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Formation and modification of dispersions using Shirasu Porous Glass membrane

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ABSTRACT

This chapter deals with the production, properties, and macrofluidic applications of Shirasu Porous Glass (SPG) membrane. The first section provides an overview of the membrane microfluidic processes used for production and modification of liquid-liquid and gas-liquid micro- and nano-dispersions, such as direct and premix membrane emulsification with and without phase inversion, membrane demulsification, membrane micromixing / direct precipitation and micro- and nano-bubbling. In the last section of this chapter, SPG membranes are compared with conventional homogenisers and microfluidic drop generators in terms of production rate, droplet size uniformity, and applied shear stresses. The second section deals with the fabrication of SPG membrane by spinodal decomposition in Na₂O–CaO–Al₂O₃–B₂O₃–SiO₂ type glass and morphological, mechanical, and hydrodynamic properties of SPG membrane. This chapter also covers modification of surface charge, contact angle and porosity of SPG membrane using different physical and chemical methods, such as deposition of silica nanoparticles onto membrane surface, coating with silicon resin, filling the pores with solvent-responsive polymer chains and chemical modification with silane coupling agents. The fourth section is focused on the effects of physical properties of the dispersed and continuous phase, operating parameters and membrane properties on the droplet size in direct and premix SPG membrane emulsification. In addition, the most common classes of micro- and nano-particles fabricated using SPG membrane were reviewed and their fabrication routes were discussed. It was concluded that a broad variety of different chemical and physicochemical processes can be combined with SPG membrane emulsification to convert droplets into uniform particle. The last section briefly discusses the generation of micro- and nano-bubbles using SPG membrane.

Keywords: Membrane Emulsification, Shirasu Porous Glass Membrane, Nanoparticles, Polymeric microspheres, Microbubbles, Janus particles, Core-Shell Particles.
1. Formation and modification of dispersions using membranes

Synthetic membranes are mainly used for separation purposes and to achieve a chemical or biochemical conversion. Membrane separation processes are characterised by the fact that a feed stream is divided into two product streams of different chemical composition: retentate and permeate (Figure 1a) (Mulder, 1996). A shear rate is applied at the retentate/membrane interface to limit concentration polarisation and accumulation of the rejected solids on the high pressure side of the membrane. In the last two decades, microfluidic applications of membranes (formation of droplets and bubbles, micromixing of miscible liquids, droplet breakup and coalescence, etc.) are gaining in popularity, as a result of rising global interest in microfluidic technologies. Membrane microfluidic processes can be classified into two groups: (i) formation of dispersions (gas-liquid, liquid-liquid, and solid-liquid) (Figure 1b), and (ii) treatment of dispersions (demulsification, homogenisation and phase inversion). In a membrane dispersion process (Figure 1b), phase I is injected through a microporous membrane into phase II for the purpose of: (i) mixing of two miscible fluids, usually two liquid phases; (ii) forming droplets or bubbles of phase I into phase II. Membrane treatment of dispersions (Figure 1c) involves passing dispersion through the membrane which results in the physicochemical and mechanical interactions between the dispersed phase entities (bubbles/droplets/particles) and the pore walls leading to the modification of the original particle size distribution.

1.1 Membrane dispersion processes

Membrane dispersion processes are direct membrane emulsification (DME) (Nakashima et al., 2000), membrane micro- and nano-bubbling (Kukizaki and Goto, 2007; Kukizaki and Goto, 2006), and membrane micromixing (Chen et al., 2004). A shear is applied at the membrane surface to improve mixing efficiency or facilitate the detachment of bubbles or droplets from the membrane surface. In DME, one liquid (a dispersed phase) is injected through a microporous membrane into another immiscible liquid (the continuous phase) (Nakashima et al., 1991) leading to the formation of droplets at the membrane/continuous phase interface (Figure 2a). Hydrophobic membranes are needed to produce water-in-oil (W/O) emulsions (Cheng et al., 2008; Jing et al., 2006), and hydrophilic membranes are required to prepare oil-in-water (O/W) emulsions (Figure 2a). In membrane microbubbling, a pressurised gas is
forced through a hydrophilic membrane into aqueous continuous phase, leading to the formation of microbubbles ($1 \mu m < d_{\text{bubble}} < 1 \text{ mm}$) or nanobubbles ($d_{\text{bubble}} < 1 \mu m$), depending on the pore size of the membrane (Figure 2b). Micromixing is interpenetration of miscible solutions at the molecular level and it is a crucial step in any homogeneous reaction (Okhonin et al., 2011). In membrane micromixing, an organic solution containing water-miscible organic solvent or an aqueous solution penetrates through a hydrophilic membrane into another aqueous phase for the purpose of mixing two solvents rapidly with each other. Membrane micromixing can be combined with direct precipitation to produce inorganic (Chen et al., 2004) and organic (Laouini et al., 2011) nanoparticles. Precipitation of inorganic compounds requires dispersion of aqueous solution of water soluble salt A into an aqueous solution of water soluble salt B and nanoparticles are formed as a result of chemical reaction between the two salts: $A + B \rightarrow C + D$, where one of the products is sparingly soluble in water (Table 1). Precipitation of organic compounds requires dispersion of water-miscible organic solvent containing particle-forming organic compounds into an aqueous phase (anti-solvent), and precipitation occurs as a result of the lower solubility of the organic solutes in the aqueous phase (Figure 2c). Particle-forming organic compounds in pharmaceutical nanodispersions are active principle ingredient (API) and excipients and typical organic phase compositions are listed in Table 2.

1.2 Membrane treatment of dispersions

Membrane processes used to modify particle size distribution of dispersions can be classified into four groups: (a) Simple premix membrane emulsification (PME) (Suzuki et al., 1996); (b) PME with phase inversion (Suzuki et al., 1996); (c) membrane demulsification (Kukizaki and Goto, 2008); and (d) homogenization of suspensions by extrusion through membrane (Olson et al., 1979). In PME (Figure 3a), a pre-emulsion is forced through a microporous membrane (Suzuki et al., 1996) or a packed bed of uniform particles (van der Zwan et al., 2008; Yasuda et al., 2010). As in DME, hydrophobic and hydrophilic membranes are needed to produce W/O and O/W emulsions, respectively. If the transmembrane pressure is lower than the capillary pressure in a pore, the membrane will reject the droplets, while allowing the continuous phase liquid to pass through, which will lead to the separation of the emulsion into droplet-free continuous phase and concentrated emulsion (Koltuniewicz et al., 1995; Park et al., 1998).
When the dispersed phase of the feed emulsion wets the membrane wall, the rate of droplet coalescence in the membrane pores is faster than the rate of droplet breakup, which leads to inversion of phases in the emulsion (Figure 3b) or separation of the feed emulsion into two distinct phases (Figure 3c). In PME with phase inversion, an O/W or W/O/W emulsion undergoes inversion into a W/O emulsion as a result of permeation through a hydrophobic membrane (Suzuki et al., 1999; Kawashima et al., 1991). Similarly, a W/O emulsion can be inverted into O/W emulsion after permeation through a hydrophilic membrane. A successful phase inversion requires that feed emulsion contains a blend of surfactants with a low and high hydrophilic-lipophilic balance (HLB) number (Suzuki et al., 1999) or otherwise, the emulsion breaking is more likely to occur than the phase inversion.

1.3 Comparison of membranes with other methods to generate and treat dispersions

Generation of droplets/bubbles in microfluidic devices such as T junctions (Thorsen et al., 2001) and flow focusing devices (Anna et al., 2003) usually involves injection of one fluid through a single microchannel into a stream of another immiscible fluid (Vladisavljević et al., 2012). The droplets/bubbles generated in microfluidic devices are highly uniform in size, with a typical coefficient of variation in dripping regime of 3% or less, and the drop generation frequency can exceed 10,000 Hz (Yobas et al., 2006). However, the volume flow rate of the dispersed phase in microfluidic devices is very low, usually 0.01–10 ml h⁻¹, because there is typically only one droplet generation unit. Membranes overcome this low throughput limitation by providing countless number of pores that serve as massively parallel drop generation units. Considering that membrane modules can easily be integrated into a system with large total membrane area, while the integration of microfluidic devices is often challenging due to significant pressure drop in microfluidic channels and difficulties of controlling the flow rates of individual streams in complicated channel networks, it is clear that membranes are more suitable for large throughput applications. An advantage of microfluidic channels over membranes is in their ability to produce droplets with a complex morphology and to manipulate individual droplets with high precision after production.

Compared to high shear rotor-stator devices, high-pressure valve homogenizers, ultrasonic and static mixers, membrane dispersion devices operate under mild shear stress conditions, allowing high yields of inner droplets in multiple emulsion production (Surh et al., 2007; Vladisavljević and Williams, 2008; Dragosavac et al., 2012). Conventional emulsification
techniques are not suitable when dealing with shear sensitive ingredients, because they apply more energy than needed to disrupt droplets (Karbstein and Schubert, 1995). In DME, a shear rate on the membrane surface is in the range of \((1–50) \times 10^3 \text{ s}^{-1}\) but droplets can be produced even in the absence of shear (Kukizaki, 2009; Kukizaki and Goto, 2009; Kosvintsev et al., 2008). A shear rate in rotor-stator devices such as high-shear in-line mixers and colloid mills is \((1–2) \times 10^5 \text{ s}^{-1}\) and it is up to \(10^7 \text{ s}^{-1}\) in microfluidizers®. In PME, a pressure drop across the membrane is typically 1–10 bar, while in high-pressure valve homogenizers it ranges from 50 to over 2000 bar. In addition, energy input in conventional dispersion devices is not spatially uniform. E.g., in rotor-stator devices, shear forces are high in close proximity to a rotor and low in “dead zones”, leading to the production of polydispersed emulsions. On the other hand, in the majority of membrane dispersion processes, shear is uniformly distributed over the membrane surface.

Another advantage of membrane emulsification compared to conventional emulsification devices is that membrane systems allow integration of emulsification step and emulsion post-processing to achieve simultaneous drop generation and separation, chemical/biochemical conversion or physicochemical transformation. The examples include integration of DME or PME with liquid-liquid extraction (Chen et al., 2004c, Xu et al., 2005), biphasic enzymatic transformation (Li and Sakaki, 2008; Mazzei et al., 2010), pervaporation (Chang and Hatton, 2012), and complex coacervation (Piacentini et al., submitted).

2. SPG membrane

Membranes used to produce and treat dispersions should have the following properties: (i) uniform pores with a broad range of available mean pore sizes to suit different applications; (ii) low hydrodynamic resistance; (iii) high mechanical strength and thermal and chemical resistance; (iv) membrane material should be suitable for surface modification (modification of contact angle, surface charge, permeability, etc); (v) membrane fabrication process should allow precise control over the pore size and pore geometry. Shirasu Porous Glass (SPG) meets the majority of the above-mentioned criteria, and it is by far the most widely used microporous membrane in membrane dispersion processes. Advantages of SPG membrane over microengineered are in typically higher porosity, more versatile surface chemistry that can be applied and broader range of pore sizes available.
2.1 Fabrication of SPG membrane

SPG membrane is fabricated from Na₂O–CaO–Al₂O₃–B₂O₃–SiO₂ or Na₂O–CaO–MgO–Al₂O₃–B₂O₃–SiO₂ type mother glass through phase separation by spinodal decomposition (Nakashima and Kuroki, 1981; Nakashima and Shimizu, 1986; Kukizaki and Nakashima, 2004). The mother glass is prepared by mixing and melting raw materials (Shirasu, limestone, and boric acid) at about 1350 °C. Typical mixing ratios of raw materials for SPG membrane are given in Table 3. Soda ash (Na₂CO₃) and sometimes MgO and ZrO₂ are added to molten glass to adjust the rate and temperature of phase separation and alkaline durability of the glass. Shirasu is a volcanic ash deposit from southern Kyushu, which contains 72–77 wt% SiO₂, 10–15 wt% Al₂O₃, and small amounts of other inorganic oxides (Table 4). Molten mother glass is shaped into tubes or flat discs by blowing or casting and then heat treated at 650–750 °C for the period ranging from several hours to several tens of hours. The thermal treatment causes a homogeneous glass melt to separate into an acid-insoluble (Al₂O₃–SiO₂ rich) phase and acid-soluble (CaO–B₂O₃ rich) phase (Figure 4). The phase-separated glass is then immersed into a hydrochloric acid solution to dissolve CaO–B₂O₃ rich phase, which results in the formation of porous skeleton, whose composition is shown in Table 4. The porosity of SPG membrane is determined by the volume fraction of the acid-soluble phase in the phase separated mother glass and ranges between 50 and 60% (Vladisavljević et al., 2005). If the fraction of acid-soluble phase is too low or too high, separation may take place by the nucleation and growth mechanism. The nucleation and growth mechanism occurs in the metastable region of the phase diagram, between the spinodal and binodal lines (Figure 5), and leads to the formation of discrete spherical particles of one phase embedded in a continuous matrix of the other. This morphology is undesirable in the fabrication of SPG membrane and must be avoided.

Figure 5 depicts spinodal decomposition induced by cooling a homogeneous glass melt from a temperature T₁ at which all components are miscible in all proportions to a temperature T₂, which lies within the spinodal (unstable) region. A homogeneous glass with composition of x₁ is separated into two immiscible phases with compositions of xₖ and xᵢ. The ratio of acid-soluble to acid-insoluble phase can be found by the lever rule and is equal to (xᵢ−x₁)/(x₁−xₖ). The mean pore diameter dₑ of SPG membrane can be controlled by adjusting the time, t and temperature, T₂ of the heat treatment process (Kukizaki, 2010):
\[ d_p = 4K^{1/2}(V_p/m_m)^{1/2} \exp\left[-E_a/(2RT_2)\right] \]  

where \( K \) is a constant depending on the composition of mother glass, \( E_a \) is the activation energy for diffusion during phase separation (400–600 kJ mol\(^{-1}\) according to Nakashima (2002) and Kukizaki (2010)), \( R \) is the universal gas constant, and \( V_p/m_m \) is the total pore volume per unit mass of dry membrane. Therefore, the mean pore diameter of SPG membrane is proportional to the square root of the heating time at any constant temperature, whereas a logarithm of the mean pore diameter is inversely proportional to \( 1/T_2 \) at constant heating time.

### 2.2 Properties of SPG membrane

SPG membrane is available from SPG Technology Ltd (Sadowara, Japan) over a wide spectrum of mean pore sizes ranging from 0.040 to 20 \( \mu \)m (Table 5). The membrane has a uniform internal microstructure, as confirmed by X-ray microtomography (Vladisavljević et al., 2007), characterised by interconnected and tortuous cylindrical pores with a tortuosity factor of \( \xi \approx 1.3 \). On SEM and XMT images, the pores have a non-cylindrical shape (Figure 6), because they extend in all directions and include pore junctions. The number of pores per unit cross-sectional area of SPG membrane is given by (Vladisavljević et al., 2005):

\[ N/A_m = 0.56/d_p^2 \]  

where \( N/A_m \) and \( d_p \) are in m\(^{-2}\) and m, respectively. The hydraulic resistance of isotropic SPG membrane is given by (Vladisavljević et al., 2005):

\[ R_{m,sym} = 32\xi^2\delta_m/(d_p\varepsilon) \]  

where \( \delta_m \) is the membrane thickness and \( \varepsilon \) is the membrane porosity. The hydraulic resistance of isotropic SPG membrane is relatively high (Table 5), due to its substantial thickness of 400–1000 \( \mu \)m, but can be reduced if the membrane is fabricated with anisotropic structure (Kukizaki and Goto, 2007b). Assuming that the pore tortuosity and porosity, \( \xi \) and \( \varepsilon \), are independent on the pore size, the hydraulic resistance of anisotropic SPG membrane is given by (Kukizaki and Goto, 2007b):

\[ R_{m,asym} = 32\xi^2\delta_{skin}(d_{p,skin}\varepsilon) + 32\xi^2\delta_{sup}(d_{p,sup}\varepsilon) \]  

where \( \delta_{skin} \) and \( \delta_{sup} \) are the thicknesses of the skin and support layer, respectively and \( d_{p,skin} \) are \( d_{p,sup} \) their mean pore diameters. According to Kukizaki and Goto (2007b), the thickness of the skin layer is 6% of the overall membrane thickness and the ratio of the pore diameters in the skin and support layer is around 7, so it can be written:
Therefore, the hydraulic resistance of asymmetric SPG membrane is just 8% of the \( R_m \) value for symmetric membrane.

SPG is more stable in water and alkaline solutions than Porous Vycor® Glass, because it contains less SiO\(_2\) and more Al\(_2\)O\(_3\) (Table 4). However, the durability of both membranes at high pH is poor, due to the attack of hydroxide ions on siloxane (Si-O-Si) bonds:

\[
\equiv \text{Si} - \text{O} - \equiv + \text{OH}^- \rightarrow \equiv \text{Si} - \text{O}^- + \equiv \text{Si} - \text{OH}
\]

Alkaline durability of SPG can be improved by incorporating about 3 mol% ZrO\(_2\) into the glass skeleton, which results in to the formation of stable Zr-O-Si bonds in the silicate network (Kukizaki, 2010). A compressive strength of SPG of 200–280 MPa is much higher than that of porous alumina or zirconia of the same porosity (Nakashima et al., 1992), because SPG is made up of a continuous glass skeleton with very few defects, while porous alumina or zirconia is composed of skeletal grains joined together discontinuously via grain boundaries.

### 2.3 Surface modification of SPG membrane

The surface of SPG membrane can be rendered hydrophobic by chemical modification with organosilane compounds such as chlorosilanes (Kukizaki and Wada, 2008) or coating with silicone resin (Vladisavljević et al., 2005). Monochlorosilanes such as trimethylchlorosilane (TMS) and octadecyldimethylchlorosilane (ODS) are the most suitable for hydrophobisation because they contain only one chlorine atom, which means that no polymerization between silane molecules can occur while they react with a silanol group on the pore surface (Figure 7a) (Kai et al., 2006). The longer the carbon chain length in the organosilane compound, more hydrophobic the membrane surface becomes (Kukizaki and Wada, 2008). The membrane hydrophobicity can be enhanced by depositing silica nanoparticles onto the surface of SPG membrane prior to treatment with TMS (Meng et al., 2013). The surface of SPG membrane can be made with thermoresponsive hydrophilic-hydrophobic properties by depositing silica nanoparticles containing poly(N-isopropylacrylamide) (PNIPAM) brushes grafted on their surface (Meng et al., 2010). The porosity and hydraulic resistance of SPG membrane can be modified over a wide range by incorporating dextran macromolecules within the pores (Kawakita et al., 2009; Seto et al., 2011). Dextran can be synthetized by in-situ enzymatic
reaction between dextransucrase immobilised within the pores and sucrose from an aqueous solution that is passed through the membrane. A reversible change in the hydraulic resistance of the modified SPG membrane is a consequence of reversible extension and shrinkage of solvent-responsive dextran chains inside the pores.

The surface of untreated SPG surface has a negative zeta potential between −15 and −45 mV within a pH range of 2−8, due to dissociation of silanol groups (⇌Si-OH ⇌SiO− + H+) (Kukizaki, 2009b). A positive charge on the membrane surface can be induced by treating the membrane with amino trialkoxysilanes, such as (3-aminopropyl)-trimethoxysilane (APTMS) and (3-aminopropyl)-trioethoxysilane (APTES) (Figure 7b). Amino trialkoxysilanes undergo hydrolysis in aqueous solution resulting in the formation of silanol groups, which can be condensed with a silanol group on the SPG surface to form stable siloxane bond (Si−O−Si), required for surface modification.

3. Emulsification using SPG membrane

SPG membrane was widely used both in DME (Vladisavljević et al., 2004; Vladisavljević and Schubert, 2002) and PME (Vladisavljević et al., 2004b; 2006; 2006b). The advantages of PME over DME are in smaller droplet sizes (Figure 8) and higher transmembrane fluxes that can be achieved for any given pore size. On the other hand, a more severe membrane fouling and broader particle size distribution can be expected, compared to DME.

Various SPG membrane devices have been used in DME: (i) Cross flow module with tubular SPG membrane with an effective length of up to 500 mm; (ii) A short SPG membrane tube with an effective length of 7−15 mm in a stirred vessel (internal or external pressure micro kit), and (iii) Rotating SPG membrane tube in a stagnant continuous phase. In the cross-flow DME system, a continuous phase liquid circulates from a storage tank through the bore of the membrane tube, and back to the tank (Figure 9). A dispersed phase-forming liquid stored in a pressure vessel is fed to the outside of the membrane tube and force to penetrate through the membrane under the pressure difference which is 1.1 to 5 times higher than the capillary pressure (Vladisavljević and Schubert, 2003a). The apparatus is operated continuously until a desired dispersed phase concentration is achieved in the emulsion. A transmembrane flux in cross-flow DME should be kept below 1–30 l m−2 h−1 to obtain uniform droplets with a
relative span factor of droplet size distribution of 0.25−0.45. To increase transmembrane flux by two orders of magnitude, the continuous phase can be introduced into SPG membrane tube radially, as shown in Figure 10. A tangential introduction of the continuous phase generates spiral streamlines in the axial direction (“swirl flow”) that exert a strong centrifugal force onto the inner surface of the membrane helping to sweep away droplets from the membrane surface (Shimoda et al., 2011). At the swirl-flow velocity of 0.85−5.4 m s$^{-1}$ and the transmembrane flux of 0.3−3 m$^3$ m$^{-2}$ h$^{-1}$, a relative span factor of droplet size distribution of 0.45−0.64 was achieved with an oil phase/water phase volume ratio in single-pass operation of up to 0.4 (Shimoda et al., 2011). Insertion of static turbulence promoters is an alternative method of increasing shear at the membrane surface in cross flow DME, while maintaining a low shear in the recirculation loop (Koris et al., 2011).

Cross-flow systems are easy to scale up and offer a constant shear stress along the membrane surface. However, at least several hundred millilitres of the continuous phase is required in the system to provide recirculation. SPG test kit shown in Figure 11a requires much smaller amount of continuous phase (<50 ml) and can be operated with a very low hold-up volume of both phases, which is useful for expensive samples, such as medical preparations (Higashi and Setoguchi, 2000). The continuous phase is kept under agitation by a magnetic stir bar, while the dispersed phase is injected through the membrane tube from outside to inside. The membrane tube serves as a draft tube, which results in more effective circulation of the continuous phase than in an internal pressure SPG kit.

In addition to DME with static SPG membrane, where shear stress is controlled by fluid flow over the membrane surface, dynamic SPG membrane systems have been investigated, where shear is controlled by rotating the membrane within a static continuous phase (Pawlik and Norton, 2012; 2013). Rotating membrane systems can be operated batchwise or continuously. In a continuous flow operation, surface shear is decoupled from the cross flow velocity, which means that sufficient shear on the membrane surface can be achieved no matter how small the flow rate of the continuous phase may be. Therefore, emulsions with a high dispersed phase concentration can be produced without emulsion recycling, that can help to prevent damage to shear sensitive components and secondary breakup of the drops formed by the membrane.

SPG membrane rig used for PME is shown in Figure 11b. A pressurised pre-mix from a pressure vessel is passed through the membrane tube from outside to inside under the driving
force of pressure difference ranging from several bars (for a 10-µm membrane) to more than 10 bar (for 1-µm membrane) and up to 50 bar for the membrane with sub-micron pore sizes. The product emulsion is collected inside the membrane tube and discharged from the bottom of the tube. In order to reduce the droplet size additionally and improve droplet size uniformity, product emulsion is passed repeatedly through the membrane (Vladisavljević et al., 2004b; 2006; 2006b). Membrane homogenisation using repeated cycles was first developed by Olson et al. (1979) and used for homogenisation of lipid vesicles using track-etch polycarbonate filters.

### 3.1 Factors affecting droplet size in DME

The size distribution of droplets produced in DME depends on a variety of factors, such as the pore size and wetting properties of the membrane, transmembrane flux, shear stress generated on the membrane surface, physical properties of the dispersed and continuous phase, a nature of the surfactant used and the surfactant concentration, emulsion formulation, etc (Joscelyne and Trägårdh, 2000).

#### 3.1.1 Influence of transmembrane pressure and flux

The minimum transmembrane pressure for driving the oil phase through the pores is known as the capillary pressure, \( P_{\text{cap}} \), and is given by the Young-Laplace equation:

\[
P_{\text{cap}} = \frac{4 \gamma_{\text{wo}} \cos \theta}{d_p}
\]  

where \( \gamma_{\text{wo}} \) is the equilibrium interfacial tension between the water and oil phase, \( \theta \) is the contact angle, i.e. the angle formed by a water phase at the three phase boundary where the water phase, oil phase, and membrane intersect (Figure 12). A hydrophilic membrane (\( \theta < 90^\circ \)) is used in the production of O/W emulsion, and thus \( P_{\text{cap}} > 0 \) and \( P_o > P_w \). A hydrophobic membrane (\( \theta > 90^\circ \)) is used in the production of W/O emulsion, and thus \( P_{\text{cap}} < 0 \) and \( P_o < P_w \), i.e. the water phase pressure should be higher than the oil phase pressure by \( P_{\text{cap}} \) to drive the water phase through the membrane. Droplet generation regime is determined by capillary number given by: \( Ca = \frac{U_d \eta_d}{\gamma_{\text{wo}}} \), where \( U_d \) is the velocity of the dispersed phase in a pore and \( \mu_d \) is the viscosity of the dispersed phase. For low capillary numbers in the pores (\( Ca < Ca_{cr} \)), droplets are formed in the dripping regime. In this regime, the interfacial tension force
dominates the viscous force (Sugiura et al., 2002) and the droplet size is virtually independent on the transmembrane flux (Figure 13). For high capillary numbers \((Ca > Ca_{cr})\), droplets grow to large sizes \((d_d > 10d_p)\) before being detached from the membrane surface, which is termed as continuous outflow regime (Kobayashi et al., 2003). In this regime, the viscous force dominates the interfacial tension force and the droplet size sharply increases with increasing the dispersed phase velocity. The critical flux, \(J_{cr}\), i.e. the transmembrane flux at which the transition from dripping to continuous outflow regime occurs is independent on the pore size and increases with decreasing the viscosity of the dispersed phase. Emulsions produced in the continuous outflow regime are highly polydisperse, due to the random nature of droplet formation process. In addition, flow transition from dripping to continuous outflow does not occur simultaneously for all pores, leading to the large variations in the droplet size for the pores operating in the dripping and continuous outflow regime.

3.1.2 Influence of membrane pore size and shear stress on the membrane surface

In dripping regime, a linear correlation between the mean droplet size and the mean pore size of SPG membrane exists: \(d_d = Kd_p\) (Figure 14), where \(K\) typically ranges between 2.8 and 3.5 (Kukizaki and Goto, 2009; 2007c; Nakashima et al., 1991; Vladisavljević et al., 2006). A gradient of \(d_d\) vs. \(d_p\) line increases with decreasing the shear stress on the membrane surface, but even in the absence of any shear, \(K\) is 3.3 for O/W emulsions stabilised with 1% Tween 80 surfactant (Kukizaki and Goto, 2009). The mean droplet size is determined by a balance between the shear force exerted on the liquid-liquid interface by the continuous phase, \(F_d\) and the capillary force, \(F_{ca}\) (Kosvintsev et al., 2005):

\[
F_{ca} = \pi d_p \gamma
\]

\[
F_d = 9 \pi \sigma_w d_d \sqrt{(d_d / 2)^2 - r_p^2}
\]

where \(r_p\) is the pore radius and \(\sigma_w\) is the shear stress on the membrane surface. The equation for the droplet diameter can be obtaining by solving Equations (6) and (7) for \(d_d\):

\[
d_d = \sqrt[3]{\frac{18\sigma_w r_p^2 + 2 \sqrt{81\sigma_w^4 r_p^4 + 4r_p^2 \sigma_w^2 \gamma^2}}{3\sigma_w}}
\]

Therefore, the mean drop diameter decreases with increasing shear stress on the membrane surface until it reaches a constant value at sufficiently high shear stresses (Figure 14). In
cross-flow DME, $\sigma_w$ is a function of the mean velocity of the continuous phase inside the membrane tube, $U_c$ (Vladisavljević and Schubert, 2003b):

$$\sigma_w = \lambda(\rho_c U_c^2 / 8) \tag{9}$$

where $\rho_c$ is the density of the continuous phase and $\lambda$ is the Moody friction factor. For laminar flow inside the membrane tube ($Re < 2300$): $\lambda = 64/Re$ and $\sigma_w = 8 \eta_c U_c/d_{mi}$, where $d_{mi}$ is the inner diameter of the membrane tube and $\eta_c$ is the viscosity of continuous phase. For the rotating SPG membrane, $\sigma_w$ can be estimated from (Vladisavljević and Williams, 2006):

$$\sigma_w = \frac{2\eta_c r_{mo}^2 \omega}{r_b^2 - r_{mo}^2} \tag{10}$$

where $\omega$ is the angular velocity of the membrane, $r_{mo}$ is the outer radius of the membrane tube and $r_b$ is the inner radius of the cylinder in which the membrane tube is rotating.

3.1.3 Influence of surfactant

The role of surfactant in ME is to rapidly adsorb to the newly formed oil-water interface to facilitate droplet detachment and stabilise the formed droplet against coalescence by reducing the interfacial tension. The effect of kinetics of adsorption of surfactant at oil-aqueous interface on the droplet size has been investigated by several groups (Schröder et al., 1998; Van der Graaf et al., 2004; Rayner et al., 2005). As a rule, the faster the surfactant molecules adsorb to the newly formed interface, the smaller the droplet size of the emulsion becomes. Surfactant molecules must not adsorb to the membrane surface, since otherwise the dispersed phase will spread over the membrane surface. This means that the functional groups of surfactant molecules must not carry a positive charge to avoid electrostatic deposition onto the negatively charged surface of SPG membrane (Nakashima et al., 1993). The use of cationic surfactants, e.g. alkyltrimethylammonium salts such as cetyltrimethyl-ammonium bromide (CTAB) leads to polydispersed O/W emulsions with $d_d/d_p > 20$ (Nakashima et al., 1993). The use of zwitterionic surfactants must also be avoided, even when they carry a net negative charge. For example, lecithin at pH 3 fouls SPG membrane due to electrostatic interactions between positively charged groups ($–N(CH_3)_3^+$ and $–NH_3^+$) on phospholipid molecules and negatively charged silanol groups on SPG surface, although at pH 3 the net charge on lecithin molecules is negative (Surh et al., 2008). To produce cationic droplets using SPG membrane, the membrane must be treated with amino trialkoxysilanes to induce a
positive charge on the surface (Figure 7b) or the charge of anionic droplets can be altered after ME by surfactant displacement (Vladisavljević and McClements, 2010).

3.2 Factors affecting droplet size in PME

The mean droplet size in PME depends on several parameters such as the mean pore size of SPG membrane, transmembrane pressure, number of passes through the membrane, viscosity of the continuous and dispersed phase and interfacial tension (Nazir et al., 2010). The mean droplet size is a non-linear function of the mean pore size of SPG membrane (Figure 15): 

$$d_d = K(d_p)^n$$

where \( n < 1 \). The \( d_d/d_p \) ratio decreases with increasing the mean pore size and ranges from 1.5 to 1 at \( d_p = 5–20 \mu m \) and the shear stress on the pore walls of 200 Pa (Vladisavljević et al., 2006). The critical pressure in PME is given by (Park et al., 2001):

$$P_{cap} = \frac{\gamma/\{2 + 2a^6/\sqrt{2a^6-1} \times \arccos(1/a^3) - 4a^2 \}}{a + \sqrt{a^2 - 1}} \tag{11}$$

where \( a = d_1/d_p \) and \( d_1 \) is the mean droplet size in pre-mix. If \( d_1/d_p \rightarrow 1 \), the capillary pressure is given by Eq. (5). In PME, the transmembrane pressure resulting in the most uniform droplets is typically 10–50 times larger than \( P_{cap} \) (Vladisavljević et al., 2004b). The mean droplet size decreases with increasing the mean shear stress on the pore walls, given by:

$$\sigma_{w,p} = 8\eta_e J \xi / (\varepsilon d_p) \tag{12}$$

where \( \eta_e \) is the viscosity of emulsion inside the pores. According to Eq. (12), the mean droplet size decreases with increasing transmembrane pressure, as shown in Figures 15 and 17b. The pressure energy is used for flow through the membrane pores and droplet disruption:

$$\Delta p_{mm} = \frac{\eta_e (R_m + R_f)J}{\Delta p_{flow}} + C\phi(1/d_1 - 1/d_p) \gamma \tag{13}$$

where \( C \) is a constant, \( \phi \) is the volume fraction of the dispersed phase, \( R_m \) is the membrane resistance, and \( R_f \) is the fouling resistance. The second term in Equation (13) is based on the assumption that the energy needed for droplet disruption is proportional to the resultant increase in surface area. The fouling resistance occurs as a result of accumulation of the dispersed phase on the membrane surface (external fouling) and inside the pores (internal fouling). External fouling dominates at high \( d_d/d_p \) ratios in the feed emulsion and low transmembrane pressures, whereas internal fouling dominates at high transmembrane pressures and small droplet sizes relative to the pore size. In repeated PME (Vladisavljević et al., 2004b):
\[ \Delta p_{\text{tm}} = \frac{\eta_c (R_m^F + R_f^F) J_i}{\Delta p_{\text{flow}}} + \frac{C \varphi (1/d_i - 1/d_{i-1}) \eta}{\Delta p_{\text{disr}}} \]  

Equation (14)

where \( J_i \) and \( R_f^F \) are \( J \) and \( R_f \) during \( i \)th pass through the membrane and \( d_i \) and \( d_{i-1} \) are the mean droplet diameter after \( i \)th and \((i-1)\)th pass, respectively. The effect of varying droplet size on the viscosity of emulsion was disregarded in Equation (14). As the number of passes through the membrane increases at \( \Delta p_{\text{tm}} = \text{const} \), the mean droplet size tends to a constant minimum value, i.e. \( d_i \rightarrow d_{i-1} \) (Figure 17 b), which means that \( \Delta p_{\text{disr}} \rightarrow 0 \) and \( \Delta p_{\text{flow}} \rightarrow \Delta p_{\text{tm}} \). Therefore, the term accounting for droplet disruption \( (\Delta p_{\text{disr}}) \) becomes progressively less important than the flow term \( (\Delta p_{\text{flow}}) \) and pressure energy of the feed mixture is increasingly used for providing emulsion flow through the membrane (Figure 16). As a consequence of redistribution of pressure terms in Eq. (14), the transmembrane flux at constant operating pressure increases after each pass through the membrane until a maximum flux is established. The maximum transmembrane flux in PME is limited by the membrane resistance, emulsion viscosity, and transmembrane pressure (Figure 17a).

The effect of continuous phase viscosity, dispersed phase concentration and transmembrane pressure on the mean droplet size and transmembrane flux in repeated PME is shown in Figure 17. The largest increase in flux between the two passes was observed between the first and second pass, because the most significant reduction in the mean droplet size was observed in the first pass. Under the same conditions, the limiting flux was substantially lower at the higher dispersed phase content, which was a consequence of both the higher viscosity of emulsion, \( \eta_c \) and the higher \( \Delta p_{\text{disr}} \) term in Eq. (14). Although the transmembrane fluxes were significantly higher at the lower viscosity of the continuous phase, the lowest droplet sizes were obtained at the higher viscosity of the continuous phase (128 mPa·s), because of the higher shear stress acting on the pore walls; at \( \Delta p_{\text{tm}} = 150 \text{ kPa} \) and \( \varphi_p = 20 \text{ vol\%} \), the shear stress acting on the pore walls in the fifth pass was \( \sigma_{w,p} = 80 \text{ Pa} \) at \( \eta_c = 1 \text{ mPa·s} \), whereas \( \sigma_{w,p} \) was 1880 Pa at \( \eta_c = 126 \text{ mPa·s} \), in spite of the smaller transmembrane flux.

3.3 Applications of direct and premix membrane emulsification using SPG membrane

SPG membrane was initially used for the preparation of simple O/W and W/O emulsions with a narrow particle size distribution and adjustable mean particle size (Nakashima et al., 1991). Since the early 1990s, applications of SPG membrane emulsification technique have been
extended to the production of multiple emulsions, such as solid-in-oil-in-water (S/O/W) (Kukizaki, 2009c), oil-in-water-in-oil (O/W/O) (Wei et al., 2013; Cho et al., 2005) and water-in-oil-in-water (W/O/W) (Surh et al., 2007), nano- and micro-emulsions (Koga et al., 2010; Oh et al., 2011; Laouini et al., 2012; Choi et al., 2012; Pradhan et al., 2013; Oh et al., 2013), emulsions with droplets laminated with multilayered biopolymer films (Vladisavljević and McClements, 2010; Gudipati et al., 2010; Nazir et al., 2012), microbubbles (Kukizaki and Goto, 2007), nanobubbles (Kukizaki and Goto, 2006), micro- and nano-particles (Vladisavljević and Williams, 2005; 2010), and vesicles (liposomes and niosomes) (Hwang et al., 2011; Pham et al., 2012).

Some examples of particles fabricated by DME or PME using SPG membrane are given in Table 6. Emulsion droplets were transformed into solid particles by implementing a variety of chemical reactions or physicochemical processes within the droplets, such as crosslinking of hydrogel forming polymers (Wei et al., 2013), polymerisation of monomer mixtures (Omi et al., 2005), solidification from a melt (Kukizaki and Goto, 2007c), polymer precipitation induced by solvent evaporation or extraction (Liu et al., 2005), redox reaction (Kakazu et al., 2010), complex coacervation (Kage et al., 1997), and thermal coagulation (El-Mahdy et al., 1998).

Crosslinking of gel-forming polymers within the droplets can be carried out using physical or chemical crosslinking methods (Wang et al., 2005). Physical crosslinking methods are helix-coil transition induced by cooling below the phase transition temperature (Zhou et al., 2007), thermal gelation induced by heating to about 37°C (Wu et al., 2008) and ionotropic gelation induced by the addition of multivalent ions (Liu et al., 2003). Melt solidification involves performing membrane emulsification above the melting point of the dispersed phase followed by emulsion cooling. This approach was used for fabrication of solid lipid particles for drug delivery applications (Kukizaki, 2009c), low-melting-point metal particles for soldering microcomponents in microelectronics (Torigoe et al., 2011) and thermochromic liquid crystal particles for heat transfer research (Segura et al., 2013).

Polymeric particles were produced by SPG membrane emulsification and subsequent suspension polymerisation (Omi et al., 1994) or solvent evaporation (Ito et al., 2011). Suspension polymerisation can be carried out in O/W (Ma et al., 2003), W/O (Hu et al., 2011) or W/O/W emulsion (Ma et al., 2004) and can be combined with droplet swelling technique.
which is known as “two-stage” suspension polymerisation) to produce microspheres from hydrophilic monomers (Omi et al., 1997). Hollow particles were produced by combining SPG membrane emulsification with interfacial polymerisation (Chu et al., 2003), internal phase separation (Liu et al., 2010), molecular imprinting (Kou et al., 2012), and coating a shell around polymer particles by a sol-gel process (Kong et al., 2013) or interfacial crosslinking (Akamatsu et al., 2010) followed by core disintegration by chemical dissolution or calcination.

4. Gas dispersion using SPG membrane

Microbubbles or nanobubbles can be produced by injecting gas phase through a hydrophilic SPG membrane into an aqueous surfactant solution (direct injection method) or by loading porous particles fabricated by SPG membrane emulsification with a suitable gas (Hou et al., 2009). Monodispersed microbubbles with a relative span factor of about 0.5 were generated when the contact angle at membrane/water/air interface was in the range of $0^\circ < \theta < 45^\circ$ and the bubble-to-pore size ratio was 7.9 (Kukizaki and Wada, 2008). Nanobubbles with a mean diameter of 360–720 nm and relative span factor of 0.45–0.48 were produced by injecting air through SPG membranes with a mean pore diameter of 43–85 nm into 0.05–0.5 wt.% sodium dodecyl sulfate (SDS) solution (Kukizaki and Goto, 2006). The mean size of nanobubbles was 8.6 times larger than the mean pore size and unaffected by the flow velocity of air in the pores within a range of 0.5–3.7 m·s$^{-1}$ (Kukizaki and Goto, 2006). Microbubbles generated by SPG membranes can find applications in the production of aerated food products (Zúñiga and Aguilera, 2008), ultrasound contrast agents for ultrasonic examinations (Hou et al., 2009) and aerobic wastewater treatment (Liu et al., 2012; 2013), which can be combined with UV irradiation (Tasaki et al., 2009) or activated sludge process (Liu et al., 2012b).

5. Conclusions

SPG membranes are increasingly being used in microfluidic applications aiming at generating uniform micro- and nano-droplets, -bubbles, and –particles. They have also been used for modification of emulsions (phase inversion, demulsification and homogenization), as well as in micromixing/direct nanoprecipitation processes for production of inorganic and organic nanoparticles. SPG membranes can overcome low throughput limitations of conventional microfluidic junctions and flow focusing devices by providing countless number of pores that serve as massively parallel T junctions. Direct and premix membrane emulsification (DME
and PME) are two main modes of operation of SPG membrane emulsification devices. In DME, the mean droplet size is proportional to the mean pore size and the proportionality constant is typically around 3, whereas in PME, the ratio of the mean droplet size to the mean pore size is less than 1.5 and can be below unity. To form uniformly sized particles, DME or PME can be combined with a variety of physichemical or chemical processes, that can be applied individually or in combination, such as polymerisation, cross-linking, solvent evaporation, electrostatic deposition, internal phase separation, coagulation, calcination, sol-gel chemistry, crystallisation, etc.
**Table 1. Formation of inorganic nanoparticles by membrane micromixing / direct precipitation method.**

<table>
<thead>
<tr>
<th>Salt A</th>
<th>Salt B</th>
<th>Membrane and pore size</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BaSO(_4) nanoparticles (d=20–200 nm)</td>
<td>0.1–0.3M BaCl(_2)</td>
<td>0.1M NaSO(_4)</td>
<td>5 μm stainless steel, 0.2–0.9 μm Ni</td>
</tr>
<tr>
<td>Anatase-TiO(_2) nanoparticles (d=9–20 nm)</td>
<td>0.03–0.15M Ti(SO(_4))(_2)</td>
<td>0.1–0.3M NH(_4)HCO(_3)</td>
<td>0.2 μm Ni</td>
</tr>
<tr>
<td>ZnO nanoparticles (d=9.4–14 nm)</td>
<td>0.2–1.2M ZnSO(_4)</td>
<td>2.25M NH(_4)HCO(_3)</td>
<td>5 μm stainless steel</td>
</tr>
</tbody>
</table>

**Table 2. Formation of organic nanoparticles by membrane micromixing / direct precipitation method.**

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Solvent and API</th>
<th>Membrane and pore size</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP-loaded liposomes (d=60–200 nm)</td>
<td>20–60mg ml(^{-1}) Lipoïd(^{®}) E80 + 4–12mg ml(^{-1}) Chl</td>
<td>Ethanol + 0.4mg/ml BDP</td>
<td>0.4–10.2 μm SPG</td>
</tr>
<tr>
<td>SPL-loaded liposomes (d=110–190 nm)</td>
<td>20–80mg/ml Lipoïd(^{®}) E80 + 4–16mg ml(^{-1}) Chl</td>
<td>Ethanol + 3 mg ml(^{-1}) SPL</td>
<td>40 nm PP hollow fiber</td>
</tr>
<tr>
<td>Vitamin E-loaded PCL nanoparticles (d=250–350 nm)</td>
<td>5mg/ml PCL</td>
<td>Acetone + 4 mg ml(^{-1}) vitamin E</td>
<td>0.2–10.2 μm SPG</td>
</tr>
<tr>
<td>caffeine and SPL-loaded niosomes (d=111–115 nm)</td>
<td>105mM Tw + 105mM Chl + 23.3 mM DCP</td>
<td>Ethanol + 10 mg ml(^{-1}) caffeine or 3 mg ml(^{-1}) SPL</td>
<td>0.9 μm SPG</td>
</tr>
</tbody>
</table>

Table 3. Typical mixing ratios of raw materials in the production of SPG from Na$_2$O–CaO–Al$_2$O$_3$–B$_2$O$_3$–SiO$_2$ mother glass (Nakashima, 2002)*.

<table>
<thead>
<tr>
<th></th>
<th>Wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shirasu</td>
<td>51</td>
</tr>
<tr>
<td>Limestone</td>
<td>23</td>
</tr>
<tr>
<td>Boric acid</td>
<td>22</td>
</tr>
<tr>
<td>Soda ash</td>
<td>4</td>
</tr>
</tbody>
</table>

*MgO (≈5 wt%) can also be added.

Table 4. Composition of primary glass*, SPG*, and porous Vycor glass and Pyrex glass (Nakashima et al., 1992; Nakashima, 2002).

<table>
<thead>
<tr>
<th></th>
<th>Primary glass for SPG, wt%</th>
<th>SPG wt%</th>
<th>Vycor® glass wt%</th>
<th>Pyrex® glass wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO$_2$</td>
<td>49</td>
<td>69</td>
<td>94–99.5</td>
<td>81</td>
</tr>
<tr>
<td>Al$_2$O$_3$</td>
<td>10</td>
<td>13</td>
<td>0–0.5</td>
<td>2</td>
</tr>
<tr>
<td>CaO</td>
<td>17</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B$_2$O$_3$</td>
<td>16</td>
<td>7</td>
<td>0.2–6.0</td>
<td>13</td>
</tr>
<tr>
<td>Na$_2$O</td>
<td>5</td>
<td>5</td>
<td>&lt; 0.1</td>
<td>4</td>
</tr>
<tr>
<td>K$_2$O</td>
<td>2</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fe$_2$O$_3$</td>
<td>1</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Based on proportions of raw materials given in Table 3.
Table 5. Properties of commercial isotropic (symmetric) SPG membrane (Vladisavljević et al., 2005; Nakashima, 2002; Kukizaki, 2009b; Nakashima et al., 1992).

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape</td>
<td>Tubes or flat discs</td>
</tr>
<tr>
<td>Thickness, $\delta_m$</td>
<td>0.4–1 mm</td>
</tr>
<tr>
<td>Compressive strength</td>
<td>200–280 Mpa</td>
</tr>
<tr>
<td>Pore diameter, $d_p$</td>
<td>0.04–20 $\mu$m</td>
</tr>
<tr>
<td>Porosity, $\varepsilon$</td>
<td>50–60 %</td>
</tr>
<tr>
<td>True density</td>
<td>2000–2500 kg m$^{-3}$</td>
</tr>
<tr>
<td>Zeta potential at pH=3–10 and $C_{NaCl}$= 1–100 mol m$^{-3}$</td>
<td>$-15$–$(-45)$ mV</td>
</tr>
<tr>
<td>Pore tortuosity, $\xi$</td>
<td>1.25–1.4</td>
</tr>
<tr>
<td>Number of pores per unit cross-sectional area, $N/A_m$</td>
<td>$10^9$–$10^{14}$ m$^{-2}$</td>
</tr>
<tr>
<td>Specific pore volume, $V_p/m_m$</td>
<td>0.5–0.6 dm$^3$ kg$^{-1}$</td>
</tr>
<tr>
<td>Hydraulic resistance, $R_{m,sym}$</td>
<td>$10^8$–$10^{12}$ m$^{-1}$</td>
</tr>
</tbody>
</table>
Table 6. Examples of microparticles fabricated using DME and PME with SPG membrane.

<table>
<thead>
<tr>
<th>Product type</th>
<th>Example</th>
<th>Secondary reaction/process after DME or PME</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceramic particles</td>
<td>Silica nano- or micro-particles</td>
<td>Polymerisation of silicic acids by interfacial or internal reaction</td>
<td>Kandori et al. (1992)</td>
</tr>
<tr>
<td>Liquid crystal particles</td>
<td>Thermochromic liquid crystal particles</td>
<td>Melt crystallization in O/W emulsion</td>
<td>Segura et al. (2013)</td>
</tr>
<tr>
<td>Carbon particles</td>
<td>Carbon cryogel</td>
<td>sol–gel polycondensation followed by freeze-drying and carbonization</td>
<td>Yamamoto et al. (2010)</td>
</tr>
<tr>
<td>Metal particles</td>
<td>Solder metal microparticles</td>
<td>Solidification of liquid metal in M/W or M/O emulsion</td>
<td>Torigoe et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Silver nanoparticles</td>
<td>Reduction of silver ions in W/O microemulsions</td>
<td>Kakazu et al. (2010)</td>
</tr>
<tr>
<td>Solid lipid particles</td>
<td>W/S microcarrier</td>
<td>Melt crystallization in W/O/W emulsion</td>
<td>Kukizaki and Goto (2007c)</td>
</tr>
<tr>
<td></td>
<td>S/S microcarrier</td>
<td>Melt crystallization in S/O/W emulsion</td>
<td>Kukizaki (2009c)</td>
</tr>
<tr>
<td></td>
<td>Coherent particles</td>
<td>Melt crystallization in O/W emulsion</td>
<td>D’oria et al. (2009); Li et al. (2011)</td>
</tr>
<tr>
<td>Gel micro- and nano-particles</td>
<td>Ca-alginate</td>
<td>Crosslinking of sodium alginate with Ca(^{2+}) in W/O emulsion</td>
<td>Liu et al. (2003); You et al. (2001); Akamatsu et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Chitosan</td>
<td>Crosslinking of chitosan with glutaraldehyde in W/O emulsion</td>
<td>Wang et al. (2005); Wei et al. (2010); Yue et al. (2011); Akamatsu et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>Alginate/chitosan</td>
<td>Crosslinking of chitosan with glutaraldehyde in O/W emulsion</td>
<td>Wei et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>HTCC/GP</td>
<td>Thermal gelation in W/O emulsion</td>
<td>Wu et al. (2008)</td>
</tr>
<tr>
<td></td>
<td>Agarose</td>
<td>Coalescence of Na-alginate droplets with Ca(^{2+}) droplets and particle coating with chitosan</td>
<td>Zhang et al. (2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Helix-coil transition induced by cooling</td>
<td>Zhou et al. (2007; 2008; 2009)</td>
</tr>
<tr>
<td>Protein microspheres</td>
<td>Albumin</td>
<td>Heat or chemical denaturation of albumin in W/O emulsion</td>
<td>El-Mahdy et al. (1998); Muramatsu and Kondo (1995); Muramatsu and Nakauchi (1998)</td>
</tr>
<tr>
<td>Composite organic-inorganic particles</td>
<td>Polymer particles with embedded TiO(_2)/Fe(_3)O(_4) nanoparticles or quantum dots</td>
<td>Solvent evaporation from oil phase in S/O/W emulsion</td>
<td>Supsakulchai et al. (2002; 2002b); Omi et al. (2001); Wang et al. (2013); Yang et al. (2010); Zhou et al. (2012)</td>
</tr>
<tr>
<td>Polymers and Coatings</td>
<td>Preparation Method</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Polymeric particles coated with silica nanoparticles</td>
<td>Solvent evaporation followed by electrostatic layer-by-layer deposition</td>
<td>Ito et al. (2010)</td>
<td></td>
</tr>
<tr>
<td>PS, P(St-co-DVB), P(St-co-MMA), PUU-VP, etc.</td>
<td>One-stage suspension polymerization in O/W emulsion</td>
<td>Yuyama et al. (2000); Omi et al. (1994); Nuisin et al. (2000); Ma et al. (2003)</td>
<td></td>
</tr>
<tr>
<td>PS-PAAm composite</td>
<td>One-stage suspension polymerisation in W/O/W emulsion</td>
<td>Ma et al. (2004)</td>
<td></td>
</tr>
<tr>
<td>P(AAm-co-AA) and PNaAMPS hydrogel</td>
<td>One-stage suspension polymerisation in W/O emulsion</td>
<td>Nagashima et al. (1998); Hu et al. (2011)</td>
<td></td>
</tr>
<tr>
<td>PMMA microspheres and large P(St-co-DVB) spheres</td>
<td>Two-stage suspension polymerisation in O/W emulsion</td>
<td>Omi et al. (1995; 1997)</td>
<td></td>
</tr>
<tr>
<td>PUU, PST-PMMA,</td>
<td>Solvent evaporation from oil phase droplets in O/W emulsion</td>
<td>Yuyama et al. (2000b); Ma et al. (1999; 1999b; 1999c)</td>
<td></td>
</tr>
<tr>
<td>Coherent PLA and PLGA spheres</td>
<td>Solvent evaporation from oil phase droplets in O/W emulsion</td>
<td>Ito et. (2011); Yue et al. (2012); Kanakubo et al. (2010)</td>
<td></td>
</tr>
<tr>
<td>PLA or PLGA capsules for hydrophilic actives, DFB loaded PLA capsules</td>
<td>Solvent evaporation from oil phase in W/O/W emulsion</td>
<td>Liu et al. (2005; 2005b; Doan et al. (2011); Hou et al. (2009)</td>
<td></td>
</tr>
<tr>
<td>mPEG-PLA capsules for hydrophilic actives</td>
<td>Solvent extraction from oil phase in W/O/W emulsion</td>
<td>Wei et al. (2008; 2011)</td>
<td></td>
</tr>
<tr>
<td>P(St-co-DMAEMA), P(St-co-DVB), PDVB</td>
<td>One-stage suspension polymerisation and internal phase separation in O/W emulsion</td>
<td>Ma et al. (2001; 2002; 2003b); Lee et al. (2010); Hao et al. (2009)</td>
<td></td>
</tr>
<tr>
<td>Polymer-supported palladium catalyst</td>
<td>One-stage suspension polymerisation, internal phase separation and ligand exchange</td>
<td>Liu et al. (2010; 2010b)</td>
<td></td>
</tr>
<tr>
<td>P(St-co-DVB-co-MAA)</td>
<td>Two-stage suspension polymerisation and internal phase separation in O/W emulsion</td>
<td>Wang et al. (2012)</td>
<td></td>
</tr>
<tr>
<td>ENB-P(M-co-U-co-F) core-shell capsules</td>
<td>In situ polymerization</td>
<td>Liu et al. (2011)</td>
<td></td>
</tr>
<tr>
<td>Chitosan</td>
<td>Crosslinking of chitosan onto alginate particles and core dissolution</td>
<td>Akamatsu et al. (2010)</td>
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<td>Molecularily imprinted P(MMA-co-EDMA) particles</td>
<td>Molecular imprinting using CAP as a template molecule</td>
<td>Kou et al. (2012)</td>
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<td>PGPR-PE2CA core-shell particles</td>
<td>Interfacial polymerization followed by solvent evaporation</td>
<td>Lee et al. (2009)</td>
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<td>Description</td>
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<td>Thermo-responsive capsules</td>
<td>Hollow porous silica nanocapsules loaded with Fe$_3$O$_4$ nanoparticles</td>
<td>One-stage suspension polymerisation, followed by sol-gel process and calcination</td>
<td>Kong et al. (2010; 2012; 2013)</td>
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<td>Porous PA shells with P(NIPAM) gates in the pores</td>
<td>Interfacial polymerisation</td>
<td>Chu et al. (2002; 2003)</td>
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<td>P(NIPAM-co-AA) capsules</td>
<td>Suspension polymerisation in W/O emulsion</td>
<td>Si et al. (2011); Wang et al. (2013)</td>
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<td>Janus particles</td>
<td>PS/PPC</td>
<td>Solvent pervaporation and internal phase separation</td>
<td>Chang and Hatton (2012)</td>
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<td>PMMA/P(S-BIEM)-g-PDMAEMA or PS/P(MMA-CMS)-b-PDMAEMA</td>
<td>Solvent evaporation, followed by internal phase separation and atom transfer radical polymerisation</td>
<td>Tanaka et al. (2010); Ahmad (2008)</td>
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<td>PS/PMMA</td>
<td>Solvent evaporation followed by internal phase separation</td>
<td>Yamashita et al. (2012)</td>
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<td>Complex coacervate microcapsules</td>
<td>gelatin/acacia microcapsules</td>
<td>Complex coacervation in O/W emulsion</td>
<td>Kage et al. (1997)</td>
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<td>Non-spherical particles</td>
<td>hemispherical polymer particles</td>
<td>Cleavage of Janus particles</td>
<td>Yamashita et al. (2012)</td>
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<td>3D colloidal assemblies</td>
<td>Clusters containing silica-encapsulated magnetite nanoparticles</td>
<td>Solvent pervaporation and coating of clusters with silica</td>
<td>Chang and Hatton (2012)</td>
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Abbreviations: AA, acrylic acid; DMAEMA, dimethylaminoethyl methacrylate; CAP, chloramphenicol; CMS, chloromethylstyrene; DFB, decafluorobutane; DVB, divinylbenzene; EDMA, ethylene dimethacrylate; ENB 5-ethylidene-2-norbornene; HTCC, N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride; GP, glycerophosphate; MAA, methacrylic acid; MMA, methyl methacrylate; mPEG, poly(monomethoxypoly ethylene glycol); NIPAM, N-isopropylacrylamide; PAAm, PAAm: polyacrylamide; PE2CA, poly(ethyl 2-cyanoacrylate); PLA, polylactic acid or polylactide; PLGA, poly(lactic-co-glycolic acid); P(M-co-U-co-F), Poly(melamine-co-urea-co-formaldehyde); PNaAMPS, poly(sodium 2-(acrylamido)-2-methylpropanesulfonate); PPC, poly(propylene carbonate); P(S-BIEM), poly(styrene-2-(2-bromoisobutyrlyoxy)ethyl methacrylate; PUU, polyurethaneurea; St, styrene; TPP, tripolyphosphate; VP, vinyl polymer.
References


'Codelivery of mTERT siRNA and paclitaxel by chitosan-based nanoparticles promoted synergistic tumor suppression', *Biomaterials*, 34: 3912–3923.


Figure captions

Figure 1. A comparison between pressure driven membrane separation and membrane microfluidic processes, where $P_1 > P_2$. In a membrane separation process (a), feed stream is split into two product streams of different chemical composition (Mulder, 1996). In a membrane dispersion process (b), two streams (miscible or immiscible) are combined together to form one product stream. Membrane treatment of dispersions (c) involves passing a whole dispersion through the membrane, which results in the modification of the particle size distribution in the original dispersion and/or phase inversion.

Figure 2. Membrane dispersion processes with hydrophilic membrane: (a) Production of O/W emulsion by DME (Nakashima et al., 2000); (b) Production of microbubbles (Kukizaki and Goto, 2007c) and nanobubbles (Kukizaki and Goto, 2006); (c) Production of nanoparticles by membrane micromixing / direct precipitation method (Chen et al., 2004).

Figure 3. Treatment of emulsions using membranes: (a) Production of O/W emulsion by PME (Suzuki et al., 1996); (b) Production of W/O emulsion by PME with phase inversion (Suzuki et al., 1999); (c) Demulsification of W/O emulsion (Kukizaki and Goto, 2008).

Figure 4. A flow diagram of different steps involved in the fabrication of Shirasu Porous Glass (SPG) membrane.

Figure 5. Spinodal decomposition of glass induced by cooling mother glass from an initial temperature $T_1$ to temperature $T_2$ lying in the spinodal region (within the spinodal line). To prevent phase separation via nucleation, a transition from the stable to the spinodal region of the phase diagram must proceed quickly or through the upper critical solution temperature (UCST).

Figure 6. (a) Scanning electron micrograph of the surface of SPG membrane polished with diamond paste and used for visualization of ME by metalographic microscope; (b) X-ray microtomography image of SPG membrane (Vladisavljević et al., 2007).
Figure 7. Chemical modification of SPG surface by treatment with organosilane compounds: (a) Hydrophobic treatment with monochlorosilanes (TMS – trimethylchlorosilane, ODS – octadecyldimethylchlorosilane) (Kai et al., 2006); (b) Introduction of amino groups by amino trialkoxysilanes to render the surface positively charged (APTMS – (3-aminopropyl)-trimethoxysilane, APTES – (3-aminopropyl)-triethoxysilane).

Figure 8. (a) A micrograph of droplets formed on the surface of SPG membrane in DME (Vladisavljević et al., 2007); (b) Micrographs of droplets before PME and after passing 5 times through 8-μmSPG membrane (Vladisavljević et al., 2010).

Figure 9. An apparatus for cross flow DME using tubular SPG membrane. During initial start up, a valve 1 is open to remove any trapped air from the module (Nakashima et al., 1994).

Figure 10. Introduction of continuous phase in cross-flow module from the tangential direction to improve a dispersed phase flux through the membrane (Shimoda et al., 2010).

Figure 11. External pressure type micro kits available by SPG Technology Co., Ltd (Sadowara, Japan) for (a) DME and (b) PME. The kits are supplied with SPG membrane tube with an effective length of 10–15 mm.

Figure 12. Typical contact angles through the water phase and phase pressures encountered in membrane emulsification: (a) Production of O/W emulsion (θ < 90°, P_o > P_w); (b) Production of W/O emulsion (θ > 90°, P_o < P_w). The contact angle θ is the angle measured through the water phase, where a liquid/liquid interface meets a membrane surface (γ_{mw} = interfacial tension between the membrane and water phase, γ_{mo} = interfacial tension between the membrane and oil phase, γ_{wo} = interfacial tension between the water and oil phase).

Figure 13. Mean droplet size in DME as a function of transmembrane flux, J. Dripping regime is characterised by formation of small droplets at high frequency and occurs at J < J_{cr}. Continuous outflow regime is characterised by the formation of large droplets at low frequency and occurs at J > J_{cr}.
Figure 14. Mean droplet size in DME as a function of mean pore size of SPG membrane and shear stress on the membrane surface.

Figure 15. Mean droplet size in PME as a function of mean pore size of SPG membrane (at $\sigma_{w,p} = \text{const}$) and transmembrane flux (at $d_{p} = \text{const}$). For comparison, a relationship between mean droplet size and mean pore size in DME is shown by the dashed line.

Figure 16. The pressure difference used to overcome the hydraulic resistances in the system and interfacial tension force as a function of the number of passes through the membrane at two different transmembrane pressures. Production of W/O/W emulsion using PME at the viscosity of the continuous phase of 126 mPas, the concentration of W/O drops in W/O/W emulsion of 10 vol%, the concentration of inner water phase in the W/O emulsion of 10 vol%, and the mean pore size of the membrane of 10.7 $\mu$m (Vladisavljević et al., 2004).

Figure 17. The effect of the number of passes through the membrane on: (a) transmembrane flux, and (b) median diameter and relative span factor of W/O drops. Production of W/O/W emulsion using PME at different transmembrane pressures (100 or 150 kPa), viscosities of the continuous phase (1 or 126 mPa·s) and concentrations of W/O drops in W/O/W emulsion (1 or 20 vol%). The mean pore size of the SPG membrane was 10.7 $\mu$m and the concentration of inner water phase in the W/O emulsion was 30 vol% (Vladisavljević et al., 2006).

Figure 18. Examples of particles fabricated using SPG membrane emulsification: (a) Doxorubicin (DOX)-loaded liposomes prepared by a film-hydration method combined with repeated SPG membrane homogenization and remote loading of DOX (Hwang et al., 2011); (b) Porous thermoresponsive capsules with poly(N-isopropylacrylamide) (PMIPAM) gates prepared by DME, interfacial polymerisation and plasma-graft pore-filling polymerization (Chu et al., 2002); (c) “Mushroom-like” Janus particles prepared by DME, internal phase separation and surface-initiated atom transfer radical polymerisation (ATRP) (Tanaka et al., 2010); (d) Silica-encapsulated magnetite nanoparticle clusters prepared by DME, solvent pervaporation and sol-gel coating (Chang and Hatton, 2012); (e) PLGA particles coated with silica nanoparticles prepared by layer-by-layer electrostatic deposition of poly(allylamine hydrochloride) (PAH) and silica nanoparticles onto PLGA particles produced by DME (Ito et al., 2010); (f) hemispherical particles produced by cleavage of Janus particles fabricated by
PME (Yamashita et al., 2012); (g) Porous silica shells loaded with magnetic nanoparticles and anticancer drug prepared by DME, polymerisation of styrene droplets, silica sol-gel coating of PS particles, removing PS core by thermal treatment and drug loading (Kong et al., 2010); (h) Janus PMMA/PS particles produced by DME and evaporation of toluene from homogeneous PMMA/PS/toluene droplets (Yamashita et al., 2012); (i) Chitosan shells prepared by coating chitosan onto alginate particles produced by DME, followed by crosslinking the shell and dissolution of the alginate core (Akamatsu et al., 2010); (j) Magnetic polymer microspheres prepared from W/O/W emulsion by PME followed by chemical coprecipitation of Fe$_3$O$_4$ within the inner water phase and solvent evaporation (Yang et al., 2010); (k) Droplets of hydrophilic drug solution embedded in solid lipid matrix prepared from W/O/W emulsion by temperature-controlled DME and melt crystallisation (Kukizaki and Goto, 2007c); (l) Surfactant-coated hydrophilic drug nanoparticles embedded in solid lipid matrix prepared from S/O/W emulsions by temperature-controlled PME and melt crystallisation (Kukizaki, 2009).
Figure 1
Figure 2
Figure 3
Shirasu
Glass fusion at 1350°C
Forming
Cooling to 760-750°C
SPG membrane

Primary glass
(Na₂O-CaO-Al₂O₃-B₂O₃-SiO₂)

Boric acid
Limestone

Additives (Na₂CO₃, MgO, ZrO₂)

Acid soluble phase
(CaO-B₂O₃ rich)

Acid insoluble phase
(SiO₂-Al₂O₃ rich)

Acid leaching
HCl

Figure 4
Figure 5
Figure 6
(a) Treatment with monochlorosilanes (TMS and ODS)

\[
\text{SiO}_2 \xrightarrow{\text{Cl-Si(CH}_3)_2R} \text{SiO}_2
\]

TMS: R = CH\(_3\)
ODS: R = C\(_{18}\)H\(_{37}\)

(b) Treatment with amino trialkoxysilanes (APTMS and APTES)

\[
\text{SiO}_2 \xrightarrow{\text{RO-Si(NH}_2}} \text{SiO}_2
\]

APTMS: R = CH\(_3\)
APTES: R = C\(_2\)H\(_5\)

\[
\text{SiO}_2 \xrightarrow{\text{RO + H}_2\text{O}} \text{SiO}_2
\]

Figure 7
pre-mix  SPG  emulsion
Figure 9
Figure 10
Figure 11
Figure 12

(a) Hydrophilic membrane ($\theta < 90^\circ$)

$$\gamma_{mw} = \gamma_{mo} + \gamma_{wo} \cos \theta$$

(b) Hydrophobic membrane ($\theta > 90^\circ$)

$$\gamma_{mo} = \gamma_{mw} + \gamma_{wo} \cos \theta$$
Figure 13
Droplet size, $d_d$

Shear stress on membrane surface, $\sigma_w$

Pore size, $d_p$

Figure 14
Figure 15
$\Delta p_{\text{disr}}$  
$\Delta p_{\text{flow}}$

$\varphi_i = 10 \, \text{vol.}\%$
$\varphi_o = 10 \, \text{vol.}\%$

$\Delta p_{\text{flow}}$, 150 kPa
$\Delta p_{\text{disr}}$, 150 kPa
$\Delta p_{\text{flow}}$, 20 kPa
$\Delta p_{\text{disr}}$, 20 kPa

Figure 16
\( \eta_c = 1 \text{ mPas}, \ \phi_o = 1 \text{ vol\%}, \ \Delta p_{tm} = 150 \text{ kPa} \)

\( \eta_c = 1 \text{ mPas}, \ \phi_o = 20 \text{ vol\%}, \ \Delta p_{tm} = 150 \text{ kPa} \)

\( \eta_c = 1 \text{ mPas}, \ \phi_o = 20 \text{ vol\%}, \ \Delta p_{tm} = 100 \text{ kPa} \)

\( \eta_c = 126 \text{ mPas}, \ \phi_o = 20 \text{ vol\%}, \ \Delta p_{tm} = 150 \text{ kPa} \)

\( \eta_c = 126 \text{ mPas}, \ \phi_o = 20 \text{ vol\%}, \ \Delta p_{tm} = 100 \text{ kPa} \)

**Figure 17**
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Figure 18