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Preparation of solid lipid microcapsules via solid-in-oil-in-water dispersions by premix membrane emulsification

Masato Kukizaki*

Miyazaki Prefecture Industrial Technology Center, 16500-2 Higashi-kaminaka, Sadowara, Miyazaki 880-0303, Japan

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ABSTRACT

This study presents a novel method for the preparation of hydrophilic drug-encapsulated solid lipid microcapsules (SLMCs) with a narrow particle size distribution for drug delivery systems via solid-in-oil-in-water (S/O/W) dispersions by premix membrane emulsification and subsequent solidification of the oil phase in the S/O/W dispersion. The primary aspect of this work is to form nano-order solid particles of hydrophilic drugs in solid lipids and the secondary is to encapsulate of the nano-order particles in size-controlled lipid microcapsules. The prepared capsules had a matrix type structure composed of a high-melting triglyceride, glycerol trimyristate with a melting point of 55 °C. In the lipophilic matrix of the capsule, nano-order particles of a hydrophilic drug, vitamin B_{12} (VB_{12}) were embedded. Initially, a solid-in-oil (S/O) dispersion was prepared by water removal of the water droplets containing 1.1 wt.% VB_{12} in a water-in-oil emulsion preliminary prepared, followed by mixing with an external water phase at 60 °C to form a coarse S/O/W dispersion. By forcing the resultant S/O/W dispersion through a Shirasu porous glass (SPG) membrane with a mean pore diameter of 14.8 μm at this temperature under a transmembrane pressure of 25 kPa, uniformly sized S/O droplets were formed at a very high transmembrane flux (11.8 $m^3\ m^{-2}\ h^{-1}$). Subsequent solidification of the oil phase in the S/O/W dispersion resulted in SLMCs with a mean particle diameter of 15.4 μm and a high encapsulation efficiency (up to 93.5%). In premix membrane emulsification the transmembrane pressure affected the properties of the S/O/W dispersion and the resultant SLMCs. At the higher transmembrane pressures, smaller S/O droplets with broader size distributions and lower encapsulation efficiencies were produced, due to the higher shear stresses inside the membrane pores. The particle size of SLMCs was controlled by adjusting the membrane pore size and transmembrane pressure in premix membrane emulsification.

1. Introduction

Microcapsules are used in many different applications in chemical, cosmetic, food and pharmaceutical industries. In most microcapsules the shell materials are commonly natural and synthetic polymers; however, fats and oils are also used. Solid lipid microcapsules (SLMCs) are an interesting particulate carrier system for controlled drug delivery because they hold several advantages of a lower toxicity, a better biocompatibility and a higher bioavailability. For oral administration in drug delivery systems, the drugs encapsulated in SLMCs are released mainly due to the gradual degradation of the solid lipid by lipase present in the small intestine in human body [1]. This mechanism enables both the prolonged release of drugs and minimization of unfavorable toxic side effects. The drug-release properties of SLMCs for oral drug delivery systems are closely related to their size and size distribution. Therefore, it is very important to control the size and size distribution of SLMCs.

In the past few years, a few studies have been made on the preparation of lipophilic drug-encapsulated SLMCs using oil-in-water (O/W) emulsions [2-4]. Pietkiewicz et al. [2] and Jaspart et al. [4] prepared SLMCs from O/W emulsions by hot emulsification technique with a high-shear homogenizer and subsequent cold solidification. However, the hot emulsification results in broad size distributions of the emulsion droplets and the resultant SLMCs, due to the high mechanical shear [5,6]. Furthermore, it is difficult to encapsulate hydrophilic drugs (e. g. peptide and protein drugs) into SLMCs. Our previous study [7] proposed a novel method for the preparation of uniformly sized SLMCs encapsulating hydrophilic drugs from water-in-oil-in-water (W/O/W) emulsions by direct membrane emulsification [8,9] using Shirasu porous glass (SPG) membranes with a narrow pore size distribution [10,11] and subsequent solidification of the oil phase in the W/O/W emulsions. SLMCs of this type contain small water droplets within larger solid lipid particles and hydrophilic drugs are dissolved into the water

Abbreviations: SLMC, solid lipid microcapsule; S/O/W dispersion, solid-in-oil-water dispersion; S/O dispersion, solid-in-oil dispersion; SPG, Shirasu porous glass.

* Tel.: +81 985 74 4311; fax: +81 985 74 4488.
E-mail address: kukizaki@miyazaki-catv.ne.jp.

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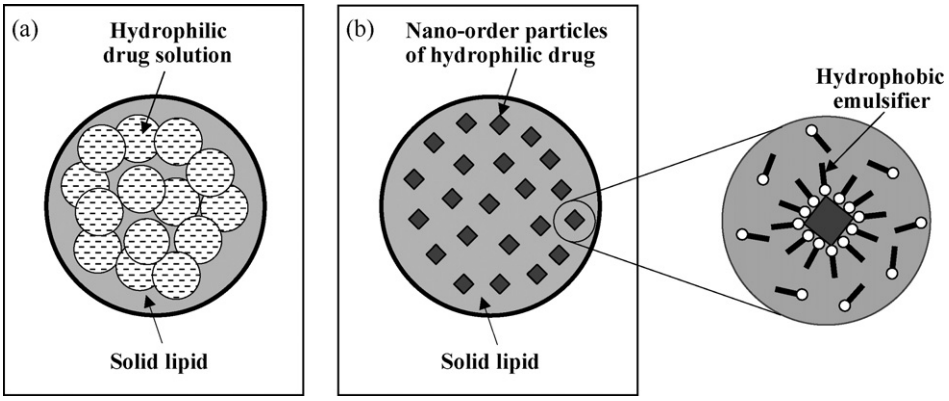

Fig. 1. Schematic illustration of the drug-encapsulated SLMCs prepared from (a) a W/O/W emulsion and (b) an S/O/W dispersion.

droplets, as shown in Fig. 1(a). With this method, a preliminary prepared water-in-oil (W/O) emulsion, in which a high-melting lipid is used as the oil phase and a hydrophilic drug is dissolved in the water phase, is forced through an SPG membrane into an external water phase at a temperature higher than the melting point of the oil phase to form a W/O/W emulsion with a narrow droplet size distribution. Subsequently, the W/O/W emulsion is cooled to room temperature to solidify the oil phase and then dried to produce SLMCs [7]. The droplet size of W/O/W emulsions and the particle size of the resultant SLMCs can be controlled by the pore size of SPG membranes employed. Furthermore, this method yields high encapsulation efficiencies because direct membrane emulsification allows the preparation of W/O/W emulsions under lower shear conditions than mechanical emulsification methods [7,12].

Despite of these advantages, there are still problems preventing the successful introduction of SLMCs to the pharmaceutical market with this method. Firstly, the SLMCs contain a considerable amount of water (up to 40 wt.%), which is a consequence of the fact that the water droplets within the SLMCs remain unchanged after the solidification of the oil phase in the W/O/W emulsions [7]. To ensure a microbiological stability of SLMCs and avoid the risk of biological degradation, it is desired that water content in SLMCs is as low as possible. Secondly, the direct membrane emulsification technique used for the production of W/O/W emulsions has the disadvantage of the low production rate. Typically, dispersed-phase fluxes through SPG membranes in direct membrane emulsification are between 0.01 and 0.1 $m^3\,m^{-2}\,h^{-1}$ [12]. The dispersed-phase flux in direct membrane emulsification has to be restrained to avoid the transition from a "size-stable" to "continuous outflow" zone [12,14,15] and to avoid the steric hindrance between droplets that may be formed simultaneously at the adjacent pores [16,17]. In direct membrane emulsification, the formation of uniform droplets is only possible within the size-stable zone, in which the mean droplet size is almost independent on the disperse phase flux [18].

The objective of the present study is to produce hydrophilic drug-encapsulated SLMCs with a narrow particle size distribution at higher production rates and to reduce the amount of water contained in the SLMCs. This study involves two main aspects: the primary aspect of this study is to form nano-order solid particles of hydrophilic drugs in solid lipids. The secondary aspect is to encapsulate of the nano-order particles in size-controlled lipid microcapsules. To minimize the water content in SLMCs, the preparation was based on solid-in-oil-water (S/O/W) dispersions instead of W/O/W emulsions. S/O/W dispersions of this type contain nano-order particles of hydrophilic drugs dispersed within the oil droplets, which are dispersed in an external water phase. In the present work, an S/O/W dispersion was prepared by water removal (dehydration) of the water droplets in a submicron-sized W/O emulsion and subsequent dispersing the resultant S/O dispersion into an external water phase by a mechanical stirring method at a temperature higher than the melting point of the high-melting triglyceride. In the W/O emulsion, hydrophilic drugs are dissolved into the water droplets. In contrast to conventional methods for preparing S/O/W dispersions reported by other authors [19,20], this process uses no organic solvents with toxic effects and allows nano-order particles of hydrophilic drugs to be dispersed into the oil phase in the S/O/W dispersion. The method chosen to produce S/O/W dispersion with a narrow droplet diameter distribution at high production rates is premix membrane emulsification [21,22], which allows the production of uniformly sized emulsion droplets at high transmembrane fluxes by forcing of a coarsely emulsified mixture (pre-mixed emulsion) through an SPG membrane. The SPG membrane acts here as a special kind of low-pressure homogenizing valve [23]. The optimal transmembrane fluxes with regard to droplet uniformity are typically above 1 $m^3\,m^{-2}\,h^{-1}$, which are one to two orders of magnitude higher than in direct membrane emulsification [23]. In this work, the coarse S/O/W dispersion prepared by the above technique was forced through an SPG membrane to disrupt the large S/O droplets in the S/O/W dispersion into uniformly sized small S/O droplets at the same temperature, followed by solidification of the oil phase in the S/O/W dispersion to form uniformly sized SLMCs. The uniformity of droplets produced by premix membrane emulsification can be often improved by passing several times through the membrane, as reported by Vladisavljevic et al. [23]. However, a single pass through the membrane is a simpler and easier process than several passes. From the viewpoint of a large-scale production of SLMCs, a simpler or easier operation is desirable for premix membrane emulsification. Therefore, the coarse S/O/W dispersion was passed only once through the membrane. Fig. 1(b) illustrates the inner structure of this type of SLMCs. In the lipid matrix of the capsule, nano-order particle of hydrophilic drugs are embedded. This work presents operating parameters involved in the preparation stages of S/O dispersions, S/O/W dispersions and SLMCs. The properties of the resultant SLMCs including particle size and size distribution, surface morphology and encapsulation efficiency of a hydrophilic model drug are reported.

2. Materials and methods

2.1. Materials

Vitamin B_{12} (VB_{12}; cyanocobalamin, molecular weight of $M_w = 1355\,g\,mol^{-1}$) with a melting point higher than 300 °C was used as a hydrophilic model drug. The density of VB_{12} determined with a pycnometer (Quantachrome-1000, YUASA-IONICS, Co., Ltd., Osaka, Japan) was 1.09 $g\,cm^{-3}$. Glycerol trimyristate with a melting point of 55 °C was used as a high-melting lipid. The lipophilic emulsifier selected for the preparation of W/O emul-

sions was polyglycerol polyricinoleate (PGPR), due to the fact that PGCR has a higher viscosity and a lower hydrophilic–lipophilic balance (HLB) value (HLB < 1) and thus prevents the aggregation and coagulation between the water droplets [24]. The oil phase was glycerol trimyristate containing 5 wt.% PGPR and the water phase was distilled water containing VB_{12} in the concentration range of 0.2–1.1 wt.%. The hydrophilic emulsifier chosen for the preparation of S/O/W dispersions was Tween 40 (polyoxyethylene (20) sorbitan monooleate), which is found to be suitable for membrane emulsification [12,13]. Distilled water containing 1.0 wt.% Tween 40 was used for the external water phase in S/O/W dispersions.

Glycerol trimyristate, VB_{12} and Tween 40 were purchased from Wako Pure Chemical Industries Co., Ltd. (Tokyo, Japan). PGPR was obtained from Sakamoto Yakuhin Kogyo Co., Ltd. (Osaka, Japan). Diethyl ether and the acetate buffer solution composed of acetic acid and sodium acetate, which were used for the determination of the actual amount of VB_{12} encapsulated into the SLMCs, were purchased from Wako. All the materials were used without any further purification.

Tubular SPG membranes (10 mm in outer diameter, 0.8 mm in thickness and 20 mm in length) were purchased from SPG Technology Co., Ltd. (Miyazaki, Japan) and used for premix membrane emulsification. SPG membranes have uniformly sized pores that form a three-dimensional network [10,11]. The mean pore diameters of the membranes were 5.4, 7.6, 9.9 and 14.8 μm. The membrane porosity was in the range of 53–58%.

2.2. Procedure for preparation of S/O dispersions and coarse S/O/W dispersions

Fig. 2 shows a preparation diagram for SLMCs. A submicron-sized W/O emulsion was prepared using a high-shear homogenizer (Ultra Turrax® Model T25, IKA Works, Inc., Wilmington, USA) at 24,000 rpm for 3 min. The emulsification was carried out at 60 °C where the oil phase was entirely melted. The volume fraction of water droplets in the W/O emulsion was fixed at 0.4. The resultant W/O emulsion was converted into a solid-in-oil (S/O) dispersion by vacuum evaporation of the solvent (water) in the water phase under a reduced pressure of 20 Pa at 60 °C until the water was removed. VB_{12} is thermally stable at this temperature, and thus VB_{12} in the S/O dispersion is expected to exist as solid nanoparticles after this water-removal process. The resultant S/O dispersion became the dispersed phase for subsequent emulsification. The S/O dispersion was gently mixed with an external water phase using a stirrer in the ratio of 1:2 to produce a coarse S/O/W dispersion.

2.3. Experimental set-up for premix membrane emulsification and procedure for preparation of SLMCs

The experimental set-up for premix membrane emulsification and the droplet disruption process are shown in Figs. 3 and 4, respectively. A tubular SPG membrane was installed inside a membrane module and an S/O/W dispersion of 200 cm^3 was placed in a pressure vessel. The tube side of the module was open to the atmosphere. The coarse S/O/W dispersion was then forced through the SPG membrane under the transmembrane pressure range of 25–200 kPa by compressed nitrogen gas at 60 °C. The product of S/O/W dispersion was collected from the interior of the tubular membrane into a measuring cylinder. The transmembrane pressure was measured with a pressure gauge attached directly to the module. Transmembrane flux of the coarse S/O/W dispersion permeated through the SPG membrane, J was calculated from the following equation:

$$J = \frac{V_p}{At} \quad (1)$$

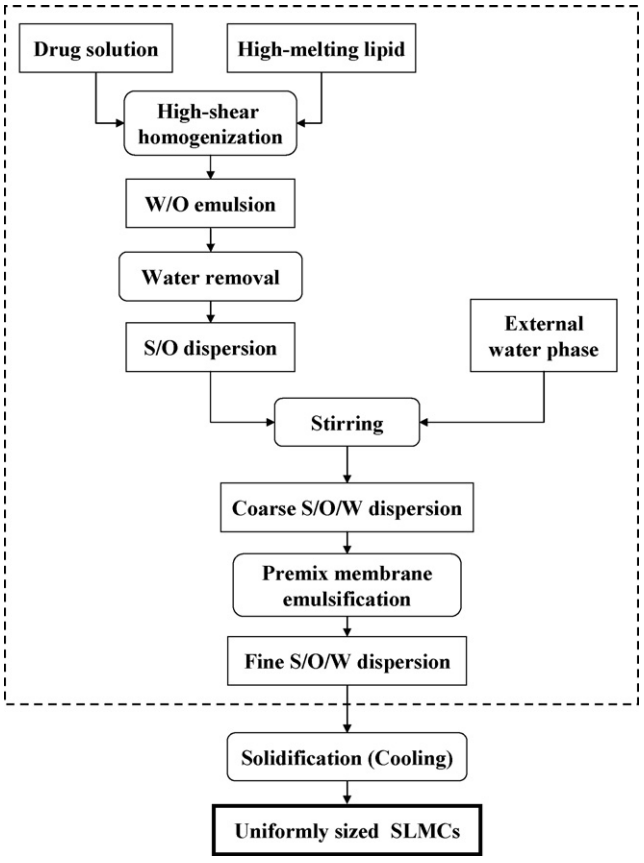

Fig. 2. Flow diagram for the preparation of SLMCs via S/O/W dispersion by premix membrane emulsification. The dashed area represents the temperature-controlled operations at a temperature higher than the melting point of lipids.

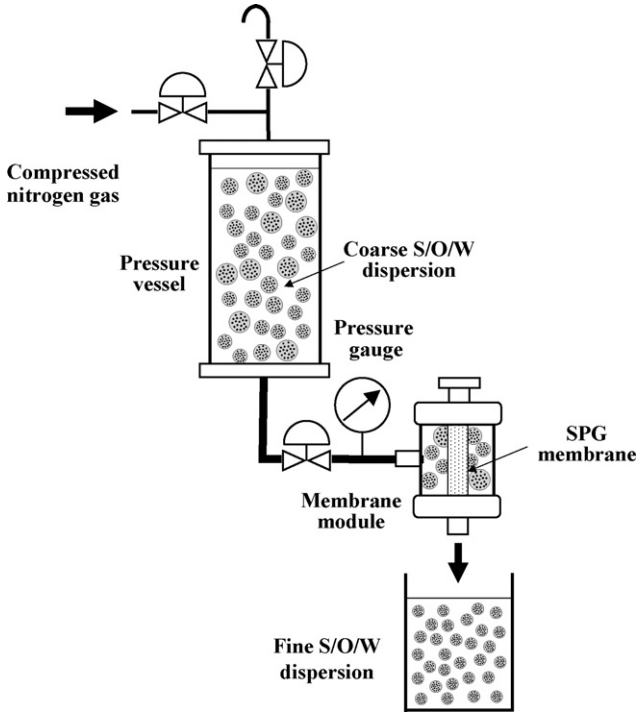

Fig. 3. Schematic diagram of the experimental set-up for premix membrane emulsification.

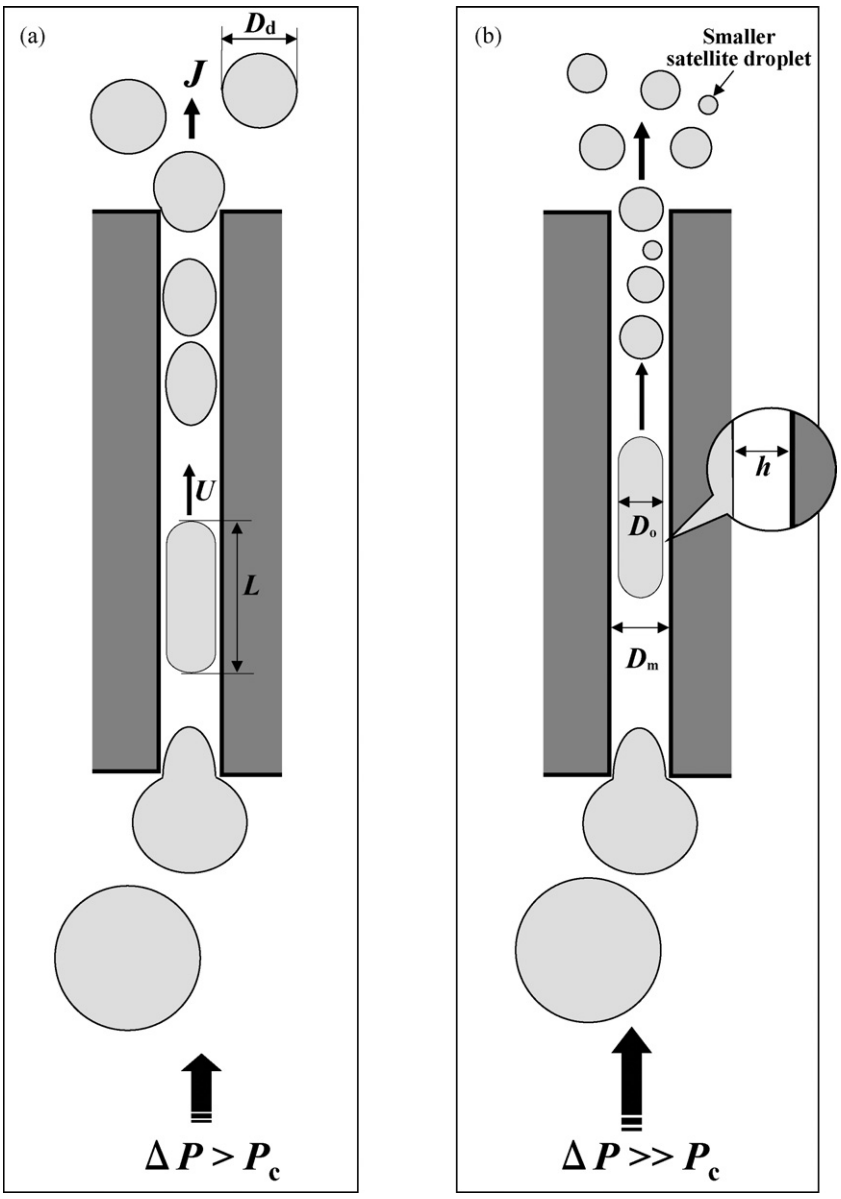

Fig. 4. Schematic diagram of the droplet disruption process in premix membrane emulsification: (a) moderate droplet disruption at lower transmembrane pressures; (b) intensive disruption at higher transmembrane pressures.

where V_p is the volume of S/O/W dispersion permeated through the membrane, A is the effective membrane area (3.75 cm^2 in this study) and t is the time taken for the permeation of the coarse S/O/W dispersion.

The S/O/W dispersions produced were cooled at room temperature to cause the oil phase to solidify and then filtered through a membrane filter (cellulose nitrate, pore diameter 1 μm; Advantech Toyo Kaisha, Tokyo, Japan). After being rinsed with pure water and dried under a reduced pressure of 20 Pa at room temperature, resulting in VB_{12}-encapsulated SLMCs.

2.4. Measurement and analysis of W/O emulsions, S/O and S/O/W dispersions, and SLMCs

The droplet size distributions of W/O emulsions and S/O/W dispersions, and the particle diameter distributions of S/O dispersions and SLMCs were determined using a laser diffraction particle size analyzer (SALD7100, Shimadzu, Kyoto, Japan), which allowed the detection of particles in the range of 50 nm to 300 μm. The monodispersity of the droplets or particles was characterized by the span of droplet/particle diameter distribution, δ [8]:

$$\delta = \frac{^{90}D - {}^{10}D}{^{50}D} \quad (2)$$

where ^{90}D, ^{50}D and ^{10}D are the droplet/particle diameters corresponding to 90, 50, and 10 vol.% on the relative cumulative size distribution curve, respectively.

The S/O/W dispersions prepared were observed using a temperature-controlled optical microscope (SRS-1, Malcom, Tokyo, Japan) at 60 °C. The morphology of SLMCs prepared was observed using a scanning electron microscope (S-800M, Hitachi High-Technologies, Tokyo, Japan). The sample of SLMCs was sputter-coated with platinum–palladium alloy (8:2) using an ion sputter coater (E-1030, Hitachi High Technology Co., Ltd., Tokyo, Japan). The amount of water contained in both the S/O dispersions and the SLMCs were determined using a Karl Fischer moisture meter (MKA-3p; Kyoto Electronics Manufacturing, Kyoto, Japan).

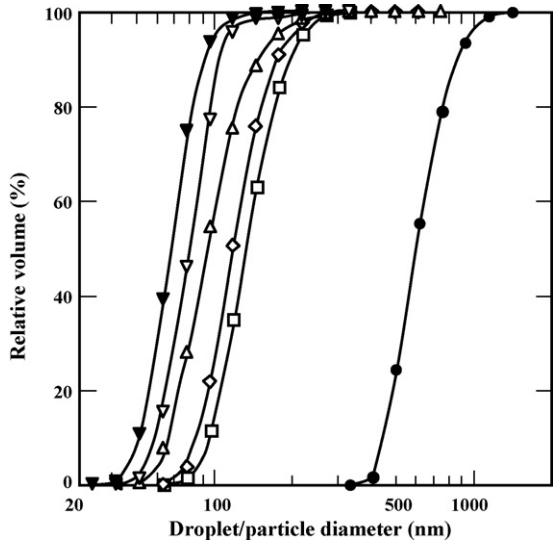

Fig. 5. A cumulative droplet diameter distribution (●) of a W/O emulsion prepared using a high-shear homogenizer and cumulative particle diameter distributions of S/O dispersions prepared by water removal of the water droplets in the W/O emulsions. The concentrations of VB12 were (▼) 0.2 wt.%, (▽) 0.3 wt.%, (△) 0.5 wt.%, (◊) 0.7 wt.% and (□) 1.1 wt.% of VB12.

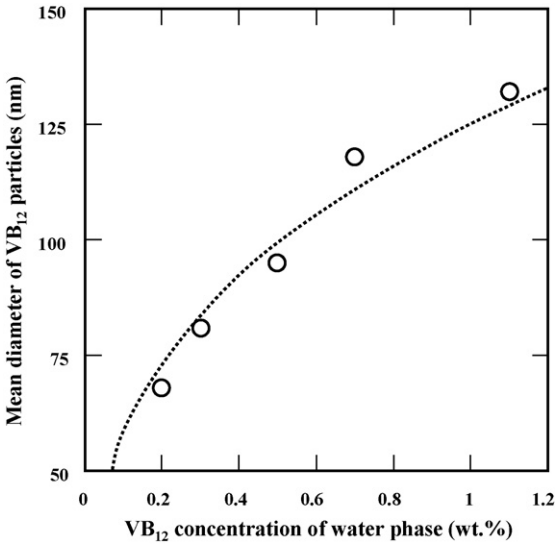

Fig. 6. Relationship between the mean particle diameter of S/O dispersion and concentration of VB12 dissolved in the water droplets in the primary W/O emulsion. The dotted line shows the particle diameter of S/O dispersion calculated from Eq. (4).

2.5. Encapsulation efficiency of VB_{12}

Encapsulation efficiency, α of VB_{12} in the SLMCs prepared was determined using the following equations:

$$\alpha = \frac{W_{the}}{W_{act}} \times 100 \quad (3)$$

where W_{act} is the actual amount of VB_{12} encapsulated into the SLMCs and W_{the} is the theoretical amount of VB_{12} contained in the SLMCs. The W_{act} values were determined as follows [7]: glycerol trimyristate is soluble in diethyl ether but insoluble in acetate buffer solution (0.1 mol dm^{-3}, pH 5), while VB_{12} is soluble in the acetate buffer solution but insoluble in diethyl ether. Therefore, SLMCs sample was mixed with diethyl ether and acetate buffer solution, followed by shaking for 1 h to extract VB_{12} with the acetate buffer solution. The amount of VB_{12} extracted was subsequently determined using a UV–visible spectrophotometer (Multispec-1500, Shimadzu, Kyoto, Japan) at a wavelength of 361 nm.

3. Results and discussion

3.1. Preparation of S/O dispersions

S/O dispersions were prepared from preliminary prepared W/O emulsions by water removal of the water droplets containing VB_{12}. This study is the first attempt to prepare S/O dispersions by dehydration of water droplets in W/O emulsions. Fig. 5 shows the particle diameter distributions of S/O dispersions prepared by dehydration of the water droplets with a mean droplet diameter of 590 nm in the W/O emulsions prepared using a high-shear homogenizer. Under the condition, VB_{12} particles with mean diameters of 68–132 nm were formed from the water droplets containing VB_{12} in the concentration range of 0.2–1.1 wt.%. The mean diameter of VB_{12} particles in the S/O dispersions decreased with increasing the concentration of VB_{12} dissolved in the water droplets in the W/O emulsions. The span values for the particle size distributions of these S/O dispersions were between 0.73 and 0.93, which were close to the δ value of 0.80 for the droplet diameter distribution of the primary W/O emulsion.

If water droplets in a W/O emulsion are entirely converted into spherical solid particles of solute (hydrophilic drug) without any coalescence and aggregation by dehydration of the water droplets, the particle diameter, D_p of the resultant S/O dispersion can be calculated from the following equation using the droplet diameter, $D_{d,w}$ of the W/O emulsion:

$$D_p = \left(\frac{M_w C}{\rho}\right)^{1/3} D_{d,w} \quad (4)$$

where M_w, C and ρ are the molecular weight, concentration and density of solute in the water droplets. In the present study, the M_w and ρ values for VB_{12} used as a hydrophilic drug are 1355 g mol^{-1} and 1.09 g cm^{-3}, respectively. Substitution of both the M_w and ρ values for VB_{12} and the measured D_d value of 590 nm into Eq. (4) gives the dotted line shown in Fig. 6. The experimental D_p values were in agreement with the calculated line, indicating that the above assumption holds in the present experimental system. This is because the molecules of lipophilic emulsifier (PGPR) adsorbed at the water–oil interface of the W/O emulsion can inhibit coalescence and aggregation between the water droplets, due to the steric repulsion by the emulsifier-molecule layers formed on the particle surface [5]. Similarly, the nano-order VB_{12} particles contained in the S/O dispersion would be stabilized by the PGPR molecules adsorbed at their solid–oil interface without coalescence and aggregation between the particles (Fig. 1(b)).

Fig. 7 shows the amount of water contained in the S/O dispersions determined using a Karl Fischer moisture meter as a function of VB_{12} concentration. Only 0.51–0.68 wt.% of water was contained in the S/O dispersion. This result indicates that the water droplets in the primary W/O emulsion were almost entirely converted into solid particles of VB_{12}. The water content slightly decreased with increasing the concentration. A small amount of water contained in the S/O dispersions is probably because the water in the water phase is slightly dissolved into the oil phase during the preparation process of the primary W/O emulsion [25]. The lower water content in the S/O dispersions for the higher VB_{12} concentration is a consequence of the fact that water in the water phase in the primary W/O emulsion is less soluble in the oil phase for the higher solute (VB_{12}) concentration due to the higher osmotic pressure of the water phase [25].

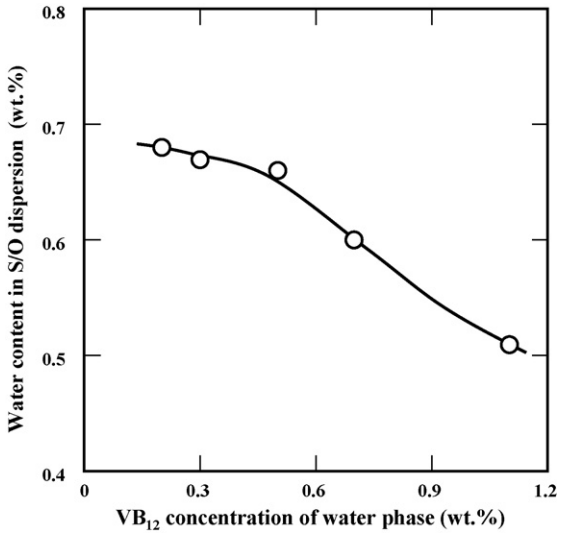

Fig. 7. Water content in S/O dispersion as a function of VB12 concentration of the water phase in the primary W/O emulsion.

These results showed that dehydration of water droplets in W/O emulsions enables to prepare S/O dispersions containing nano-order particles and to control the particle size by adjusting the droplet size of the primary W/O emulsions and the solute concentration of the water phase.

3.2. Preparation and characterization of S/O/W dispersions and SLMCs

The S/O dispersion with a mean particle diameter of 132 nm prepared under the condition given in Fig. 5 was gently mixed with an external water phase (1.0 wt.% Tween 40 solution) using a stirrer, resulting in a coarse S/O/W dispersion with a mean droplet diameter of approximately 100 μm as shown in Fig. 8(a). To achieve additional homogenization and size reduction of the S/O droplets in the S/O/W dispersion, the S/O/W dispersion was then forced through an SPG membrane with a mean pore diameter of 14.8 μm at 60 °C under a transmembrane pressure of 25 kPa. As shown Fig. 8(a), the resultant S/O/W dispersion had a narrow droplet diameter distribution, and the mean diameter of the S/O droplets was 15.5 μm, which was slightly larger than that of the membrane pores (14.8 μm). Fig. 9(a) is an optical micrograph of the S/O/W dispersion formed from the coarse S/O/W dispersion by premix membrane emulsification under the condition given in Fig. 8(a). The particle diameter distribution of SLMCs obtained by solidification of the resultant S/O/W dispersion is shown in Fig. 8(b). It can be seen that the SLMCs had a narrow diameter distribution and there was no significant change in the diameter distribution of the S/O droplets in the S/O/W dispersion during their solidification. Under these conditions, up to 93.5% of VB_{12} was encapsulated in the SLMCs, owing to a low and controllable shear stress inside the membrane pores in premix membrane emulsification compared to mechanical emulsification techniques [23]. This result also shows that during premix membrane emulsification of the S/O/W dispersion, pore plugging by the VB_{12} particles hardly occurred under the given operating conditions. A small amount of leakage of VB_{12} would be ascribed to VB_{12} particles expulsed from the S/O droplets into the external water phase, due to a shear stress caused by forcing the S/O/W dispersion through the membrane pores in premix membrane emulsification. Only 0.55 wt.% of water was contained in the SLMCs, owing to the use of S/O/W dispersions instead of W/O/W emulsions. This water content value was extremely lower than that of SLMCs prepared from W/O/W emulsions, which is approximately 40 wt.% [7]. The surface morphology of the SLMCs was observed by SEM. As shown in Fig. 9(b), the SLMCs prepared are nearly spherical in shape and their surface is pleat-like, indicating that glycerol trimyristate used as a high-melting lipid was crystallized [3,7].

3.3. Influence of transmembrane pressure in premix membrane emulsification

The production process of S/O/W dispersions by premix membrane emulsification would have a great influence on the properties of the resultant SLMCs including their size and size distribution, production rate and encapsulation efficiency. In premix membrane emulsification, transmembrane pressure is the most important factor because it affects the transmembrane flux and droplet disruption in membrane pores. In this section, the influence of transmembrane pressure in premix membrane emulsification using an SPG membrane with a mean pore diameter of 14.8 μm at 60 °C was investigated to optimize the production of S/O/W dispersions and hence SLMCs. Figs. 10 and 11 show the influence of applied transmembrane pressure on the transmembrane flux and the mean size of S/O droplets in the S/O/W dispersion permeated through the membrane, respectively. The smaller sizes of S/O droplets at the

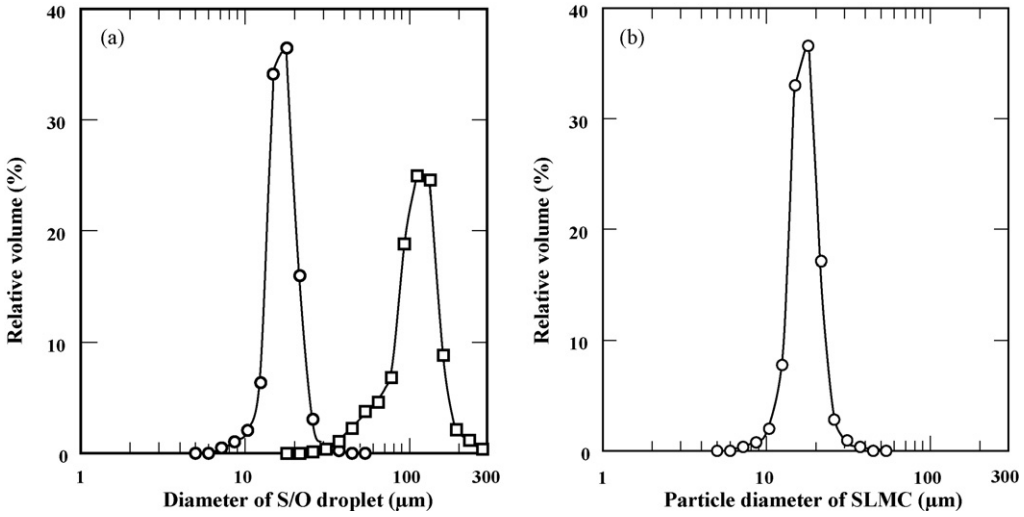

Fig. 8. (a) Droplet diameter distributions of S/O/W dispersion (□) before and (○) after permeation through an SPG membranes with a mean pore diameter of 14.8 μm at 60 °C under a transmembrane pressure of 25 kPa, and (b) a particle diameter distribution of the resultant SLMCs.

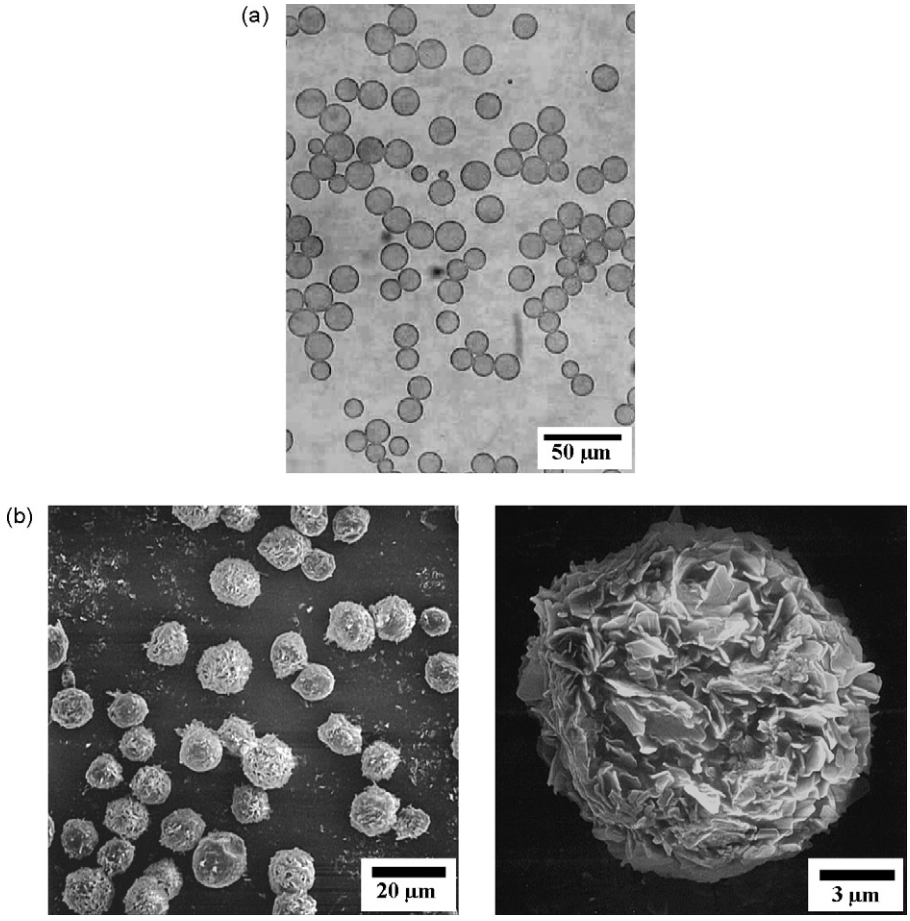

Fig. 9. (a) An optical micrograph of S/O/W dispersion after permeation through an SPG membrane with a mean pore diameter of 14.8 μm at 60 °C under a transmembrane pressure of 25 kPa; (b) scanning electron micrographs of SLMCs prepared from the S/O/W dispersion under the same condition.

higher transmembrane pressures are a consequence of the higher shear stress inside the pores. The transmembrane flux increased linearly with increasing the transmembrane pressure. The similar results were found earlier by Vladisavljevic et al. [23] for the production of W/O/W emulsion by premix membrane emulsification. At the transmembrane pressures higher than a critical pressure, all the S/O droplets in S/O/W dispersion can pass through the membrane pores, irrespective of their size. The critical pressure, P_c estimated

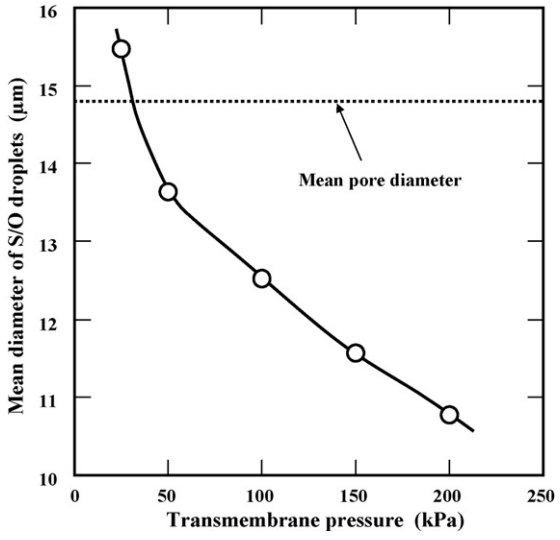

Fig. 10. Influence of transmembrane pressure on the mean diameter of S/O droplets in S/O/W dispersion permeated through an SPG membranes with a mean pore diameter of 14.8 μm at 60 °C. The dotted line shows the mean pore diameter of 14.8 μm of an SPG membrane employed.

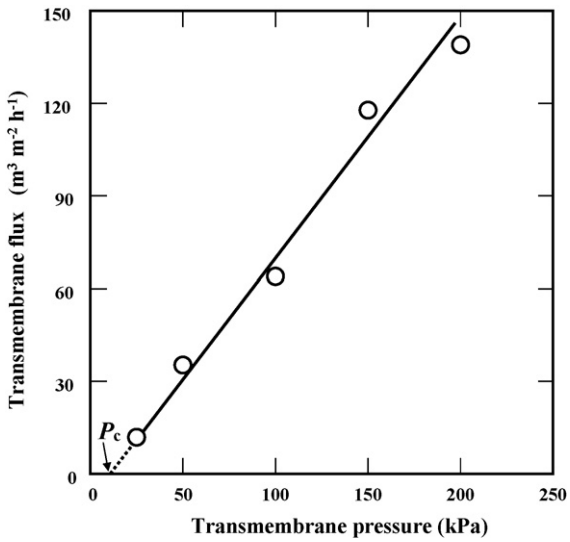

Fig. 11. Influence of transmembrane pressure on the transmembrane flux of a coarse feed S/O/W dispersion through an SPG membrane with a mean pore diameter of 14.8 μm at 60 °C.

by extrapolating the J and ΔP line to $J = 0$ was approximately 10 kPa (Fig. 11). The transmembrane pressure in premix membrane emulsification is used here to overcome the flow resistance forces of S/O/W dispersion inside the pores and the interfacial tension forces associated with the disruption of S/O droplets [23]:

$$\Delta P = \Delta P_{\text{flow}} + \Delta P_{\text{disr}} \tag{5}$$

where ΔP_{flow} is the pressure loss required for overcoming flow resistances in the pores and proportional to the transmembrane flux, J according to the Darcy's law; ΔP_{disr} is the pressure loss for droplet disruption and is proportional to the interfacial tension, γ between the S/O droplets and external water phase. Therefore, ΔP_{flow} and ΔP_{flow} are expressed as follows [23]:

$$\Delta P_{\text{flow}} = \eta(R_{\text{m}} + R_{\text{f}})J \tag{6}$$

$$\Delta P_{\text{disr}} = C_{\text{d}}\ \varphi\gamma\left(\frac{1}{D_{\text{d}}} - \frac{1}{D_{\text{d,f}}}\right) \tag{7}$$

where η is the viscosity of S/O/W dispersion in the pores; R_{m} is the hydraulic resistance of membrane; R_{f} is the overall fouling resistance caused by the accumulation of S/O droplets on the membrane surface and inside the pores; C_{d} is a constant; φ is the volume fraction of S/O droplets in S/O/W dispersion; D_{d} is the mean diameter of S/O droplets permeated through a membrane; $D_{\text{d,f}}$ is the mean diameter of S/O droplets in feed S/O/W dispersion. The transmembrane flux shown in Fig. 11 was in the range of 11.8–114.2 $\text{m}^3\ \text{m}^{-2}\ \text{h}^{-1}$, which were at least two orders of magnitude higher than in direct membrane emulsification with the same membrane [12].

During droplet permeation process through a pore, the deformed droplet becomes an oil cylinder of length, L and diameter, D_{o}, in which the ratio of length to diameter is defined as the slenderness (Fig. 4). If the slenderness, L/D_{o} exceeds π, the oil cylinder becomes unstable and breaks up into smaller droplets [26,27]:

$$\frac{L}{D_{\text{o}}} > \pi \tag{8}$$

This critical length is known as the Rayleigh–Plateau length, λ [27]. In previous studies [28,29], it was found that the tendency of oil-cylinder disruption is affected by the thickness of the lubrication layer between the oil cylinder and the pore wall. The oil cylinder moving through the membrane pore with a diameter, D_{m} is separated from the hydrophilic pore walls by the lubrication layer of water phase (Fig. 4). If the thickness of the lubrication layer, h is smaller than the length of the oil cylinder, the thickness of the lubrication layer is a function of the velocity, U of the oil cylinder in the pore and expressed from the following equation [27,29]:

$$h = C_{\text{L}} D_{\text{m}}\left(\frac{\eta_{\text{w}} U}{\gamma}\right)^{2/3} \tag{9}$$

where η_{w} is the viscosity of water phase; γ is the oil–water interfacial tension; C_{L} is a constant. As the thickness of the lubrication layer increases, the slenderness of the oil-cylinder increases, causing a disruption of the oil cylinder into smaller droplets. The droplet velocity increases with increasing the transmembrane flux and thus the transmembrane pressure. Therefore, the tendency of droplet disruption increases with increasing transmembrane pressure, leading to the formation of smaller satellite S/O droplets [23] (Fig. 4(b)). Therefore, smaller S/O droplets with broader size distributions are formed at the higher transmembrane pressures (Figs. 10 and 12).

As shown in Fig. 10, the diameter of S/O droplets permeated through the membrane was larger than the membrane pore size at a transmembrane pressure of 25 kPa, due to smaller shear stresses

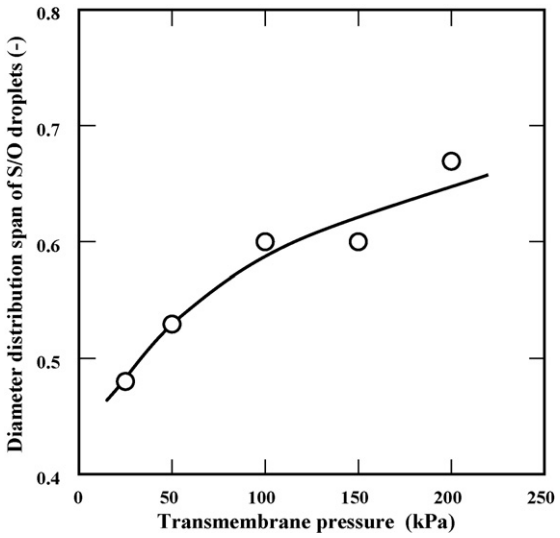

Fig. 12. Influence of the transmembrane pressure on the size distribution span of S/O droplets in the S/O/W dispersion permeated through an SPG membranes with a mean pore diameter of 14.8 μm at 60 °C.

inside the pores. In this case the large S/O droplets of the feed S/O/W dispersion are deformed at the pore inlets to enter the pores, followed by droplet disruption. The deformed fine S/O droplets are transformed again into a spherical shape at the pore outlets (Fig. 4(a)). At transmembrane pressures equal to or higher than 50 kPa, the droplets are more intensively disrupted inside the pores, resulting in the final droplet size smaller than the pore size (Fig. 4(b)). In this condition, no droplets at the pore outlets are deformed because the final droplet size is smaller than the pore size.

As shown in Fig. 13, the encapsulation efficiency of VB_{12} was reduced with increasing the transmembrane pressure. As the transmembrane pressure increases, the flow velocity of S/O droplets inside the pores increases and thus the shear stress acting on the S/O droplets enhances, leading to an increase in the leakage of VB_{12} particles from the S/O droplets into the external water phase.

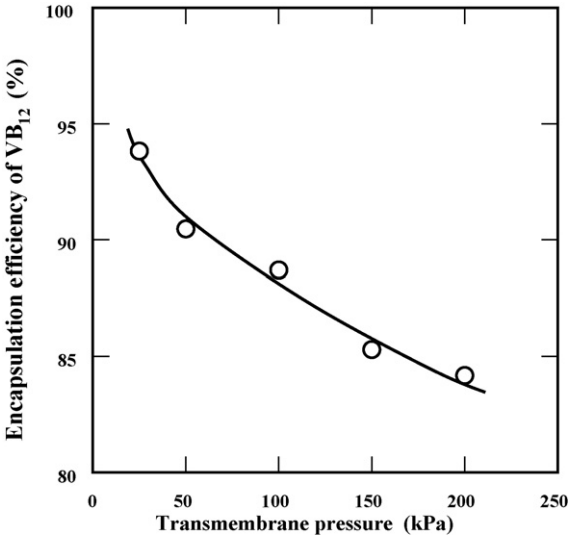

Fig. 13. Influence of transmembrane pressure on the encapsulation efficiency of VB12 in the S/O/W dispersion permeated through an SPG membranes with a mean pore diameter of 14.8 μm at 60 °C.

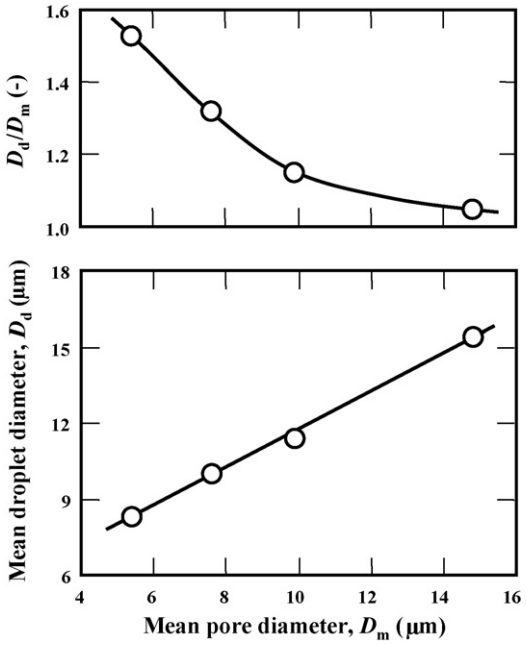

Fig. 14. Relationship between the mean diameter of S/O droplets and the mean pore diameter for S/O/W dispersion produced by premix membrane emulsification at a transmembrane/critical pressure ratio of 2.5. The emulsification temperature was kept at 60 °C.

3.4. Influence of membrane pore size in premix membrane emulsification

The particle size of SLMCs would be controlled by adjusting the pore size of SPG membrane used in the production process of S/O/W dispersions by premix membrane emulsification. In this section, the influence of membrane pore size on the particle size of S/O/W dispersion produced by premix membrane emulsification. Fig. 14 shows the relationship between the mean diameter of S/O droplets and the mean pore diameter for S/O/W dispersion produced by premix membrane emulsification at a transmembrane/critical pressure ratio of 2.5. The emulsification temperature was kept at 60 °C. As can be seen, the mean diameter of S/O droplets increased with increasing the mean pore diameter of SPG membrane. However, the ratio of mean particle diameter to the mean pore diameter decreased from 1.53 to 1.05 with increasing the pore diameter. Similar results were reported earlier in the production of W/O/W emulsion by premix membrane emulsification [28]. The results shown in Figs. 10 and 14 indicates that the mean particle diameter of SLMCs can precisely be tuned by adjusting the membrane pore diameter and the transmembrane pressure in the production of S/O/W dispersions by premix membrane emulsification.

4. Conclusions

For drug delivery applications, a novel method for the production of uniformly sized SLMCs encapsulating hydrophilic drugs via S/O/W dispersions by premix membrane emulsification was developed using a high-melting triglyceride. The prepared SLMCs had a matrix type structure with nano-order particles of hydrophilic drugs embedded in the capsule. Initially, a coarse S/O/W dispersion was prepared by water removal of W/O emulsions and subsequent mixing with an external water phase at a higher temperature than the melting point of the triglyceride. VB_{12} was used as a hydrophilic model drug and dissolved into the water phase in the primary W/O emulsion. The resultant S/O/W dispersion was forced through an SPG membrane to achieve additional homogenization and size reduction of the S/O droplets in the S/O/W dispersion. After cooling to room temperature to solidify the oil phase in the S/O/W dispersion, uniformly sized SLMCs were produced and up to 93.5% of VB_{12} was encapsulated into the capsules. The properties of the S/O/W dispersion and hence SLMCs were affected by the homogenization process of S/O/W dispersions by premix membrane emulsification, in which the size and uniformity of the S/O droplets in S/O/W dispersions and the encapsulation efficiency of VB_{12} decreased with increasing the transmembrane pressure because of the lower shear stresses inside the membrane pores. The transmembrane flux of the S/O/W dispersion linearly increased with increasing transmembrane pressure. The particle size of SLMCs was controlled by adjusting the membrane pore size and transmembrane pressure. Micro-encapsulation of hydrophilic drugs into solid lipids by this novel method may have great potential as drug carriers. Our further study will focus on the release profiles of hydrophilic drugs encapsulated SLMCs and the preparation of solid lipid nanocapsules from S/O/W dispersions.

Nomenclature

A	effective membrane area (m^2)
C	concentration of VB_{12} (wt.%)
C_d	constant in Eq. (7)
C_L	constant in Eq. (9)
D_d	mean diameter of S/O droplets in the permeated S/O/W dispersion (m)
$D_{d,f}$	mean diameter of water droplets in the feed S/O/W dispersion (m)
$D_{d,w}$	mean diameter of water droplets (m)
D_p	mean particle diameter (m)
${}^nD$	droplet/particle diameter at n% of cumulative volume (m)
D_o	diameter of oil cylinder in a pore (m)
D_m	membrane pore diameter (m)
h	thickness of lubrication layer (s)
J	transmembrane flux ($m^3\ m^{-2}\ h^{-1}$)
L	length of oil cylinder in a pore (m)
M_w	molecular weight ($g\ mol^{-1}$)
P_c	critical pressure (Pa)
ΔP	transmembrane pressure (Pa)
ΔP_{disr}	pressure loss for droplet disruption (Pa)
ΔP_{flow}	pressure loss for overcoming flow resistances in the pores (Pa)
R_m	hydraulic resistance of membrane (m^{-1})
R_f	fouling resistance (m^{-1})
t	time taken for permeation of feed S/O/W dispersion (m)
U	droplet velocity inside pores ($m\ s^{-1}$)
V_p	volume of S/O/W dispersion permeated through a membrane (m^3)
W_{the}	theoretical amount of VB_{12} contained in SLMCs (kg)
W_{act}	actual amount of VB_{12} encapsulated into SLMCs (kg)

Greek letters

α	encapsulation efficiency of VB_{12}
γ	interfacial tension between oil and water phases ($N\ m^{-1}$)
δ	span of the diameter distribution of droplets or particles
η	viscosity of S/O/W dispersion in the pores (Pa s)
η_w	viscosity of water phase (Pa s)
λ	Rayleigh–Plateau length (m)
ρ	density of VB_{12} ($kg\ m^{-3}$)
φ	volume fraction of S/O droplets in S/O/W dispersion

Subscripts

d droplet
p particle
m membrane pore

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