were found to be statistically significant ($p>0.05$) compared with initial condition as presented in Table 3. This may be attributed to a rearrangement of the solid lipid (GMS) core, leading to changes in particle size and the presence of emulsifier that may lead to drug expulsion from solid lipid nanoparticles (Mulla et al., 2009; Radaic et al., 2014). Therefore, lowered entrapment

efficiency may be due to expulsion during lipid modification.

Table 3 Physicochemical stability of octyl methoxycinnamate (OMC)-loaded solid lipid nanoparticles (SLNs)

Conditions	Particle diameter (nm)	Polydispersity index (PDI)	Entrapment efficiency (% EE)
Initial	693.07±0.05[a]	0.56±0.04[a]	99.89±0.02[a]
Room temperature	821.93±2.87[b]	0.70±0.04[b]	98.07±0.17[b]
4°C	869.60±4.23[c]	0.47±0.05[a]	98.44±0.25[c]
40°C	879.70±6.68[d]	0.65±0.08[a]	98.76±0.22[d]

Remark: Values are given as mean ± S.D of triplicate. The different superscript letter in the same column represents significant differences when compared with initial condition at $p<0.05$

Conclusion

The findings of the study showed that OMC-loaded SLN were prepared successfully by microemulsion method. The preparation of the first oil in water microemulsion were investigated. Optimal microemulsions composed of glyceryl monostearate (GMS) as solid lipid, Tween 80 and PEG-40 hydrogenated castor oil as surfactant and ethanol as co-surfactant which gave the transparent form. The OMC-loaded SLNs prepared by the warm microemulsions were dispersed into a cold water at the ratio of 1:25, mixed with a high-speed homogenizer at 8000 rpm for 15 min, according to various process variables for SLNs investigated. The mean diameter of OMC-loaded SLNs was 693.07±0.05 nm, PDI was 0.51±0.04 and very high entrapment efficiency was achieved at about 99.89% . The TEM and SEM studies confirmed the particle size analysis and showed spherical shape morphology. The OMC-loaded SLN showed a good physicochemical stability during the shelf life. No obvious changes of color, degradation, or phase separation were observed. The mean particle size and PDI of OMC-loaded SLN showed larger than initial condition, however, they showed particle in nanosize and without aggregation. The entrapment efficiency was found to be slightly decreased at the range of 98.07-98.76% from initial condition. A further study is, planned to examine the OMC release and application to sunscreen formulation including a stability study.

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