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June 30th – July 1st, 2022

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Cosmetic nanoemulsion containing antioxidant honeysuckle essential oil formulated by ultrasonic emulsification

Wannisa Keawbankrud* and Atittaya Meenongwa
Health Science and Aesthetic Program, Department of Science, Faculty of Science and Technology, Rajamangala University of Technology Krungthep, Bangkok 10120, Thailand
**E-mail: Wannisa.k@mail.rmutk.ac.th*

Abstract:

The nanoemulsion containing antioxidant honeysuckle essential oil has been developed by ultrasonic emulsification. *Lonicera japonica* essential oil was extracted using a supercritical carbon dioxide process in ethanol, yielding 3.25 % w/w. The chemical constituents of the extract were analyzed using GC-MS, and 25 compounds were identified. In the total phenolic content (TPC) and total flavonoid content (TFC) analyses, gallic acid and quercetin were utilized as standards, respectively. The results showed TPC of 53.17 ± 0.17 mg GAE/ g and TFC of 104.37 ± 0.27 mg QE/ g. The antioxidant activity determined by the DPPH assay was expressed in the IC_{50} value of 20.835 ± 0.51 mg/mL. The nanoemulsion containing the extract, Tween 80 and DI water was further formulated by ultrasonic emulsification. The nanoemulsion formulation that worked best was a 12 %v/v surfactant concentration and a 1:2 oil-surfactant mixing ratio with a 30-minute ultrasonic duration. The results shows that ultrasonic emulsification can reduced the particle size to 71.1 ± 0.42 nm. The polydispersity index of this formulated nanoemulsion is 0.216 ± 0.01 indicating small size distribution of particle. The findings demonstrate the advantages of using an ultrasonic approach to create nanoemulsions that can be used in medication and cosmetic manufacture.

1. Introduction

Currently, cosmetic formulae are being developed to be more effective by using a dedicated delivery system that uses nanoparticles. Nanoemulsion is a nanoparticle-based application that combines oil, water, and a substantial amount of surfactant. It's a transparent liquid with excellent thermodynamic stability. The particle droplets in the formulation are typically smaller than 100 nm in size. In addition, it can be maintained from the film surface of the surfactant.[1] Nanoparticle delivery systems, such as nanoemulsion, have several intriguing properties, including increasing the absorption of active compounds through the skin, preventing dehydration, controlling the release of active substances, and providing a pleasant tactile sensation on the skin after use.[2-4] Nanoemulsion characteristics are determined by particle composition, manufacturing method, active material to be contained, and intended particle delivery mechanism. The physicochemical features of nanoemulsion, such as particle size, particle surface, and particle stability, are greatly influenced by these parameters.

Emulsification is a process of preparing emulsions that can be classified into two categories: high-energy emulsions and low-energy emulsions. High-powered preparations using the rotor-stator, high pressure homogenizer (HPH), or ultrasound are popular ways for preparing emulsions. The HPH has a turbulent flow pattern that causes shear stresses and cavitation in the samples, resulting in a smaller emulsion particle size (< 0.2 μm).[5,6] The ultrasonic homogenizer technique (UH) uses high frequencies in the range of 16 kHz to 1 MHz to continuously create numerous small cavities that break out quickly with the sample. Because of the turbulent flow and shear created by this approach, particle size is reduced. Furthermore, the type of oil used to make nanoemulsion is one importance in achieving the necessary nanoemulsion properties. The lightweight oils should be used in the preparation of nanoemulsions since it is simple to produce nanoparticles.

Honeysuckle, or *Lonicera japonica* (*L. Japonica*), is a member of the *Caprifoliaceae* family and is widely present to East Asia, including China, Korea, and Japan. Honeysuckle flowers can be utilized to extract essential oils that are light in weight. It's frequently seen in spa products to create a feeling of relaxation. Additionally, antioxidant, antiviral, anti-inflammatory, and antibacterial effects of the essential oil have also been reported.[7,9] It is due to the present of polyphenol compounds,[10,11] triterpene saponins, fatty acid esters and long-chain hydrocarbon[12] in the essential oil of *L. japonica* flower. Furthermore, it is often used in food and cosmetics due to its aromatic and highly bioactive activity.[7,13]

The goal of the research is to create new nanoemulsions with the ultrasonic preparation method that comprise essential ingredients such as essential oils, honeysuckle flowers, and surfactants (Tween 80). The antioxidant activity of the essential oils from honeysuckle flowers are also studied to be probably further an application in the cosmetic industry.

2. Materials and Methods

2.1 Materials and instrumentation

The plant material, dried honeysuckle flowers were commercially purchased from the shop in Chiang Mai province, Thailand. All chemicals were analytical-reagent grade and used without further purification. The chemicals included ethanol (LAB L), gallic acid (Sigma-Aldrich), sodium carbonate (Kemaus), DI water (Fisher, HPLC grade), Folin Ciocaltue's reagent (Loba

Chemie), quercetin (Sigma, HPLC grade), sodium nitrite (Kemaus), aluminium chloride hexahydrate (Kamaus), sodium hydroxide (Univar), 2,2-Diphenyl-1picrylhydrazyl (DPPH) (Aldrich) and Tween 80 (Krungthep Chemi).

The essential oil was extracted from honey suckle flowers on supercritical CO_2 extraction equipment, Guangzhou Heaven-Sent Industrial Co., Ltd. The chemical constituents of the extract were analyzed using a gas chromatography/mass spectrometry (GC-MS) system, gas chromatography, Agilent, 7890A linked to a mass selective detector, 5975C and the column DB-5MS, 30 m × 250 µm × 0.25 µm. The absorbance was measured on a UV-Vis spectro-photometer, Jasco, V-630. The DPPH assay was performed on a microplate reader, BioTek, Synergy H1. The nanoemulsion was prepared on an ultrasonic sonicator, Cole-parmer, CP-750. with a maximum power output of 750 W. Particle size and size distribution of the nanoemulsion were determined by scanning electron microscope (SEM), JEOL, JSM-6610LV. The nanoparticle size distribution was determined on a particle analyzer, Beckman counter, Delsa Nano C. The stability of nanoemulsion was tested on a centrifuge equipment, Hettich mikro 22r,

2.2 Honeysuckle essential oil extraction by supercritical carbon dioxide (SC-CO_2) in ethanol

The crushed honeysuckle flowers (25 g) and ethanol (20 mL) was added into the equilibrium cell. To increases carbon dioxide contact with honeysuckle, a hollow cylinder with glass fibers was installed. Before the experiment, the metering valve and the solute trap were weighed. The tools were assembled using a set of equipment that included a pressure booster pump and a heater. Then, the temperature within the bathtub was adjusted as needed to 35, 40 and 45 °C to complete the experiment. The pressure was then set to 130, 150, and 170 bars and let it balance for 30 minutes. After that, valves 2 and 3 were slowly opened to set the CO_2 flow rate to 0.5 mL/min, and samples were collected for every 100 mL of CO_2 consumed. Finally, valve 3 and solute trap were removed to determine the extract, then rinsed with ethanol (15 mL).

2.3 Determination of total phenolic and flavonoid content

The total phenolic content (TPC) was determined by the Folin-Ciocalteu colorimetric method adapted from previous report.[14] To produce the standard curve, gallic acid was diluted in 80% (v/v) ethanol to make the standard solutions, which had concentrations from 6.25 to 100 µg/mL. The extract was prepared by diluting it in the ratio of 1:5 (w/v) with 80% (v/v) ethanol. The test tube was filled with distilled water (0.5 mL) water and 10% (w/v) FolinCiocalteu reagent (125 µL) followed by standard or extract (125 µL), set for 6 min at room temperature in the dark. After that, 7% (w/v) Na_2CO_3 (1.25 mL) was added and adjusted the total volume to 3 mL by distilled water, the mixtures were set aside for 90 min at room temperature in the dark. The absorbances of the mixtures were measured at 760 nm, and the amount of phenolic compounds in the extract was determined by comparing it to the gallic acid standard curve, $y = 171.29x$, $R^2 = 0.9968$. The results were calculated to the ratio of mg of gallic acid equivalent/ g of extract.

The total flavonoid content (TFC) was analyzed by aluminium chloride colorimetric method according to the reference.[15] Quercetin was used to prepare the standard solutions with the concentration from 6.25 to 100 µg/mL in 80% (v/v) ethanol. The extract solution was prepared to the concentration of 1 mg/mL. In the test tubes, 95% (v/v) ethanol (1.5 mL), 10% (w/v) $AlCl_3$ (0.1 mL), 1 M CH_3COOK (0.1 mL) and distilled water (2.8 mL) were mixed, then the standard solution or the extract (0.5 mL) was added. The mixtures were set aside for 30 min at room temperature. Subsequently, the absorbance of each mixture was measured at 415 nm. The total flavonoid content was calculated from the quercetin standard curve, $y = 20.879x$, $R^2 = 0.9997$. The results show the mg of quercetin equivalent/g of extract. The determination of total phenolic and flavonoid content was repeated three times.

2.4 Antioxidant activity

Antioxidant activity of the extract was determined by DPPH radical scavenging assay compared with ascorbic acid.[16] The 0.25 mM DPPH solution was prepared in 80% (v/v) ethanol. Ascorbic acid was dissolved in distilled water to achieve the concentration from 0.01 to 100,000 µg/mL. The extract was dissolved in 80% (v/v) ethanol to obtain the concentration from 50 to 1000 µg/mL. In a 96-well microplate, DPPH (50 L) was added first, followed by standard or extract or 50 L blank, mixed well, and left for 30 minutes at room temperature in the dark. The absorbance was then measured at 515 nm. The absorbance was calculated for the %scavenging activity according to the equation below.

$$\text{Scavenging activity (\%)} = (A_0 - A_1)/A_0 \times 100$$

When A_0 is the absorbance of control (DPPH), A_1 is the absorbance of samples. Then, 50% scavenging concentration (IC_{50}) of the sample was determined, demonstrating the concentration that can trap 50% of free radical. The tests were repeated three times.

2.5 Nanoemulsion preparation

The preparation the nanoemulsion (Figure 1) was made utilizing the oil-in-water (O/W) method, which involved formula creation with honeysuckle flower oil and a nonionic surfactant (Tween80) with three ratios, 1:1, 1:2 and 1:3 (v /v). The composition of each formulation was shown in Table 1. A magnetic stirrer was used to mix at 400 rpm obtaining large particle emulsions. The emulsion was then placed in ultrasonic

sonicator with a maximum power. The sonication time was varied to 10, 20 and 30 min. The sonotrode head was immersed in a coarse emulsion, where the sonicator probe provides a disrupting force that reduces the droplet diameter to a nanoemulsion.[17]

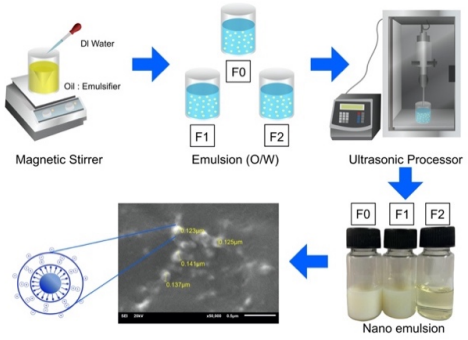

Figure 1. Preparation of nanoemulsion.

Table 1. The composition of different formulas of honeysuckle essential oil nanoemulsion.

Formulation	Oil: surfactant ratio (v/v)	Composition of different components in formulations (%)		
		oil	surfactant	DI water
F0	1:1	6	6	88
F1	1:2	6	12	82
F2	1:3	6	18	76

The stability of the emulsion was tested by Heating-Cooling cycle method. The emulsion was centrifuged at 10,000 xg for 30 min and kept at 4 °C for 48 h and then stored at 40 °C for 48 h. The experiment was repeated for 6 cycles. The it was further tested by Freezing-Thawing cycle method. The emulsion was frozen at -21 °C for 48 h and then stored at 25 °C for 48 h. This experiment was done for 3 cycles. The change was observed with bare eyes. The emulsion is stable if there is no separation in the layer.[18]

3. Results & Discussion

3.1 Honeysuckle flower extraction

Honeysuckle essential oil was extracted in ethanol using supercritical carbon dioxide (SC-CO_2), yielding a green solution with mild scent of the flower. The solution was concentrated by evaporation to get a 3.25% yield (Figure 2). The addition of ethanol would boost the polarity of the solvent, allowing large-scale extraction of essential compounds.[19] Supercritical carbon dioxide extraction can extract essential oils for 4-5 times longer than distillation, and the essential oils have no solvent contamination.

3.2 Chemical composition analysis of honeysuckle essential oil

The chemical composition of the essential oil analyzed by GC-MS (Figure 3) is found a total of 25 substances. According to the classification, saturated fatty acids with 6-18 C-atoms include hexanoic acid, dodecanoic acid, tetradecanoic acid, hexadecanoic acid and octadecanoic acid. There are unsaturated fatty acids with 18 C-atoms which are linoleic acid and linolenic acid. It confirms that the essential oil contains a fatty acid that can be used to make nanoemulsions. Phenylethyl alcohol, an aromatic molecule also found in honeysuckle flower essential oil, is particularly important.

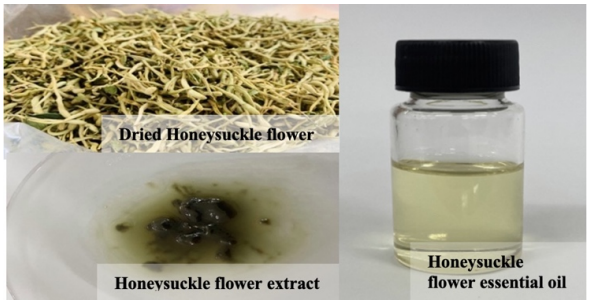

Figure 2. The essential oil extracted from honeysuckle flower by supercritical carbon dioxide in ethanol.

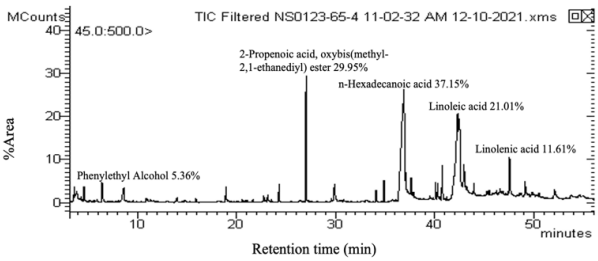

Figure 3. GC-MS chromatograph of honeysuckle essential oil.

3.3 Total phenolic and flavonoid content and antioxidant activity of honeysuckle essential oil

The antioxidant compounds in honeysuckle essential oil were determined in the term of the total phenolic and flavonoid content. Table 2 shows that the essential oil contains both phenolic and flavonoid compounds that are related to antioxidant activity expressed by the IC_{50} value.

Table 2. Total phenolic content (TPC), total flavonoid content (TFC) and IC_{50} value of honeysuckle essential oil.

Extract	TPC (mg GAE/g)	TFC (mg QE/g)	IC_{50} (mg/mL)
honeysuckle essential oil	53.17± 0.17	104.37 ± 0.27	20.835 ± 0.51

3.4 The preparation and stability of nanoemulsion

Three formulas of nanoemulsion (F0, F1 and F2) were prepared by honeysuckle flower essential oil and surfactant in various ratios (see Table 1). Under ultrasonic conditions, when the sonication time is

increase to 30 min, F0 appears as a white opaque liquid emulsion with smooth texture and enhanced luster. F1 is a smooth, milky white to yellow liquid emulsion with higher shine, whereas F2 is clear yellow liquid emulsion (Figure 4).

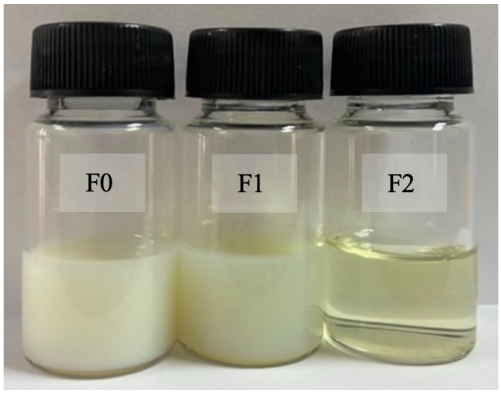

Figure 4. Three formulas of nanoemulsion reduced in size particle with ultrasonic emulsification at 30 min.

As indicated in Table 3, the stability of nanoemulsion was determined by centrifugation at 10,000 rpm for 30 min., a Heating-Cooling test and Freezing–Thawing test have found that there is no layer separation in the nanoemulsion.

Table 3. Stability of Nanoemulsion.

Formulation	Centrifugation	H–C [a]	F–T [b]	Inference
F0	+	+	+	Passed
F1	+	+	+	Passed
F2	+	+	+	Passed

[a] Heating–Cooling cycle
[b] Freezing–Thawing cycle

3.5 Particle size and Zeta potential measurements of nanoemulsion

Tween 80 was chosen as an emulsifier in this experiment because of its tiny molecular size and flexible structure. It contributes to make the final oil particle size small and stable, and it operates in conjunction with the size reduction achieved using an ultrasonic process, the energy utilized to reduce the size, and the emulsification period at 10, 20, and 30 min.

The particle size of the three formulas F0, F1 and F2 is observed the different reduction in size when the emulsification time changes. At 10 min, the mean droplet size appears 159.2, 146.8 and 415.3 nm, respectively. When increase the emulsification time to 20 min, the particle size was reduced to be 130.9, 87.2 and 146.2 nm, respectively. At 30 min, it induces more reduction of the particle size to be 127.6, 71.1 and 33.7 nm, respectively (Figure 5). It may be deduced that extending the emulsification time reduces particle size, resulting in a nanoparticle emulsion with smaller particles.

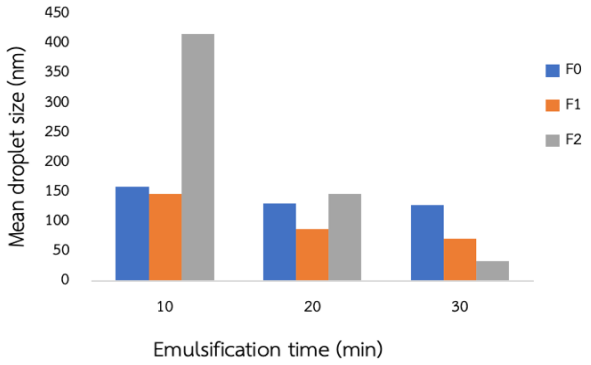

Figure 5. Effect of emulsification time on the droplet size of nanoemulsion.

In addition, the amount of emulsifier, Tween 80 has as effect on the particle size of each formulation (Figure 6). At 30 min, the formulation with the highest percentage of emulsifier (18% for F2) has the smallest nanoemulsion particle size of 33.7 ± 5.32 nm, compared to F0 and F1 with lower amount of emulsifier, inducing lager particle size. Although F2 nanoemulsion has the smallest mean droplet size at emulsification time of 30 min, it has a small agglomeration, indicating that it is unstable. According to the previous report, the smaller size of nanoemulsion shows more stability.[20] While the surfactant content also affects the stability of the nanoemulsion. The appropriate amount of surfactant helps to produce a small-sized and stable nanoemulsion. An excessive surfactants with fixed oil can make smaller size nanoemulsion but it is less stability resulting in agglomeration.

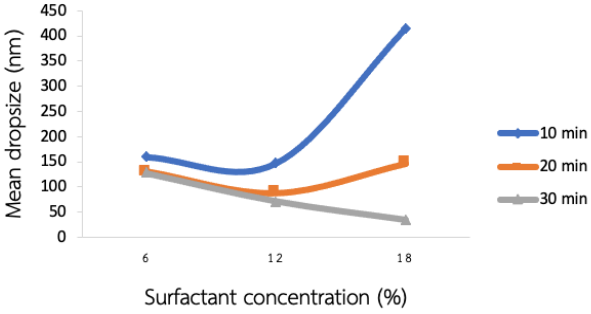

Figure 6. Effect of surfactant concentration on the droplet size of nanoemulsion at different emulsification time.

Table 4. Physicochemical characterization of three formulas of honeysuckle essential oil nanoemulsion after ultrasonic emulsification for 30 min.

Formulation code	Particle size (nm)	Polydispersity index	pH	Viscosity (cP)	Zeta potential (mV)
F0	127.6 ± 0.85	0.245 ± 0.01	5.44 ± 0.08	0.88 ± 0.01	-32.23 ± 1.21
F1	71.10 ± 0.42	0.216 ± 0.01	5.61 ± 0.11	0.88 ± 0.01	-31.35 ± 2.56
F2	33.70 ± 5.32	0.143 ± 0.02	4.01 ± 0.09	0.78 ± 0.01	-18.03 ± 3.48

All results shown by mean ± SD (n=5).

Moreover, the different dignity (Zeta potential) of nanoemulsion can indicate the stability of the formula. It involves the charges that surround each particle in the nanoemulsion, which should be negatively charged in oder to produce weak repulsion between particles and prevent coalescence. The data of Zeta potential different of the nanoemulsion are shown in Table 4. The F0 and F1 have a difference of more than -30 mV, indicating that they are stable. On the other hand, F2 has a difference of less than -30 mV, suggesting that it is unstable. This observation corresponds to the particle size distribution results and the previous reports[21-23] which has claimed that the unstable Zeta potential is between +30 and −30 mV and the stable potential should be greater or less than that value. The correlation between the Zeta potential difference and pH demonstrates that F0 and F1 have similar pH values, however F2 has a lower pH value, indicating higher acidity. The positive charge (H^+) increases, resulting of the Zeta potential difference shifts to more positive value.[21] The pH is the one of the most important parameters for the Zeta potential difference. If acid is added to nanofluid, the pH will drop, increasing the positive charge on the particle surface, resulting in more positive value of the Zeta potential.

3.6 Assessment of morphological alterations of nanoemulsion by scanning electron microscopes (SEM)

The average particle size and particle size distribution of nanoemulsions are determined to be between 20–200 nm because of the small droplet size and high stability. The polydispersity index (PDI) of nanoemulsion droplet emulsified for 30 min was determined using photon correlation spectroscopy at 25 °C. The nanoemulsion has a PDI value of less than 0.2 µm, which is in the range of 33-127 nm and has a spherical form (Figure 7). For skin permeability, a nanoemulsion size of 1-100 nm is ideal.[24] The F1 and F2 give the nanoemulsion size in this range (71.10 ± 0.42 nm and 33.70 ± 5.32 nm, respectively). F2 is smaller, but it is more unstable. As a result, F1 is suited for the development of cosmetic products.

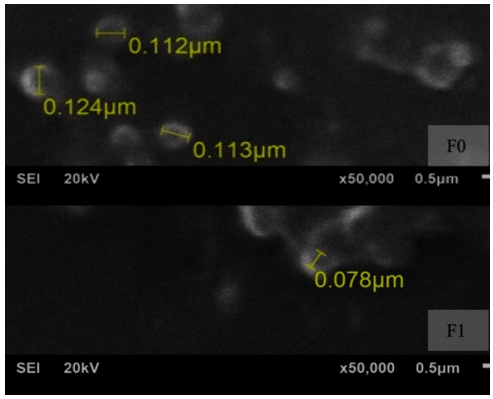

Figure 7. Particle size (µm) of F0 and F1 nanoemulsion at 30 min measured by scanning electron microscopes (SEM).

4. Conclusion

Honeysuckle *(Lonicera japonica*) from Chiang Mai province in Thailand is a flower with aromatic essential oil containing 25 compounds and antioxidant activity. When developed nanoemulsion combined with the oil (honeysuckle essential oil), surfactant (Tween 80) and water by ultrasonic emulsification method with appropriate oil-to-surfactant ratio of 1:2 and emulsification time of 30 minutes, it has small particle sizes of 71.1 nm. These findings support the further use of nanoemulsion in the cosmetics business.

Acknowledgements

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