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Effect of process parameters on nanoemulsion droplet size and distribution in SPG membrane emulsification

Dong Hoon Oh[a], Prabagar Balakrishnan[a], Yu-Kyoung Oh[c], Dae-Duk Kim[c], Chul Soon Yong[a,**], Han-Gon Choi[a,b,*]

[a] College of Pharmacy, Yeungnam University, 214-1, Dae-Dong, Gyongsan 712-749, South Korea
[b] College of Pharmacy, Hanyang University, 1271, Sa-3-Dong, Ansan 426-791, South Korea
[c] College of Pharmacy, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Ku, Seoul 151-742, South Korea

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ABSTRACT

A Shirasu-porous-glass (SPG) membrane with a mean pore size of 2.5 μm was used to produce an oil/water (O/W) nanoemulsion of flurbiprofen consisting of methylene chloride as the dispersed phase, polyvinyl alcohol (PVA) as the stabilizer and a mixture of Tween 20 and Tween 80 in demineralized water as the continuous phase. Emulsion droplets with a mean droplet size of 25 times smaller than the mean pore size and a narrow droplet size distribution were produced using 5% emulsifier at a feed pressure of 15 kPa. Under these conditions the *z*-average diameter and size distribution of the emulsion droplets formed were influenced by the type of surfactant, agitator speed (150–1200 rpm), feed pressure (15–80 kPa), stabilizer concentration (0–4, w/v) and the temperature of the continuous phase. Increasing the agitator speed and stabilizer concentration increased the *z*-average diameter and decreased the size uniformity. There was a linear relationship between the increased feed pressure and the decreased *z*-average diameter of the emulsion droplets. However, the uniformity of the size distribution decreased with increasing feed pressure. The continuous phase temperature played an important role in particle size and distribution. The nanoemulsion composed of oil, water, PVA and the surfactant mixture at the weight ratio of 10/100/1/5 was prepared using a SPG membrane at an agitator speed of 300 rpm, a feed pressure of 15 kPa and a continuous phase temperature of 25 °C. Our results indicated that these conditions led to relatively uniform emulsion droplets with a narrow size distribution and high zeta potential. This emulsion was stable for at least 13 h. Furthermore, the droplets in the emulsion containing the drug were not smaller but were more uniform with a narrower distribution compared to those without the drug.

1. Introduction

Numerous studies have been done on the preparation of both oil-in-water (O/W) and water-in-oil (W/O) emulsions by utilizing the physicochemical properties of surfactants as emulsifiers, i.e., using the phase inversion technique, the surfactant phase emulsification technique, etc. (Kandori et al., 1991). Furthermore, many pieces of emulsification equipment such as the colloid mill, homogenizer and ultrasonic emulsifier have been developed and improved (Kandori et al., 1991). However, the droplet sizes of emulsions prepared using these emulsification techniques and equipment are not highly monodispersed, because their emulsification conditions cannot be precisely controlled. Membrane emulsification is a process that is used to produce an emulsion, or dispersion, of one liquid phase (such as oil) in a second immiscible liquid phase (such as water). The process usually employs shear at the surface of the membrane in order to detach the dispersed phase liquid drops from the membrane surface, after which they become dispersed in the immiscible continuous phase. In many cases the liquid drops are then polymerized, or otherwise solidified, in order to produce solid particles, usually with a very narrow particle size distribution. Ito and Makino (2004) produced droplets of monodispersed microspheres using the SPG membrane technique, with the result that the size of droplets prepared by membrane emulsification was smaller and narrower than that without membrane emulsification. Examples of such products include calibration materials, food and flavour encapsulates, controlled release depots under the skin and ion exchange resins (Serguei et al., 2008). The first investigation on using membrane emulsification can be traced

* Corresponding author at: College of Pharmacy, Hanyang University, 1271, Sa-3-Dong, Ansan 426-791, Kyunggi, South Korea. Tel.: +82 31 400 5802; fax: +82 31 400 5958.
** Co-corresponding author. College of Pharmacy, Yeungnam University, 214-1, Dae-Dong, Gyongsan 712-749, South Korea. Tel.: +82 53 810 2812; fax: +82 53 810 4654.
E-mail addresses: csyong@yumail.ac.kr (C.S. Yong), hangon@hanyang.ac.kr (H.-G. Choi).

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back to the late 1980s when Nakashima et al. (2000) fabricated a particular glass membrane, called Shirasu porous glass (SPG). Highly uniform-sized kerosene-in-water and water-in-kerosene emulsions were successfully produced, and since that time the method has continued to attract attention due to its effectiveness in producing narrow droplet size distributions with low energy consumption (Nakashima et al., 2000). Shirasu porous glass (SPG) membranes are potentially suitable for membrane emulsification due to their uniform-sized pores and wide range of available mean pore diameters (0.05–50 μm) (Kukizaki and Nakashima, 2004).

The objective of this work was to characterize the process variables in the preparation of a uniform-sized nanoemulsion by a conventional direct membrane emulsification technique using standard SPG. In direct membrane emulsification, one immiscible liquid (the disperse phase) is forced through the membrane into the other immiscible liquid (the continuous phase). Fine droplets are then formed at the interface between the membrane surface and the continuous phase. To ensure regular droplet detachment from the pore outlets, shear stress is generated at the membrane–continuous phase interface by re-circulating the continuous phase using a low-shear pump or agitating in a stirring vessel (Vladisavljević et al., 2004). Moreover, it has been reported that in membrane emulsification the speed of the continuous-phase flow and the adsorption kinetics of the surfactant, which is added in the continuous phase, have a significant effect on the size and size distribution of the droplets (Babak et al., 2007; Vladisavljevic and Williams, 2005). During the droplet formation process, the surfactant molecules adsorb onto the newly formed oil–water interface and reduce the interfacial tension and consequently facilitate droplet formation. The rate of transfer of the surfactant molecules from the bulk solution to the newly formed oil–water interface partly depends on the continuous-phase flow. The surfactant type and concentration greatly influence the adsorption kinetics of the surfactant and thus the dynamic interfacial tension (Schröder et al., 1998). In addition, the flow state of the dispersed phase in membrane pores has a great influence on the spontaneous droplet formation behaviour and itself depends on the viscosities of the dispersed and continuous phases and the flow velocity of the dispersed phase through the membrane pore (Sugiura et al., 2002).

Although a considerable amount of work has been carried out in the field of membrane emulsification in the last decade, the influence of process parameters on droplet size distribution has not yet been fully investigated. Furthermore, in some investigations only the mean droplet diameter was given as a parameter of distribution, although the width of the droplet size distribution is a key emulsion property in the case of membrane emulsification. Thus, we investigated the influence of surfactant type, the cross-flow of the continuous phases (agitator speed), the temperature of the continuous phase, the stabilizer concentration (polyvinylalcohol) and the feed pressure (transmembrane pressure) on the size and size distribution of the droplets generated using SPG membranes.

2. Materials and methods

2.1. Materials

Flurbiprofen was supplied by Kolon Life Sciences, Inc. (Kwacheon, Korea). Labrafil M 2125 and Labrafil M 1994 were supplied by Gattefosse (Saint-Priest Cedex, France). Methylene chloride, polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), sorbitan monolaurate 20 (Span 20), sorbitan monooleate 80 (Span 80), polyethylene glycol 4000 and polyethylene glycol 6000 were purchased from Duksan Chemical Co. (Ansan, Korea). Poloxamer 188 and poloxamer 407 were purchased from BASF (Ludwigshafen, Germany). Polyvinylalcohol (PVA) was purchased from Sigma–Aldrich (St. Louis, MO, USA). All other chemicals were of reagent grade and were used without further purification. A miniature kit for emulsification with an MPG module (microporous glass, a brand name of SPG) was purchased from Kiyomoto Iron Works Co. (Miyazaki, Japan).

Table 1
Effect of surfactants on the solubility of flurbiprofen.

Surfactants	Solubility (μg/ml)
Water	5.1 ± 0.2
Polyethylene glycol 6000	71.2 ± 22.1
Polyethylene glycol 4000	46.3 ± 9.4
Poloxamer 188	487.0 ± 251.5
Poloxamer 407	2351.0 ± 548.4
Labrafil M 1994	328.3 ± 1.4
Labrafil M 2125	428.2 ± 262.2
Span 20	496.8 ± 81.7
Span 80	553.5 ± 21.3
Tween 20	8735.1 ± 1220.6
Tween 80	11,193.2 ± 3074.9

Each value means the solubility of flurbiprofen in distilled water containing 10% surfactant. Each value represents the mean ± S.D. ($n = 3$).

2.2. Solubility studies

An excess of flurbiprofen powder (about 100 mg) was added to 10 ml of 10% surfactant as shown in Table 1. An excess of solid dispersions (about 100 mg) was also added to 10 ml of water. They were shaken in a water bath at 25 °C for 7 days, centrifuged at 3000 × *g* for 10 min (Eppendorf, USA) and filtered through a membrane filter (0.45 μm) (Balakrishnan et al., 2009; Choi et al., 1998; Li et al., 2008). The concentration of flurbiprofen in the resulting solution was analysed using an HPLC system (Hitachi, Japan) consisting of Class VP computer software, an L-2130 pump and an L-2400 UV/VIS detector. The column was an Inertsil ODS-3 C18 column (5 μm, 15 cm × 0.46 cm i.d.). The mobile phase consisted of a mixture of phosphate buffer (pH 3.5) and acetonitrile (4:6, v/v). The eluent was monitored at 220 nm with a flow rate of 1 ml/min. The inter- and intra-day variances of this HPLC method were within the acceptable range ($R^2 = 0.999$).

2.3. Pseudo-ternary phase diagram

The existence of emulsion fields that form emulsions under agitation was identified from ternary phase diagrams of systems containing oil–surfactant–water. The effect of surfactant (Tween 20, Tween 80 or a mixture of these two surfactants at 1:1, w/w ratio) and water on the pseudo-ternary phase diagram was systematically observed at room temperature. The surfactant and water were weighed at different ratios (0:1 to 1:3, w/w) in each vial, and were vortexed vigorously for 30 s. Afterwards, the oil phase (methylene chloride) was added in 5% increments to each clear mixture of water and surfactant. This was vortexed for 5 min and kept in a water bath at 25 °C for 30 min. The mixture was then visually examined for emulsion formation. The points from uniform milky solution to separation were designated as the emulsion- and no emulsion-forming regions, respectively (Ping et al., 2005; Yan et al., 2009).

2.4. Experimental set-up and procedure

A schematic diagram of this kit for emulsification with an MPG module (microporous glass, a brand name of SPG) is shown in Fig. 1. The hydrophilic SPG membrane was tube-shaped with an outer diameter of 10 mm, a thickness of 0.75 mm and a pore size of 2.5 μm. Ten grams of dispersed phase (oil phase) were stored in