Production of uniform droplets using membrane, microchannel and microfluidic emulsification devices

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ABSTRACT

This review provides an overview of major microengineering emulsification techniques for production of monodispersed droplets. The main emphasis has been put on membrane emulsification using Shirasu Porous Glass (SPG) and microsieve membrane, microchannel emulsification using grooved-type and straight-through microchannel plates, microfluidic junctions and flow focusing microfluidic devices. Microfabrication methods for production of planar and 3D poly(dimethylsiloxane) (PDMS) devices, glass capillary microfluidic devices and single crystal silicon microchannel array devices have been described including soft lithography, glass capillary pulling and microforging, hot embossing, anisotropic wet etching and deep reactive ion etching. In addition, fabrication methods for SPG and microsieve membranes have been outlined, such as spinodal decomposition, reactive ion etching and ultraviolet LIGA (Lithography, Electroplating, and Moulding) process. The most widespread application of micromachined emulsification devices is in the synthesis of monodispersed particles and vesicles, such as polymeric particles, microgels, solid lipid particles, Janus particles, and functional vesicles (liposomes, polymersomes and collloidosomes). Glass capillary microfluidic devices are very suitable for production of core/shell drops of controllable shell thickness and multiple emulsions containing a controlled number of inner droplets and/or inner droplets of two or more distinct phases. Microchannel emulsification is a

very promising technique for production of monodispersed droplets with droplet throughputs of up to 100 litres per hour.

1. INTRODUCTION

Conventional devices for emulsification are high-pressure valve homogenisers, static mixers, and rotor stator systems (colloid mills, stirred vessels, toothed disc dispersing machines, etc) (Karbstein and Schubert, 1995). In these devices, a pre-emulsion with large drops is forced through a high shear region in such a way as to promote turbulence and/or cavitation and thereby to disrupt large drops into smaller ones. A disadvantage of this "top-down" approach is that it is not easily possible to control the mean drop size of the product emulsion and the resulting droplets are usually highly polydisperse. This is due to exposure of the drops to a variable shear and pressure field, with very high shear stress in close proximity to the rotor and negligible shear in "dead zones". Over the past two decades novel microengineering techniques have been developed for production of droplets directly from two immiscible liquids, without pre-emulsification step. These "bottom-up" emulsification techniques involve the injection of a liquid (the dispersed phase) through microchannels or membrane pores into another immiscible liquid (the continuous phase) and include membrane emulsification (Nakashima et al., 1991), microchannel emulsification (Kawakatsu et al., 1997), ink-jet printing (Lub et al., 2006) and various microfluidic processes (Teh et al., 2008). They can afford uniformly sized droplets of tuneable size, because the droplet size is controlled by the size of the pores or channels, rather than turbulent eddies or cavitation nuclei. Although the mean droplet size in microengineered systems is mainly controlled by the system geometry, hydrodynamic conditions, emulsion formulation, and wetting effects often play a significant role.

This paper reviews latest developments in formation of emulsions using membrane, microchannel and microfluidic techniques. A brief comparison of different micromashining devices for droplet generation is provided in Table 1. Membrane emulsification can produce droplets at much higher throughputs than can be obtained in microfludic and microchannel

devices, but at the expense of lower degree of monodispersity (Table 1). For example, in premix membrane emulsification, 10^{18} droplets per second can be produced using a membrane area of 3.75 cm^2 (Vladisavljević et al., 2006a), while in microfluidic devices the throughput is typically less than 10^4 droplets per second. The reason for the large difference in throughputs is because in the former case the number of drop generation units (pores) was more than 10^5 per cm^2 compared to typically just one drop generation unit in microfluidic devices. Considering that membrane devices can easily be integrated into systems with large membrane area, while on-chip integration of microfluidic drop generators is often challenging, it is clear that membrane emulsification is superior in terms of the droplet throughput that can be achieved. The important advantage of microfluidic devices over membrane and microchannel emulsification is the ability to produce droplets with a highly controlled internal morphology (Fig. 1) with the added benefit of providing *in situ* droplet manipulation (merging, sorting, deformation, single-cell loading, etc.).

The particle polydispersity will be expressed in terms of the coefficient of variation or the relative span factor. The coefficient of variation is defined as $CV = (\sigma/d_{av}) \times 100$, where σ is the standard deviation of the droplet diameters and d_{av} is the mean droplet diameter. The relative span factor is given by $(d_{90}-d_{10})/d_{50}$, where d_{x0} is the diameter corresponding to $x0$ vol. % on a relative cumulative droplet diameter distribution curve.

2. MEMBRANE EMULSIFICATION (ME)

Membrane emulsification is a process that forms emulsion by injecting a pure dispersed phase or pre-mix through a microporous membrane into the continuous phase. In the former case, fine droplets are produced directly at the membrane/continuous phase interface, whereas in the latter case, pre-existing droplets are homogenised by passing pre-mix through the membrane. Various operating methods and devices for ME are illustrated in Figure 2.

2.1 Direct Membrane Emulsification

In conventional direct ME, Fig. 2(a) to 1(e), droplets are produced *in situ* by injecting a pure liquid (the dispersed phase) through the membrane into a second immiscible liquid (the continuous phase) (Nakashima et al., 1991). Hydrophobic and hydrophilic membranes are needed to produce water-in-oil (W/O) and oil-in-water (O/W) emulsions, respectively. At low

production rates, droplets can be formed in the absence of any shear on the membrane surface, solely by the action of interfacial tension (Kukizaki, 2009; Kosvintsev et al., 2008). At small interpore distances the push-off force as a result of droplet-droplet interactions on the membrane surface may assist in droplet detachment. In order to obtain uniform droplets at commercially viable throughputs, shear stress is generated at the membrane surface, usually using a cross-flow pump (Fig. 2 (a)) (Nakashima et al., 1991) or stirring (Figs. 2(b) and (c)) (Fuchigami et al., 2000; Kosvintsev et al., 2005; Ito and Makino, 2004; You et al., 2001; Dragosavac et al., 2008). In a typical cross-flow system, the continuous phase flows through the membrane tube parallel to the membrane surface, whereas the pressurised dispersed phase flows radially across the membrane wall from the module shell side to the inner membrane surface (Schröder et al., 1998). To further increase droplet throughput, the continuous phase can be introduced into the membrane tube radially, thereby forming spiral streamlines in the axial direction ("swirl flow"), that exert a strong centrifugal force on the inner surface of the membrane (Shimoda et al., 2011). Insertion of static turbulence promoters is an alternative method of increasing shear stress at the membrane surface 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. On the other hand, stirring systems are simpler and easier to operate, because the recirculation pump is not required, and a batch volume can be very low, 10 mL or even less, which can be advantageous in some applications, e.g. for preparation of small amounts of expensive drug formulations (Higashi and Setoguchi, 2000).

The shear stress can also be generated by a dynamic membrane shown in Fig. 2(d) and (e), in which case the droplet detachment from the membrane surface is facilitated by rotating (Williams et al., 2001, Vladisavljević and Williams, 2006; Schadler and Windhab, 2004, Manga et al., 2012) or vibrating (Zhu and Barrow, 2005; Holdich et al., 2010) the membrane within the otherwise static continuous phase. In the dynamic membrane systems, the shear on the membrane surface is decoupled from the cross-flow velocity, which means that cross flow is applied only to carry the droplets away from the module and not to provide a detachment force. The surface shear is controlled by the speed of rotation of membrane or the frequency and amplitude of membrane oscillation. Thus, very low cross-flow velocities can be used and recirculation of the product stream is not needed, which can be useful to prevent secondary breakup of large droplets. Kosvintsev et al. (2005) modified a commercial Weissenberg 'plate and cone' rheometer by replacing normally impervious plate underneath the cone with the

membrane and permitting the injection of oil from underneath the membrane into an aqueous phase under constant shear-stress condition, Fig. 2(d). It has been shown that a simple paddle-stirred cell, Fig. 2(d), with non-uniform shear profile on the membrane surface provides the same degree of drop size uniformity as the modified Weissenberg rheometer with a constant shear-stress operation (Kosvintsev et al., 2005). Therefore, the modified Weissenberg rheometer was abandoned as a drop formation device and a simple paddle-stirred cell has become increasingly popular as a viable alternative to cross-flow ME systems. Membrane vibration through piezoactuation has been applied by Zhu and Barrow (2005) to provide extra control over droplet detachment in cross-flow ME. Holdich et al. (2010) have introduced a vibrating tubular membrane system to control drop generation without any cross flow.

2.2 Premix Membrane Emulsification

In premix ME shown in Fig. 2(f), fine droplets are produced by passing pre-mix through the membrane (Suzuki et al., 1996) or porous bed of uniform particles (Yasuda et al., 2010). If the membrane surface is wetted by the dispersed phase of the original emulsion, a phase inversion may occur during the process, leading to the formation of W/O emulsion from an O/W pre-mix or *vice versa* (Suzuki et al., 1999). Another important factor for operation of the process is the pressure difference across the membrane. If the pressure difference is lower than the capillary pressure in a pore, the droplets cannot pass through the pores, which leads to demulsification (Koltuniewicz et al., 1995), rather than homogenisation. In order to achieve additional droplet size reduction and improve droplet size uniformity, emulsion can repeatedly be passed through the same membrane (Altenbach-Rehm et al., 2002; Park et al., 2001; Yafei et al., 2006; Vladisavljević et al., 2004b; 2006a; 2006b). The advantages of premix over direct membrane emulsification are in smaller droplet sizes and higher droplet throughputs that can be achieved. Repeated membrane homogenisation was originally developed for homogenisation of large multilamellar and unilamellar lipid vesicles using track-etch polycarbonate filters (Olson et al., 1979). An overview of droplet break-up mechanisms in premix ME and governing process parameters has been provided by Nazir et al. (2010).

2.3. Choice of membrane for ME

The most commonly used membranes for ME are Shirasu Porous Glass (SPG) membrane and microsieve membranes. However, many other microporous materials have been used including ceramic membranes fabricated by sintering of fine inorganic oxide powders (Vladisavljević and Schubert, 2003a) and polymeric hollow fiber membranes (Vladisavljević et al., 2002a).

2.3.1 SPG membrane

SPG membrane is the earliest membrane for ME, manufactured from Na_2O–CaO–MgO–Al_2O_3–B_2O_3–SiO_2 mother glass through phase separation by spinodal decomposition (Nakashima and Shimizu, 1986; Nakashima et al., 1991). The mother glass is prepared by mixing and melting Shirasu, calcium carbonate, and boric acid (Kukizaki and Nakashima, 2004). Shirasu is a Japanese volcanic ash deposit from southern Kyushu, which contains about 77 wt% SiO_2 and 10–15 wt% Al_2O_3 in addition to small amounts of other inorganic oxides. After the mother glass is formed into tubes, it is subjected to thermal treatment at 650–750 °C for the period ranging from several hours to several tens of hours. The thermal treatment causes phase separation of the homogeneous glass melt into an acid-insoluble Al_2O_3–SiO_2 phase and acid-soluble Na_2O–CaO–MgO–B_2O_3 phase, as shown in Fig. 3. The phase-separated glass is then immersed into a hydrochloric acid solution to dissolve Na_2O–CaO–MgO–B_2O_3 phase, which results in the formation of porous Al_2O_3–SiO_2 skeleton with a porosity of 50–60%. If the fraction of acid soluble phase is outside the above optimum range, separation may take place by the nucleation and growth mechanism leading to the formation of discrete spherical particles of one phase embedded in a continuous matrix of the other, which must be avoided.

SPG membrane has uniform internal structure with no voids or cracks (Vladisavljević et al., 2007) and is commercially available with a wide range of mean pore sizes (0.050–20 μm) (Kukizaki, 2009). The surface of SPG membrane can be rendered hydrophobic by chemical modification with organosilane compounds (Kukizaki and Wada, 2008) or physical coating with silicone resin (Vladisavljević et al., 2005). The surface of SPG membrane can be made with thermoresponsive hydrophilic-hydrophobic properties via layer-by-layer deposition of silica nanoparticles containing poly(N-isopropylacrylamide) (PNIPAM) brushes grafted on their surface (Men et al., 2010). A hydraulic resistance of SPG membrane is relatively high

due to the high wall thickness of 700–900 μm, but it can be reduced if the membrane is made with an asymmetric structure (Kukizaki and Goto, 2007a). Chemical durability of SPG against alkaline solutions is relatively poor, but can be improved by incorporating ZrO_2 into the glass skeleton (Kukizaki, 2010). In direct ME, the mean droplet size is 3–4 times larger than the mean pore size of SPG membrane and a relative span is 0.25−0.45 (Vladisavljević et al., 2002b). A disadvantage of direct ME using SPG membrane is that transmembrane flux should be maintained at low levels (10–100 $Lm^{-2}h^{-1}$) to avoid transition from a dripping to continuous outflow regime (Kobayashi et al., 2003). Uniformly sized droplets can only be formed in the dripping regime (Vladisavljević et al., 2004a; Vladisavljević and Schubert, 2002b; 2003b).

2.3.2 Microsieve membranes

Microsieves are increasingly being used in ME to achieve high transmembrane fluxes at low transmembrane pressures (Wagdare et al., 2010). Microsieves are microfiltration membranes with a controlled pore geometry and spatial arrangement manufactured by semiconductor fabrication methods (Brans et al., 2006). Typical microsieves used in ME are silicon nitride Aquamarijn™ microsieves fabricated by reactive ion etching (van Rijn et al., 1997), nickel microsieves manufactured using UV-LIGA process by Stork Veco BV (Nazir et al., 2011; Schadler and Windhab, 2006) and Micropore Technologies Ltd (Egidi et al., 2008), and laser drilled aluminium and stainless steel foils fabricated by pulsed laser drilling (Dowding et al., 2001; Vladisavljević and Williams, 2006; Gerkeen et al., 2008). Because of the fact that microsieves are ultra-thin foils with rectilinear pores and very low internal pore area, they are less prone to fouling by emulsion ingredients than highly tortuous SPG membranes. It is especially important in pre-mix ME, when a whole emulsion, rather than a pure dispersed phase, is injected through the membrane.

LIGA is German acronym for *LIthographie, Galvanoformung, Abformung*, which means Lithography, Electroplating, and Moulding. UV-LIGA process for fabrication of nickel microsieves consists of three main steps: UV lithography (UVL), nickel electroplating and membrane release (Fig. 4(a)). UVL starts with spin coating positive photoresist on a flat conducting metal substrate. The photoresist is exposed to UV light through a mask that determines the geometry of the pores. The photoresist is then developed to remove the

exposed parts of the photoresist, rinsed in deionised water and dried. The sieve is then electroformed in a nickel electroplating bath by depositing a nickel film in the voids left by the removed photoresist. The nickel foil will be perforated at the regions on the substrate masked by the photoresist. Starting from a particular size of the photoresist areas on the substrate, the final perforation diameter can be adjusted as small as desired by overgrowth of nickel over the masked areas in the electroplating operation. The membrane is released from the substrate using an ultrasound bath. Pure nickel membrane is hydrophobic, but can be made hydrophilic by oxygen plasma treatment, coating with diamond like carbon, and other hydrophilic agents. Nickel microsieves can be produced with a variety of different pore morphologies, including slotted pores (Holdich et al., 2006) and micronozzles protruding above the membrane surface (Geerken, 2006).

The process used for fabrication of Aquamarijn® microsieves is described in Fig. 4(b). It consists of four main steps: chemical vapour deposition (CVD) of silicon nitride film on a single crystal silicon substrate, photolithography, reactive ion etching (RIE) of silicon nitride film, and anisotropic wet etching of the substrate. First, a layer of silicon nitride is deposited on the surface of the substrate by CVD, which involves a reaction between dichlorosilane (SiH_2Cl_2) and ammonia (NH_3) at elevated temperature and low pressure. A positive photoresist is then applied to the surface of the silicon nitride film and exposed to UV light through the mask. After exposure, the photoresist is developed in a dilute NaOH solution to remove the exposed photoresist and form the photoresist mask having openings. The silicon nitride exposed in these openings is etched by RIE in CHF_3/O_2 plasma to form a pattern of pores corresponding in locations to the openings in the photoresist mask. After dry etching of silicon nitride, the silicon underneath the membrane is etched by anisotropic wet etching using a KOH solution. Finally, the microsieve is treated with air plasma to grow hydrophilic silicon dioxide layer on the membrane surface.

2.4 Operating parameters in Membrane Emulsification

The effect of process parameters on droplet generation behaviour in direct ME has been the subject of several reviews (Joscelyne and Trägårdh, 2000; Rayner and Trägårdh, 2002; Charcosset et al., 2004; Lambrich and Vladisavljević, 2004; Gijsbertsen-Abrahamse et al., 2004; Yuan et al., 2010). The main factors affecting the drop size are wetting properties and microstructure of the membrane (pore size distribution, pore shape, spatial distribution of the

pores, pore tortuosity, etc), but other parameters also play an important role, such as transmembrane flux, shear stress on the membrane surface, viscosity of the continuous and dispersed phase, surfactant type and concentration, emulsion formulation, etc. The droplet size in ME has been predicted analytically, using several force balance and torque balance models (Timgren et al., 2010; De Luca et al., 2008; Christov et al., 2008; Williams et al., 1998; Hao et al, 2008; Xu et al., 2005) and computationally, using Computational Fluid Dynamics (CFD) simulations (Timgren et al., 2010; Kobayashi et al., 2004b; Abrahamse et al., 2001) and the Surface Evolver software (Rayner et al., 2004, 2005).

2.4.1 Surfactant type

The role of surfactant in ME is to rapidly adsorb to the newly formed oil-water interface to facilitate the droplet detachment and stabilise the formed droplet by reducing the interfacial tension. The effect of kinetics of adsorption of surfactants at liquid-liquid interface on droplet size has been investigated by several workers (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 resultant emulsion becomes. Surfactant molecules should not adsorb to the membrane surface, since otherwise the membrane can become fouled by the surfactant molecules and the dispersed phase can spread over the membrane surface. The functional groups of surfactant molecules must not carry the charge opposite to that of the membrane surface (Nakashima et al., 1993; Kobayashi et al., 2003). Oxidized silicon surface and untreated SPG surface has a negative surface potential within a pH range of 2–8, due to dissociation of silanol groups ($\equiv$Si-OH $\leftrightarrows$ $\equiv$SiO$^-$ + H$^+$). For these membranes, the use of cationic and zwitterionic surfactants must be avoided, even when they carry a net negative charge. For example, lecithin at pH 3 may foul SPG membrane due to electrostatic interactions between positively charged groups (*e.g.* –N(CH$_3$)$_3$$^+$ or –NH$_3$$^+$) on the phospholipid molecules and negatively charged silanol groups on the SPG surface, although at pH 3 the net charge of lecithin molecules is negative (Surh et al., 2008). Consequently, the choice of surfactants in SPG emulsification is limited to nonionic and anionic surfactants. To overcome this limitation and obtain cationic droplets, emulsion can be originally prepared using a nonionic or anionic surfactant and then the droplet charge can be altered using the surfactant-displacement method (Vladisavljević and McClements, 2010).

2.4.2 Transmembrane pressure and wall shear stress

The minimum transmembrane pressure for driving the dispersed phase through the pores is known as the capillary pressure P_{cap} and is given by the Laplace equation:

$$P_{cap} = \frac{4\gamma \cos\theta}{d_p} \qquad (1)$$

where γ is the equilibrium interfacial tension at the dispersed phase/continuous phase interface, θ is the contact angle at the interfacial line between the two liquid phases and the membrane surface, and d_p is the mean pore diameter of the membrane. The critical pressure in premix ME is given by (Park et al., 2001):

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

where $a = d_1/d_p$ and d_1 is the mean droplet size in pre-mix. If $d_1/d_p \gg 1$, the capillary pressure is given by Eq. (1). In premix ME, the optimum transmembrane pressure is typically 10–50 times greater than the capillary pressure (Vladisavljević et al., 2004b). In direct SPG, the operating pressure is usually up to $10P_{cap}$ and the wall shear stress is 2–40 Pa (Vladisavljević et al., 2004a). In the absence of secondary drop breakup, the mean drop size decreases with increasing the shear stress on the membrane surface until it reaches a constant value at high shear stresses. The higher the wall shear stress, the higher the maximum pressure that can be applied to obtain uniform droplets (Vladisavljević et al., 2003a).

2.5 Applications of membrane emulsification

The most widespread application of ME is in synthesis of particles through solidification of droplets (Vladisavljević and Williams, 2005). The mean particle size primarily depends on the mean droplet size and can range from less than 1 μm to several hundred μm with a typical CV of 10–20%. ME can be used to produce particles from a wide range of organic and inorganic materials, including hydrogels (Liu et al., 2003), polymers (Ma et al., 1999), inorganic oxides (Yanagishita et al., 2004), carbon (Yamamoto et al., 2010), metals (Kakazu et al., 2010), and solid lipids (Kukizaki and Goto (2007b). In addition to coherent solids, ME can also be used for generation of porous particles (Wagdare et al., 2011), particles with core/shell morphology (Sawalha et al., 2008; Chu et al., 2003), and colloidosomes (Thompson et al., 2011). Another promising field of application of ME is the production of low-fat foods based on multiple W/O/W emulsion with high fraction of inner water phase (Surh et al., 2008). Micro- and

nanobubbles can be produced if a gas phase is injected through the membrane into an aqueous phase (Kukizaki and Goto, 2007c; 2006). Injection of one liquid through the membrane into another miscible liquid can be combined with chemical precipitation to prepare nanoparticles. Using this membrane micromixing/precipitation method, $BaSO_4$, TiO_2 and ZnO nanoparticles were fabricated by injecting $BaCl_2$, $Ti(SO_4)_2$, and $ZnSO_4$ solution, respectively, through the membrane into the main flow of another salt solution (Chen et al., 2004; Wang et al., 2010). Similarly, liposomes were prepared by injecting ethanolic solution of phosholipids through the membrane into a flowing aqueous phase (Jaafar-Maalej et al., 2011). ME can be combined with liquid-liquid extraction (Chen et al., 2004b, Xu et al., 2005b) and enzymatic reaction (Li and Sakaki, 2008; Mazzei et al., 2010) to achieve simultaneous drop generation, chemical conversion and interfacial mass transfer.

3. PLANAR MICROFLUIDIC DEVICES

Microfluidics is the science of handling and processing fluids in microchannels that have at least one dimension smaller than 1 mm (Whitesides, 2006). The first applications of microfluidic techology in blood rheology (Kikuchi et al., 1989; 1992) and chemical analysis (Manz et al., 1992) were prompted by the ability of microfluidic devices to use very small amounts of samples and reagents, to carry out analysis in short time and to achieve high levels of process integration. The growth of microfluidic drop generation processes in the past decade was driven by a rising number of applications that can take advantage of precision generation and manipulation of droplets on a microscale (Atencia and Beebe, 2005). These applications range from capillary electrophoresis (Kameoka et al., 2001) and immunoassays (Hatch et al., 2001) to cellomics (Andersson and van den Berg, 2003; Wu et al., 2011), proteomics (Figeys and Pinto, 2001), DNA analysis (McClain et al., 2001), and interfacial tensiometry (Cabral et al., 2006).

The most common planar microfluidic devices are microfluidic junctions and flow focusing devices. They are usually fabricated by soft lithography (Whitesides, 2006; Xia and Whitesides, 1998). The most common elastomer in soft lithography is poly(dimethylsiloxane) (PDMS), although a number of other polymeric materials can be used, such as polyurethanes (Nie at al., 2005), polyimides, and phenol formaldehyde polymers. Soft lithography begins with a creation of reusable master that has a relief structure on its surface, as shown in Figure 5(a) (Xia and Whitesides, 1998). One master can be used to fabricate more than 100 PDMS

replicas (Xia and Whitesides, 1998). After master fabrication, a mixture of PDMS prepolymer, a catalyst and curing agent is poured over the master, degassed, cured at elevated temperature, and peeled off the master. The channels fabricated using conventional soft lithography are rectangular and open. To enclose the channels, the PDMS mould is sealed to a flat surface of a glass slide or PDMS block either covalently by plasma oxydation or non-covalently by applying pressure. Cylindrical channels in PDMS can be fabricated by stereolithography (Morimoto et al., 2009), aligning and adhering two semi-circular PDMS channels face-to-face (Wilson et al., 2011), embedding a microfiber in PDMS mould before curing (Takeuchi et al., 2005) or introducing pressured air stream inside rectangular PDMS channels filled with liquid PDMS (Abdelgawad et al., 2011). PDMS is inherently hydrophobic, but can be rendered hydrophilic by oxidation of the PDMS surface (Hillborg et al., 2004), coating with inorganic materials such as silica and titania *via* sol–gel chemistry (Abate et al., 2008), through layer-by-layer deposition of polyelectrolytes (Bauer et al., 2010), ultraviolet graft polymerization of acrylic acid (Li et al., 2007), etc.

Microfluidic channels can be fabricated in poly(methyl methacrylate) (PMMA) by hot embossing (Eusner et al., 2010), laser ablation (Yeh et al., 2010), injection molding (Jiang, 2010), and mechanical micromilling (Xu et al., 2006). Hot embossing is a three-step process shown in Figure 5(b). The silicon mould and PMMA plate are brought into contact and heated up above the glass transition temperature of PMMA. The mould is then pressed into a softened polymer to force it to flow into the cavities of the mould. Once the polymer has conformed to the shape of the stamp, it is cooled to a temperature below the glass transition temperature so that it is sufficiently hard to be separated from the mould. Finally, a transparent cover plate must be bonded to the PMMA substrate, which can be done using several methods including low-temperature bonding under ultrasound (Li et al., 2009).

3.1 T junction

T junction is the simplest microfluidic structure for producing and manipulating droplets (Thorsen et al., 2001; Link et al., 2004; Yi et al., 2003; He et al., 2005; Van der Graaf et al., 2005b; Dendukuri et al., 2005). As shown in Fig. 6(a), the continuous phase is introduced from the main channel and the dispersed phase flows through the perpendicular channel. The combination of shear stresses generated by the continuous phase and evolution of pressure upstream of the emerging droplet causes the tip of the dispersed phase to elongate into the

main channel until the neck of the dispersed phase breaks up into a droplet (Zhao and Middelberg, 2011; Teh et al., 2008). Several modifications of the common T junction geometry have been investigated, including double-pore T junction, which is a hybrid structure between membrane emulsification and standard T junction (Wang et al., 2009), T junction with perpendicular channel extended into the horizontal channel (Wang et al., 2011) and T junction with injection of the dispersed phase through the main channel (Wang et al., 2011).

Three distinct regimes of droplet formation in T junction are squeezing, dripping, and jetting (De Menech et al., 2008). In squeezing regime, the tip of the dispersed phase stream initially occupies almost the entire cross section of the main channel because the shear stresses exerted by the continuous phase are small compared to interfacial stresses. As a result, the continuous phase is confined to thin films between the tip and the channel walls, which leads to a build-up of pressure in the continuous phase upstream of the tip (De Menech et al., 2008; Garstecki et al., 2005). It causes the continuous phase to squeeze the neck of the stream until breakup occurs. Within squeezing regime, the droplet size is a function of the ratio of the flow rates of the two fluids and does not depend significantly on the interfacial tension (De Menech et al., 2008) or the viscosities of the two liquids (De Menech et al., 2008). In dripping regime, the size of the droplet is determined by a balance between the drag force that the continuous phase exerts on the emerging droplet and the interfacial force that opposes the elongation of the neck (De Menech et al., 2008). The capillary number calculated for the continuous phase, Ca_c, can be used to predict a dominant mechanism of droplet formation: $Ca_c < 0.002$ within squeezing regime and $0.01 < Ca_c < 0.3$ within dripping regime (Xu et al., 2008). As the capillary number is further increased, the breakup point moves progressively downstream, which leads to a transition from the stable dripping regime to a jetting regime.

The dispersed phase should not wet the walls at the junction, for example hydrophilic T junctions are required to produce O/W emulsions or W/O/W multiple emulsions. The wetting properties of microchannel walls can be altered by surface modification (Shui et al., 2009) or changing the concentration of surfactants in liquid streams (Xu et al., 2006b). It has been found that both O/W and W/O emulsions can be prepared in the same T junction device, solely by an appropriate choice of surfactants added to the oil or water phase (Xu et al., 2006c).

Two T junctions in series with alternating surface wettabilities (e.g. an upstream hydrophilic junction followed by downstream hydrophobic junction) can produce multiple emulsions with a controlled number of inner drops (Okushima et al., 2004; Nisisako et al., 2005). When reversing the flow direction, T junctions with differently sized exit channels will passively sort droplets according to size (Tan et al., 2004) or break large droplets into two uniform smaller droplets, with each daughter droplet flowing into a separate exit channel, Fig. 6(b). The droplet breakup process can be facilitated and/or additionally controlled by inserting features in the exit channels that hinder droplet motion (Link et al., 2004) or using exit channels with moving walls (Lao et al., 2009).

Apart from passive hydrodynamic control, the size of droplets generated in T junction can be controlled actively (mechanically) using pneumatically actuated membrane valves (Lin and Su, 2008; Lee et al., 2009) or magnetically driven microtools (Yamanichi et al., 2009). When using these actuators, the resulting droplet volume and breakup frequency can be controlled independently from each other by varying the open time (t_{open}) and cycle time ($t_{\text{close}} + t_{\text{open}}$) of the valve, respectively (Lin and Su, 2008).

3.1.1. Applications of T junction

T junction can be used for screening of multiple samples against a single reagent or screening of a single sample against multiple reagents (Zeng and Ismagilov, 2005). For example, to screen a set of enzymes for alkaline phosphatase (AP) activity, an array of droplets, each containing a different enzyme solution, was merged with a solution of fluorescein diphosphate (FDP) at a T junction (Fig. 6(c)). In the presence of AP, the nonfluorescent FDP reagent is hydrolysed to highly fluorescent fluorescein, which can be detected by fluorescence microscopy. The droplets can be separated by air bubbles to prevent cross-communication between the droplets (Zeng and Ismagilov, 2005). To screen a single protein against multiple crystallising agents, an array of droplets, each containing a different precipitant, can be merged with a protein solution (Zeng and Ismagilov, 2005).

T junction can be used to achieve rapid mixing shortly before drop generation. In a modified T junction shown in Fig. 6(d), two reagents supplied from two converging side channels are mixed together just before forming a drop to prevent premature reaction. Using this strategy, Choi et al. (2007) have produced calcium alginate beads by injecting alginate and $CaCl_2$

solutions from two different side channels into a hexadecane stream, where they mix together and form droplets. Due to shear forces on the droplet from the continuous phase, the reagents in the droplet rapidly mix together forming a gel. T junction with three side channels that converge to each other (Fig. 6(e)) can be used for rapid formation of droplets of multiple reagents without bringing reagents into contact prior to drop generation (Song et al., 2006). The concentration of reagents within the droplet can be controlled by varying the relative flow rates of the two reagent streams and a buffer stream in the middle, which allows rapid determination of rate constants or optimal reaction conditions.

3.2 Cross junction

A cross junction can be used for generation of droplets in two different configurations. In a configuration shown in Fig. 6(f), droplets are generated using a microfluidic extension of Rayleigh's approach (Rayleigh, 1879), with two streams of a continuous phase fluid flanking a stream of the dispersed phase (Nisisako et al., 2004; Tan et al., 2006; Tan et al., 2008). Droplets are formed when the dispersed phase jet becomes too thin to persist in the surrounding continuous phase. Two cross junctions in series with alternating wettability will produce core/shell droplets (Abate et al., 2011). An extension of this principle to three or more cross junctions in series can lead to production of higher-order multiple emulsions, such as triple, quadruple, and quintuple emulsions (Abate and Weitz, 2009). Two hydrophobic cross junctions in series with varying channel depths can produce core/shell droplets with an ultra-thin (<1 μm) oil shell (Saeki et al., 2010; 2010b).

The dispersed phase can also be introduced from the two opposite T inlets into the continuous phase flowing through the central channel. When two different liquids are injected from the two opposite inlets, cross junction can produce an array of droplets with alternating composition, e.g. an array of red and blue droplets, as shown in Fig. 6(g). Nisisako and Torii (2008) have integrated 156 such cross junctions on a 4×4 cm chip to produce droplets of photopolymerizable acrylate monomer at a throughput of 320 mL h^{-1}.

3.3 Y junction

Generation of droplets and two-phase stream in Y junction is illustrated in Fig. 6(h) and (i). The size of droplets formed in a Y junction is independent on the flow rate and viscosity of the dispersed phase (Steegmans et al., 2009), which is a behaviour different to that in a T junction. At low Reynolds numbers, two distinct fluid streams are formed (Fig. 6(i)), which can be used to generate anisotropic (Janus) particles (Nisisako et al, 2004; 2006; Shepherd et al., 2006), continuous lines of crystals and metals that are less than 10 μm wide (Kenis et al., 1999) or to achieve localised etching of the inner wall of the exit channel (Kenis et al., 1999).

3.4 Microfludic flow focusing devices

When droplets are generated at a cross junction, the combined two-phase flow is often forced through a small orifice which is known as hydrodynamic flow focusing (Garstecki et al., 2005; Lewis et al., 2005; Xu and Nakajima, 2004). Standard microfludic flow focusing device (MFFD) developed by Anna et al. (2003) is depicted in Fig. 7(a). The dispersed phase (liquid A) flows through the middle channel and the continuous phase (liquid B) flows through the two outside channels. Both phases are forced to flow through a small orifice located downstream of the three channels. The continuous phase exerts pressure and shear stress that force the dispersed phase into a narrow thread, which breaks inside or downstream of the orifice. In Fig. 7(a), the dispersed phase (liquid A) does not wet the channel walls and thus, hydrophilic and hydrophobic walls are used to produce O/W and W/O emulsions, respectively. If liquid A wets the orifice walls, droplets of liquid B would be formed downstream of the orifice. In Fig. 7(b), a coaxial jet composed of two immiscible liquids (A and B) breaks up and forms core/shell droplets in liquid C (Nie et al., 2005). In Fig. 7(c), core/shell droplets are formed using two consecutive flow focusing generators with alternating wettability (Seo et al., 2007). If liquid C is a monomer solution, these core/shell droplets can be used as templates in the production of hollow polymeric particles (Nie et al., 2005). The size of the resulting droplets can be additionally reduced by the electric field (Kim et al., 2007), using active pneumatic choppers (Chen and Lee, 2006), and controllable moving wall structures (Lee et al., 2007).

The droplet throughput can be increased by integrating several flow focusing droplet generators (FFDGs) using bifurcated or coupled design of inlet and outlet channels. In coupled configuration (Hashimoto et al., 2008), every two adjacent FFDGs share one of the inlets of the continuous phase, and all of the FFDGs share a common outlet channel (Fig.

7(d)). In bifurcated design (Li et al., 2007), the continuous phase is progressively split into multiple streams via a series of T junctions and each FFDG is supplied with two separate inlets of the continuous phase. Simultaneous generation of monodispersed droplets with different dimensions can be achieved by integrating into a single chip multiple parallel FFDGs with distinct geometries (Li et al., 2008). Simultaneous generation of monodispersed droplets with nearly identical dimensions but different compositions can be achieved by integrating into a single chip mixromixers, bifurcated channels with distinct dimensions and multiple parallel FFGs with an identical geometry (Yeh et al., 2011; Ji et al., 2011).

Four distinct regimes of drop generation in MFFDs are squeezing, dripping, jetting and tipstreaming (Anna and Mayer, 2006). The squeezing or "geometry-controlled" regime is characterised by droplet sizes that are roughly equal to the orifice size and independent on the capillary number (Anna and Mayer, 2006). The mechanism of droplet breakup is similar to that observed in T junction geometry at low capillary numbers (Garstecki et al., 2005). The dispersed phase liquid occupies a significant portion of the cross-sectional area of the orifice, forcing the continuous phase to flow in a narrow region between the interface and the orifice wall. To maintain the applied flow rate, a higher upstream pressure is needed in the continuous phase stream, which leads to pinching of the interface. In dripping regime, the dispersed phase jet narrows due to viscous stresses from the continuous phase, and the resulting droplet sizes are within one order of magnitude smaller than the orifice size. In jetting regime, the dispersed phase forms a long jet that extends downstream of the orifice resulting in less controlled droplet breakup. The droplet size is larger than in dripping regime and can be larger than the orifice size (Anna and Mayer, 2006). In both dripping and jetting regimes, droplet breakup occurs because of the combined effects of capillary instability and viscous drag (Zhou et al., 2006). Tipstreaming regime occurs in the presence of surfactants and at very high flow rate ratios of outer to inner phase of 300 and above (Anna and Mayer, 2006). Here, a very thin and long thread is formed, which breaks up into small droplets with a diameter of 1/20 of the orifice size and smaller.

4. MICROCHANNEL ARRAY DEVICES

Flow focusing devices can generate highly uniform droplets with a CV in the dropping regime of less than 3 %. Although the frequency of droplet generation can be as high as 12,000 Hz for water-in-oil droplets (Yobas et al., 2006), the volume flow rate of dispersed phase is very

low because droplets are formed from a single microchannel (MC). In MC array devices, the droplets are formed simultaneously from hundreds or even hundreds of thousands of parallel MCs (Kobayashi et al., 2005a). MC arrays can be fabricated onto the surface of a silicon wafer as microgrooves (Kikuchi et al., 1989) or straight-through holes (Kobayashi et al., 2002).

First microfluidic device consisting of parallel microgrooves was fabricated by Kikuchi et al. (1989) using photolithography and anisotropic wet etching in (100) single-crystal silicon as shown in Fig. 8(a). Photolithography includes masking of substrate with SiO_2 and photoresist, UV exposure, and developing. A channel structure that will be etched into the substrate is first generated by computer and then drawn onto a transparent plate (mask). A positive photoresist is then applied to the substrate in a thin layer and exposed to UV light through the mask. The patterned areas are then dissolved in a developer, exposing SiO_2 and the silicon substrate below to the etchant. Wet etching includes: (i) etching the SiO_2 layer by hydrofluoric acid at locations unprotected by photoresist; (ii) removing the remaining photoresist, usually by a mixture of sulfuric acid and hydrogen peroxide, and (iii) etching the silicon substrate. Anisotropic etching occurs when etchant (typically a KOH solution) etches silicon at different rates depending upon which crystal face is exposed. KOH etches silicon 1−2 orders of magnitude faster than SiO_2, so the SiO_2 layer remains intact. Anisotropic etching is greatly preferred in fabrication of microfluidic devices, because it produces channels with sharp, well defined edges. Grooved MC arrays have also been fabricated by microcutting in stainless steel (Tong et al., 2001) and injection moulding in poly(methyl methacrylate) (PMMA) (Liu et al., 2005). PMMA channels are inherently hydrophobic and suitable for generation of W/O emulsions (Liu et al., 2005).

4.1 Grooved-type microchannel arrays

Modules with microgrooves can be either dead-end or cross-flow. In a typical dead-end module (Fig. 9(a)), MCs are fabricated on a terrace and there are four terraces arranged on all four sides of a silicon plate. Each MC is typically 6−12 μm in width, 4−7 μm in depth and 25−140 μm long (Kawakatsu et al., 1997; Sugiura et al., 2002a). In operation, MC plate is tightly sealed with a transparent cover plate. The dispersed phase is supplied through a central hole and flows out through MCs on all four sides. MC emulsification exploits the interfacial

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tension as a driving force for droplet formation. The dispersed phase exiting the MCs takes a disk-like shape on the terrace, which is characterised by a higher interfacial area per unit volume than a spherical shape, resulting in hydrodynamic instability. This instability is a driving force for spontaneous transformation of dispersed phase into spherical droplets (Sugiura et al., 2002b). Droplet formation behaviour drastically changes above the critical velocity, due to transition from dripping to continuous outflow regime. The critical velocity can be predicted from the physical properties of the dispersed and continuous phase, interfacial tension and system geometry. Different designs of grooved MC arrays have been developed including MCs with partition walls on the terrace (Nakagawa et al., 2004; Sugiura et al., 2001) and MCs without any terrace (Sugiura et al., 2000).

Dead-end modules with grooved MC arrays provide a dispersed phase flow rate of less than 0.1 mL h^{-1} for vegetable oils (Tab. 2), due to limited number of MCs (100–1,500). Cross-flow modules with grooved MC arrays are more suited for higher production rates because many parallel cross-flow channels with MC arrays can be incorporated on a single plate (Kobayashi et al., 2010). A simplest cross-flow module (Fig. 9(b)) has only one cross-flow channel and two holes at its both ends for introduction and withdrawal of the continuous phase. MCs are arranged at both longitudinal sides of the cross-flow channel (Kawakatsu et al., 1999, 2000; Sugiura et al., 2002c). The purpose of cross flow is to collect droplets from the module and not to control the droplet size. In the dripping regime, the droplet size is independent on the flow rate of dispersed or continuous phase. In contrast, in flow focusing devices and T junctions, the flow rate of all fluid streams has a strong effect on the droplet size. Cross-flow modules with multiple cross-flow channels are available with a maximum size of MC plate of 60×60 mm (Tab. 1 and Fig. 10). This module contains 11,900 microgrooves arranged in 14 parallel arrays and can provide a dispersed phase flow rate of 1.5 mL h^{-1} for soybean oil-in-water emulsions (Kobayashi et al. 2010).

4.2 Straight-through microchannel arrays

Grooved-type modules have a limited droplet throughput, due to poor utilization of MC plate surface, because MCs are arranged on the plate surface in longitudinal direction and feed channels for dispersed and continuous phase must be provided on the plate surface. A vertical array of straight-through MCs allows much better utilisation of the plate surface resulting in

significantly higher throughputs (Tab. 1). For example, 60×60 mm grooved-type plate with 12,000 MCs can accommodate only 3.3 MCs per 1 mm^2 and provides a maximum soybean oil flow rate of 1.5 mL h^{-1}. On the other hand, 40×40 mm straight-through MC plate has 211,248 MCs, i.e. 132 MCs per 1 mm^2 and a soybean oil flow rate can exceed 30 mL h^{-1}.

Deep vertical MCs that completely penetrate the substrate are fabricated by deep reactive ion etching (DRIE) (Kobayashi et al., 2002a). DRIE requires aluminium mask to protect the underlying substrate against etching (Fig. 8(b)). DRIE is a three step process that involves: (i) etching a shallow trench into silicon substrate using sulfur hexafluoride (SF_6) plasma; (ii) passivating that newly formed cavity with teflon-like polymer created with the addition of octafluorocyclobutane (C_4F_8) plasma, and (iii) etching a subsequent and deeper trench with SF_6 plasma (Fig. 11). Passivation with polymer prevents lateral etching of the sidewalls, while the hole becomes deeper. The reactive species (neutral radicals and ions) are formed by the collision of SF_6 molecules with a cloud of energetic electrons excited by an electric field. The reactive species (e.g. F and SF_x^+) react with silicon forming a gaseous substance (SiF_4) that can be removed by a vacuum pump. Deep vertical MCs in a PMMA plate can be fabricated by synchrotron radiation and subsequent etching (Kobayashi et al., 2008a). PMMA straight-through MCs were used successfully for the production of W/O emulsions without any surface modification (Kobayashi et al., 2008a).

Straight-through MCs can have either symmetric (Fig. 12(a)) or asymmetric (Fig. 12(b)) structure. Symmetric MCs are of the same size and shape (e.g., circular or rectangular) along the whole cross section of the plate. Rectangular MCs provide better performance in MCE than circular MCs and an aspect ratio of slot length to slot width should be at least 3–3.5 to ensure production of uniform droplets (Kobayashi et al. 2004, 2009a; van Dijke et al., 2010c). Asymmetric MC plate typically contains circular channels on the upstream (bottom) side and slots on the downstream (top) side (Fig. 12(b)). Asymmetric structure is particularly useful for generation of uniform droplets when the dispersed phase viscosity is less than 1 mPa s, e.g. when the dispersed phase is a volatile (C6-C10) hydrocarbon, such as decane (Kobayashi et al. 2005b). Asymmetric straight-through MCs have also been used successfully for production of W/O emulsions (Kobayashi et al., 2009b), polyunsaturated fatty acids (PUFA)-loaded O/W emulsions (Neves et al., 2008) and n-tetradecane emulsions (Vladisavljević et al., 2008, 2011a). The size of droplets produced using asymmetric silicon MCs can range from several

microns (Kobayashi et al., 2008b) to several hundred microns (Kobayashi et al., 2009b). Using asymmetric MCs micromachined in stainless steel plates, the droplet size can reach several millimetres (Kobayashi et al., 2008c). Straight-through micronozzle (MN) array (Fig. 12(c)) can be used to increase the velocity of continuous phase at the channel outlet, because the channel outlets are above the plate surface, which could be useful if the viscosity of dispersed phase is relatively high (Sugiura et al., 2005). A maximum throughput of n-tetradecane droplets in asymmetric MC plate with a standard size (24×24 mm) was found to be 270 mL h^{-1} (Vladisavljević et al., 2011a). Kobayashi et al. (2012) have recently achieved a throughput of n-tetradecane droplets of 1,400 mL h^{-1} using a large 40×40 mm asymmetric MC plate with four arrays. A maximum droplet throughput per unit area of MC plate is independent of the MC diameter, as determined by CFD simulations (Kobayashi et al., 2011). On the other hand, the maximum number of droplets produced per unit time per channel is inveresely proportional to the MC diameter.

4.3 Applications of microfluidic devices with parallel microchannel arrays

The first application of microfluidic devices with parallel MC arrays was in MC-FAN (MicroChannel array Flow Analyzer) system for measurement of blood flow rate (fluidity) commercialised by Hitachi Haramachi Electronics Ltd (Kikuchi et al., 1989). The time required for 100 μL of blood to pass through an array consisted of about 8700 MCs with a width of 7 μm and a length of 30 μm under a driving pressure of 20 cmH$_2$O was found to range normally from 40 to 60 s for men and 35 to 50 s for women. In the case of considerable platelet aggregability in blood, significantly longer transit times were recorded and these persons may have higher risk of embolism. A modified MC-FAN system was first used for droplet generation by Kawakatsu et al. (1997) and the process was referred to as microchannel emulsification (MCE). The main application of MCE is in synthesis of microparticles with a CV below 5% via secondary reactions or processes within the generated droplets, such as gelation, polymerisation, evaporation, coacervation, electrostatic layer-by-layer deposition, etc. The examples of such microparticles produced using MCE are polymer microspheres (Sugiura et al., 2001; Sugiura et al., 2002d), gel microbeads (Iwamoto et al., 2002; Sugiura et al., 2005; Ikkai et al., 2005; Chuah et al., 2009), solid lipid microparticles (Sugiura et al., 2000; Kobayashi et al., 2003b), complex coacervate microcapsules (Nakagawa et al., 2004), and giant lipid vesicles (Kuroiwa et al., 2009). MC array devices have also been used for

production of monodispersed microbubbles (Yasuno et al., 2004), discoid droplets (Kobayashi et al., 2006), surfactant-free droplets stabilized by silica nanoparticles (Xu et al., 2005c) and oil droplets stabilised by lecithin-chitosan interfacial bilayers (Chuah et al., 2009b). Because of its ability to generate monodisperse droplets of tunable size on a larger scale than planar microfluidic devices, MCE is a usuful technique for fundamental studies on emulsions, for example studies of emulsion stability (Liu et al., 2001), crystallisation of emulsion droplets (Hamada et al., 2002), *in vitro* digestability of emulsified lipids, etc.

5. EDGE-BASED DROPLET GENERATION (EDGE) DEVICES

In Edge-based Droplet GEneration (EDGE) device, multiple droplets are formed at the edge of a shallow but rather wide rectangular plateau (van Dijke et al., 2009a) (Fig. 13). The plateau is typically 1–3 μm deep, 200 μm long and 500–10,000 μm wide (van Dijke et al., 2009a). Unlike the grooved-type MC arrays, where the droplet volume is of the same order of magnitude as the volume of the terrace from which they are formed, the volume of the droplets formed in EDGE device is only a small fraction of the volume of the plateau. The ratio of the droplet size to the plateau depth is typically 5.5–6.5 (van Dijke et al., 2010a). Van Dijke et al. (2009b) have fabricated 196 plateaus (200×500×1.2 μm) on a 1.5 × 1.5 cm chip to produce up to 300,000 droplets per second per chip. The plateaus are arranged in 14 parallel arrays, with 14 plateaus per array, and a channel for the continuous phase meandering around the plateau lines. Other EDGE devices have been developed, with 14 plateaus per chip and a single 9500 μm wide plateau per line and with trapezoidal plateaus (Dijke et al., 2009b). These devices have been tested for production of various food-grade emulsions and foams (van Dijke et al., 2010b).

6. THREE-DIMENSIONAL AXISYMMETRIC MICROFLUIDIC DEVICES

6.1 PDMS and acrylic axisymmetric devices

In planar (two-dimensional) microfluidic devices, an emerging droplet typically contacts the walls of the channels, which can be exploited for fabrication of particles with non-spherical shapes (Kumacheva and Garstecki, 2011). However, it can also lead to damage of the newly formed fragile particles or wetting problems (Takeuchi et al., 2005). In an axisymmetric

device, the dispersed phase is completely surrounded by the continuous phase at all flow rates due to circular cross section of the outlet channel. The axisymmetric flow focusing device (AFFD) shown in Fig. 14 was fabricated in PDMS using insulated optical fibre as a master for circular channel. A section of the insulation was removed using a scalpel to expose the bare fibre in the central region. The fibre was moulded in PDMS, and after curing, the fibre was removed from the PDMS block, leaving the circular channel with a narrow section in the middle. An inlet for the dispersed phase and an outlet for the droplets were formed by inserting glass capillaries into both sides of the orifice. Since the device was fabricated from a single piece of PDMS, rather than by bonding two parts together, it did not leak at higher flow rates and pressures. However, these AFFDs are non-reproducible as they are handmade, and thus unsuitable for mass production. Recently, monolithic acrylic AFFDs have been fabricated by stereolithography (Morimoto et al., 2009), which is a rapid and automatic process for building three-dimensional microstructures highly accurately (Zissi et al., 1996). The added benefit of stereolithography is that peripheral units such as inlet and outlet ports can be incorporated within the device without bonding. However, the resolution of commercial stereolithography equipment is limited to ~100 μm, making it difficult to produce an orifice small enough to produce droplets with the diameters smaller than 50 μm. In order to overcome this limitation of the stereolithography, a hybrid AFFD device was fabricated by a combination of photolithography and stereolithography (Morimoto et al., 2011). In this device, a narrow orifice was fabricated by photolithography and the remaining parts were fabricated by stereolithography.

6.2 Glass capillary axisymmetric devices

PDMS channels swell in strong organic solvents and siloxane-based compounds and tend to deform with applied pressure due to their high elasticity. Glass is more chemically robust than PDMS, does not swell, and can easily be functionalized to control surface properties. For example, a treatment with octadecyltrimethoxysilane will make the glass surface hydrophobic, whereas a treatment with 2-[methoxy(polyethyleneoxy)propyl]trimethoxysilane will enhance the hydrophilicity of the glass surface. Glass capillary microfluidic devices are pioneered at Harvard by Utada et al. (2005, 2007). They consist of coaxial assemblies of borosilicate glass capillaries glued onto the surface of a microscopic glass slide.

6.2.1 Co-flow glass capillary device

The fabrication of co-flow glass capillary device begins with a creation of tapered-end glass capillary. First, a circular glass capillary is heated and pulled using a micropipette puller. As a result of the pulling process, the capillary breaks into two identical parts, each with a tapered end that culminates in a fine orifice (Fig. 16). The orifice is then enlarged to the desired diameter by immersing the tip into the molten glass bead on the heated microforge filament. It is then followed by cooling the glass bead and breaking the tip by a quick pull. The tapered capillary with the desired orifice size is then inserted into a square glass capillary and the two capillaries are glued on a glass slide. Coaxial alignment of the two capillaries is ensured by choosing the capillaries such that the outer diameter of the circular capillary is the same as the inner dimensions of the square capillary. The dispersed phase flows inside the circular capillary, whilst the continuous phase flows through the square capillary in the same direction (Fig. 15(a)) (Utada et al., 2008; Umbanhowar et al., 2000). Under dripping regime, monodisperse drops are formed at the tip of the injection capillary (Shah et al., 2008). Another tapered circular capillary can be inserted into the square capillary at the other side to confine the flow near the injection tip (Breslauer et al., 2010).

In laminar flow, local stagnation zones are formed in the continuous phase at the front and the back of the droplet, which can lead to spatially non-uniform mass transfer to and away from the droplet. Using this approach toroidal polymer particles have been fabricated as a result of non-uniform evaporation of solvent from the polymer solution droplets (Wang et al., 2009).

6.2.2 Counter-current flow glass capillary device

An alternate flow configuration is a counter-current flow shown in Fig. 15(b). In contrast to co-flow device, the two fluids are supplied from the two ends of the same square capillary in opposite directions and both fluids are collected and exit through the circular capillary. The dispersed phase is hydrodynamically flow focused by the continuous phase in the tapered section of the circular capillary, which causes the dispersed phase to break into drops inside the collection capillary. A major advantage of flow focusing is that it can afford monodisperse drops with sizes smaller than that of the orifice. This feature is useful because for any given drop size, a capillary with a larger orifice size can be used compared to that in the co-flow design, which minimizes the probability of clogging the orifice by the suspended particles or any entrapped debris. Small droplets are formed using capillary with a small orifice at high

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flow rates of the continuous phase and low flow rates of the dispersed phase, i.e. for the high values of Q_c/Q_d. Typical images of drop generation in flow focusing glass capillary device are shown in Fig. 17(a)-(c). The dispersed phase was 5 wt.% poly(lactic acid) (PLA) in dichloromethane (DCM) and the continuous phase was 5 wt.% poly(vinyl alcohol) in milli-Q water. The drop formation occurs near the orifice in the dripping regime (Fig. 17(a) and (b)) and farther downstream in the jetting regime (Fig. 17(c)). The drops formed in the jetting regime are significantly bigger and have a broader size distribution because the point at which a drop separates from the jet can vary. PLA particles were formed after evaporation of DCM. The production rate in the dripping regime can range from 100 to 7000 Hz (Utada et al., 2005).

6.2.3 Three-phase glass capillary devices

Three-phase devices are used for controllable generation of multiple emulsions with tuneable morphology, such as core/shell droplets and multiple emulsion droplets containing a controlled number of inner droplets and/or inner droplets of two or more distinct phases.

Core/shell droplets

Glass capillary device for making core/shell droplets is shown in Fig. 15(c). It consists of two circular capillaries arranged end-to-end within the same square capillary. The inner fluid is pumped through the tapered circular capillary while the middle fluid, which is immiscible with the inner and outer fluids, flows through the corners of the outer capillary in the same direction. The outer fluid flows through the square capillary in the opposite direction and hydrodynamically flow focuses the coaxial stream of the other two fluids, which approach from the opposite end. When the three fluids enter the collection tube, double emulsion with core/shell structure is formed under proper flow conditions (Fig. 18). If the resultant double emulsion is reinjected into another capillary device with a tapered channel, the inner drop can be released from core/shell droplets in the tapered nozzle under certain flow conditions (Chen et al., 2011). Hence, glass capillary devices can also be used for controlled breakup of double emulsion drops.

Typical inner diameters of the tapered end of the injection tube are 10–50 μm and diameters of the orifice in the collection tube vary from 50 to 400 μm. The drop size and shell thickness

can be precisely tuned by adjusting the diameters of the orifices and the flow rates and physical properties of the three fluids. The most important parameter affecting the shell thickness is the ratio of the middle fluid flow rate to the inner fluid flow rate. As shown in Fig. 18, the higher the Q_m/Q_i ratio, the thicker the shell around the droplet becomes. The ratio of shell thickness to outer drop radius typically ranges from 3 to 40% (Utada et al., 2005). In order to produce core-shell drops with an ultra-thin shell (less than 100 nm), a modified device can be used with a biphasic flow in the injection capillary (Kim et al., 2011b). The shell material can be polymerised to produce monodisperse polymer shells around the inner drops (Kim et al., 2007b; Liu et al., 2010; Ye et al., 2010; Kanai et al., 2010) or a reaction can take place within the core material (Shum et al., 2009). Alternatively, a shell may contain dissolved amphiphilic molecules or particles which can undergo self-assembly upon solvent evaporation, leading to the generation of vesicles such as liposomes (Shum et al., 2008), polymersomes (Lorenceau et al., 2005; Kim et al., 2011) and colloidosomes (Lee and Weitz, 2008).

Multiple emulsions with a controlled number of inner drops

A glass capillary device shown in Fig. 15(d) employs stepwise emulsification of co-flowing streams to create a double emulsion containing a controlled number of inner drops in each outer drop. The device consists of an injection tube that is inserted into a transition tube. The other end of the transition tube is also tapered and is inserted into a third, coaxially aligned square capillary, the collection tube. The inner fluid flowing through the injection tube is emulsified in the transition tube by coaxial flow of the middle fluid. The single emulsion is subsequently emulsified in the square capillary by coaxial flow of the outer fluid, which is injected into the space between the square capillary and the injection and transition tube. The number of inner drops can be adjusted by controlling the flow rates of the three fluids. Multiple emulsions containing between one and seven inner droplets in each larger droplet have been produced and the size of both inner and outer drops was precisely controlled (Chu et al., 2007). These emulsions can be used as templates for synthesis of non-spherical particles (Shum et al., 2010). Higher-order multiple emulsions can be made by adding more sequential stages (Wang et al., 2011, Chu et al., 2007). For example, Chu et al. (2007) have made monodisperse triple emulsions by adding a third co-flow stage and both the diameter and the number of the individual drops could be controlled at every level. Using this

approach, triple emulsions have been formed containing between one and seven innermost drops and between one and three middle drops in each outer drop.

Multiple emulsions with two distinct inner phases

Double emulsions with multiple compartments can be formed using a two-bore injection tube containing two separate internal channels for injection of the two distinct inner phases of the double emulsions, as shown in Fig. 15(e). These devices have been used for fabrication of particles with two distinct inner compartments, such as two-compartment polymersomes (Shum et al., 2011), solid lipid particles (Sun et al., 2010) and polymeric particles (Zhao et al., 2011). It is possible to switch from having two separate inner droplets to having a single Janus inner droplet by turning the middle phase off temporarily (Zhao et al., 2011).

Particles with two distinct inner compartments can be used for co-encapsulation of two incompatible actives. By tuning the distance between the two compartments during solidification of the middle fluid, it is possible to manipulate the release profile of actives (Sun et al., 2011). If the two inner compartments are far enough away from each other, the two actives will be released to the surroundings separately. However, if the inner compartments are close to each other, they will coalesce with each other before releasing its content to the outer phase (Sun et al., 2011). It allows an unprecedented level of control and flexibility in the release process.

6.3 Single crystal silicon axisymmetric devices

The main advantage of silicon axisymmetric devices is that many individual flow focusing drop generators can be integrated into bidimensional arrays (Luque et al., 2009). Flow focusing microchannel arrays can be built from two silicon plates using the fabrication process depicted in Fig. 19 (Luque et al., 2007). The fabrication process starts with coating positive photoresist onto the surface of the first wafer. The photoresist is then exposed to UV light through the mask that determines the area that each drop generation unit will occupy. The photoresist is then developed and the open silicon region is etched by reactive ion etching (RIE). The depth of this etching determines the spacing H between the orifice and the dispersed phase channel. A new deep RIE is required in order to pattern the channel for the delivery of the continuous phase. A circular channel for the delivery of the dispersed phase is

then opened. First, the backside of the wafer is oxidized and the created oxide is patterned. Using the remaining oxide as a mask, a DRIE process is performed on the backside through the whole wafer. The wafer is then oxidized to protect the microfabricated structures from being etched when the exit orifice is opened. After oxidation of the first wafer, a second silicon wafer is bonded to the first one and an aluminium layer is sputtered and patterned on its surface. Finally, using this patterned aluminum film as a mask, the exit orifice is opened through the second wafer using DRIE (Luque et al., 2007).

7. CONCLUSIONS

Microengineering strategies for emulsion formation offer a great potential in manufacturing 'made-to-measure' droplets with a controlled size, shape and internal structure. Microfluidic junctions and flow focusing devices can generate single, double, triple and multiple emulsion droplets in a single step with a coefficient of variation in the dripping regime of less than 3%. The entrapment efficiency of encapsulants in microfluidic junctions and flow focusing devices can reach 100% and the number of drops encapsulated within each outer drop or shell thickness can be controlled. Microchannel emulsification can generate emulsions with a coefficient of variation of droplet sizes of less than 5% at throughputs much higher than those in microfluidic devices (up to 100 kg per hour). Membrane emulsification is a suitable technique for production of droplets with a controlled size distribution at even higher productivity (several tonnes per hour), but monodipsersity cannot be achieved (CV =10−20%). Droplets produced using microengineering fabrication methods can be used for a number of different applications including as microcompartments for screening of samples and templates for fabrication of monodispersed particles and vesicles. The main benefit of using microfluidic devices is in their ability to precisely control droplet size, shape, anisotropy, uniformity, and internal structure, which opens up new possibilities in chemical synthesis, particle engineering, molecular biology, and other areas.

Table 1: Typical performance of membrane, microchannel and microfluidic devices for controlled generation of droplets.

	Membrane emulsification	Microchannel emulsification	Microfluidic junctions and flow focusing devices
Minimum droplet size	0.1 μm[*]	1 μm	10 μm
Quazi-monodispersity	No (CV=10–20%)	Yes (CV<5%)	Yes (CV<3%)
Control over inner structure of multiple emulsion droplets	No	No	Yes
Ability to produce Janus (bifacial) droplets	No	No	Yes
Ability to produce non-spherical droplets	No	Yes	Yes

[*]In premix membrane emulsification

Table 2: Typical plate dimensions, number of MCs, average size of resultant droplets and maximum throughput of grooved and straight-through silicon MC plates

	Grooved MC cross-flow	Grooved MC dead end	Straight-through
Typical size of MC plate	8×22.5 mm 60×60 mm	15×15 mm 24×24 mm 40×40 mm	15×15 mm 24×24 mm 40×40 mm
Channel number	Up to 12,000	100–1,500	5,000–210,000
Average droplet diameter	1–100 μm	1–100 μm	4 μm –4 mm
Maximum droplet generation frequency per module[*]	$<5\times10^5$ droplets s^{-1}	$<8\times10^3$ droplets s^{-1}	$<5\times10^5$ droplets s^{-1}
Maximum dispersed phase flow rate[*]	1.5 mL h^{-1}	0.1 mL h^{-1}	50 mL h^{-1}

[*]For triglyceride oil-in-water emulsion

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Figure captions

Figure 1: Some examples of droplets with a controlled morphology that can be manufactured using microfluidic drop generators.

Figure 2: Different membrane emulsification (ME) methods and systems.

Figure 3: A flow diagram of the defferent steps involved in the fabrication of Shirasu Porous Glass (SPG) membrane.

Figure 4: Fabrication of nickel and silicon nitride microsieve membranes.

Figure 5: Fabrication of microfluidic channel by: (a) soft lithography; (b) hot embossing lithography.

Figure 6: Droplet formation and manipulation in microfluidic junctions: (a) Droplet formation at a T junction (Thorsen et al., 2001). (b) Droplet break up at a T junction (Link et al., 2004; Tan et al., 2004). (c) Merging of droplets with a target sample stream at a T junction (Shestopolov et al., 2004; Zheng and Ismagilov, 2005). (d) Mixing of two liquid streams within a droplet using two converging side channels (Choi et al., 2007). (e) Mixing of three liquid streams within a droplet using three converging side channels (Tice et al., 2004). (f) Droplet formation at a cross junction (Nisisako et al., 2004). (g) Formation of droplets of alternating composition at a cross junction (Zheng et al., 2004; Hung et al., 2006); (h) Formation of droplets at a Y junction (Steegmans et al., 2009). (i) Formation of two distinct fluid streams using a Y junction (Kenis et al., 1999; Nisisako et al., 2004).

Figure 7: Microfluidic Flow Focusing Devices (MFFD): (a) Standard geometry developed by Anna et al. (2003) with a constriction placed downstream of three coaxial inlet stream. Liquid B wets channel walls. (b) Modified design with three coaxial streams for generation of core/shell droplets. Liquid C wets channel walls (Nie et al., 2005). (c) Two consecutive flow focusing droplet generators (FFDGs). FFDGs 1 and 2 are wetted by liquid B and C, respectively (Seo et al., 2007). (d) Two parallel coupled FFDGs (Hashimoto et al., 2008).

Figure 8: Photolithographic methods for fabricating silicon MC array devices: (a) Photolithography and anisotropic wet etching (adapted from Manz et al., 1992) for fabricaton of shallow microgrooves. (b) Photolithography and Deep Reactive ion Etching (DRIE) for fabrication of straight-through channels (adapted from Kobayashi et al., 2002a).

Figure 9: Grooved-type MC plates: (a) Dead-end plate (Kawakatsu et al., 1997). (b) Cross-flow plate (Kawakatsu et al., 1999, 2000).

Figure 10: A large cross-flow plate (60×60 mm) with 14 paralel parallel MC arrays, each consisting of 850 MCs; not all MCs are shown in the figure for simplicity (Kobayashi et al., 2010).

Figure 11: Steps in deep reactive ion etching using the Bosch process. The vertically oriented SF_x^+ ions enhance the effect of neutral fluorine radicals in removing the protective film at the bottom of the trench, while the film remains relatively intact along the sidewalls.

Figure 12: Straight-through MC plates: (a) symmetric plate with microslots on both sides (Kobayashi et al., 2002a). (b) Asymmetric plate with circular channels on upstream side and slots on dowstream side (Kobayashi et al., 2005b). (c) symmetric plate with micronozzles (MNs) (Sugiura et al., 2005).

Figure 13: Edge-Based Droplet GEneration (EDGE) system (van Dijke et al., 2009a).

Figure 14: Axisymmetric flow focusing device (AFFD) fabricated in PDMS: (a) Fabrication process; (b) Operation of AFFD oriented vertically to avoid accumulation of droplets on the wall of the outlet channel (Takeuchi et al., 2005).

Figure 15: Axisymmetric glass capillary devices: (a) Co-flow of two immiscible fluids (Utada et al., 2008). (b) Countercurrent flow of two immiscible fluids with flow focusing (Utada et al., 2007). (c) Combination of co-flow and countercurrent flow of three immiscible fluids (Utada et al., 2005). (d) Two sequential co-flow droplet generators (Chu et al., 2007). (e) injection of two distinct inner phases of double emulsions using a two-bore injection tube (Sun et al., 2010).

Figure 16: Fabrication of tapered-end borosilicate glass capillary using a Flaming/Brown type micropipete puller and a microforge.

Figure 17: Generation of droplets in flow focusing glass capillary devices: (a) Q_c=0.5 mL h^{-1}, Q_d=0.003 mL h^{-1}, $d_{orifice}$=60 μm, $d_{droplet}$= 33 μm. (b) Q_c=5 mL h^{-1}, Q_d=1 mL h^{-1}, $d_{orifice}$=130 μm, $d_{droplet}$= 100 μm. (c) Q_c=6.5 mL h^{-1}, Q_d=0.7 mL h^{-1}, $d_{orifice}$=130 μm, $d_{droplet}$=230 μm. Q_d and Q_c is the dispersed and continuous phase flow rate, respectively. (d) Micrograph of collected droplets. The continuous phase is 2 wt.% poly(vinyl alcohol) in milli-q water and the dispersed phase is 5 wt.% PLA in DCM (G.T. Vladisavljević et al., 2011b).

Figure 18: The shell thickness of core/shell droplets as a function of the ratio of middle fluid flow rate to inner fluid flow rate: (a) Q_m/Q_i = 6. (b) Q_m/Q_i = 5. (c) Q_m/Q_i = 1.5. (d) Q_m/Q_i = 0.25. The diameter of the orifice of the injection and collection tube is 44 and 115 μm, respectively. (e) and (f): Collected core/shell droplets with a core diameter of 62 μm and a shell thickness of 8 μm. The inner fluid is milli-q water, the middle fluid is 2 wt.% Dow Corning 749 in PDMS (10 cSt) and the outer fluid is 2 wt.% poly(vinyl alcohol), 87-89 % hydrolysed, in milli-q water (G.T. Vladisavljević et al., 2011c).

Figure 19: Axisymmetric flow focusing device (AFFD) built from two single crystal silicone wafers: (a) fabrication process based on repetitive reactive ion etching (RIE) and deep reactive ion etching (DRIE); (b) 3D representation of the device showing cylindrical channel for injection of dispersed phase and orifice for flow focusing (H – distance between the nozzle for injection of the dispersed phase and the orrifice (Luque et al., 2007).

(a) Core-shell droplets

(b) Bifacial (Janus) droplets

Phase A   Phase B

(c) Triple, quadruple, quintuple , etc emulsions

(d) Controlled number of inner droplets

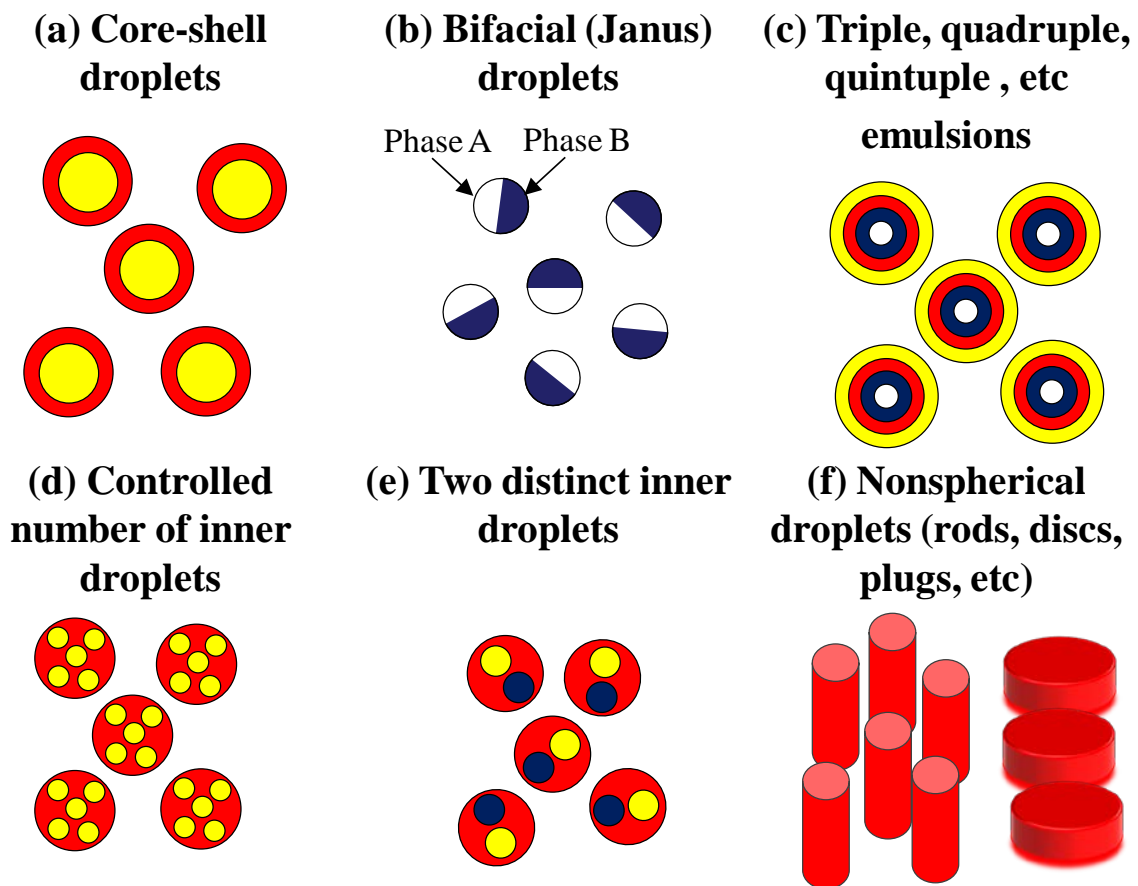**(e) Two distinct inner droplets**

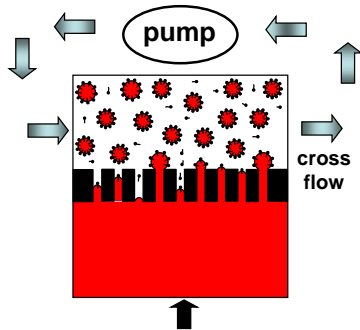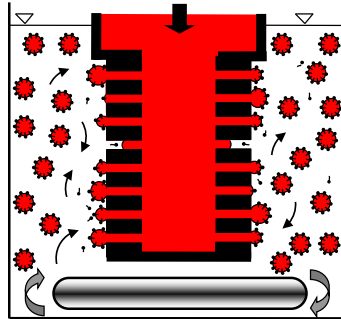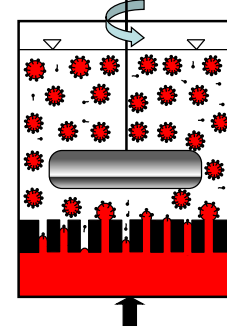**(f) Nonspherical droplets (rods, discs, plugs, etc)**
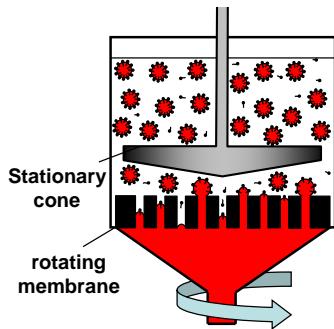
Figure 1

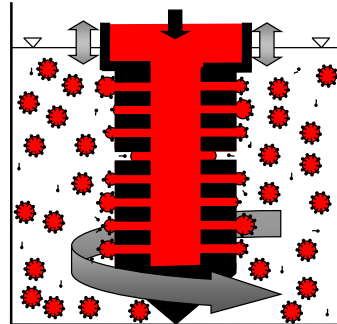**(a) Cross flow system**

(b) Stirred cell – tube membrane

(c) Stirred cell – flat membrane

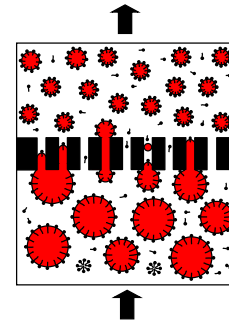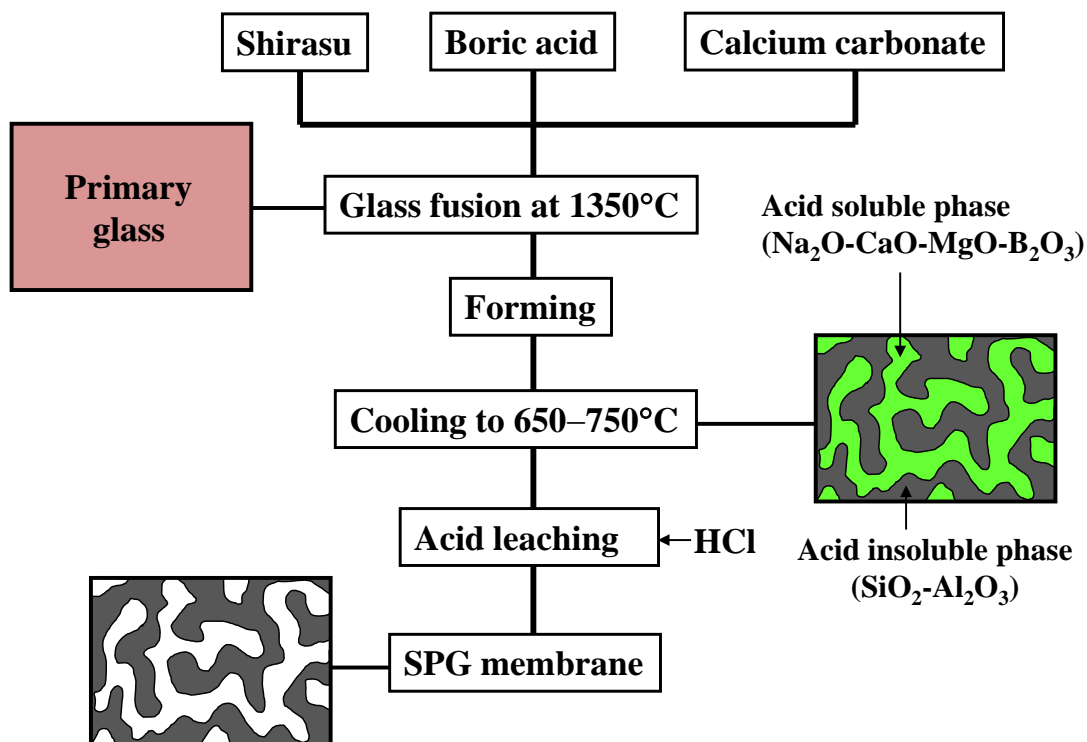**(d) Rotating flat membrane**

(e) Vibrating/rotating tube membrane

(f) Premix ME

pump

cross flow
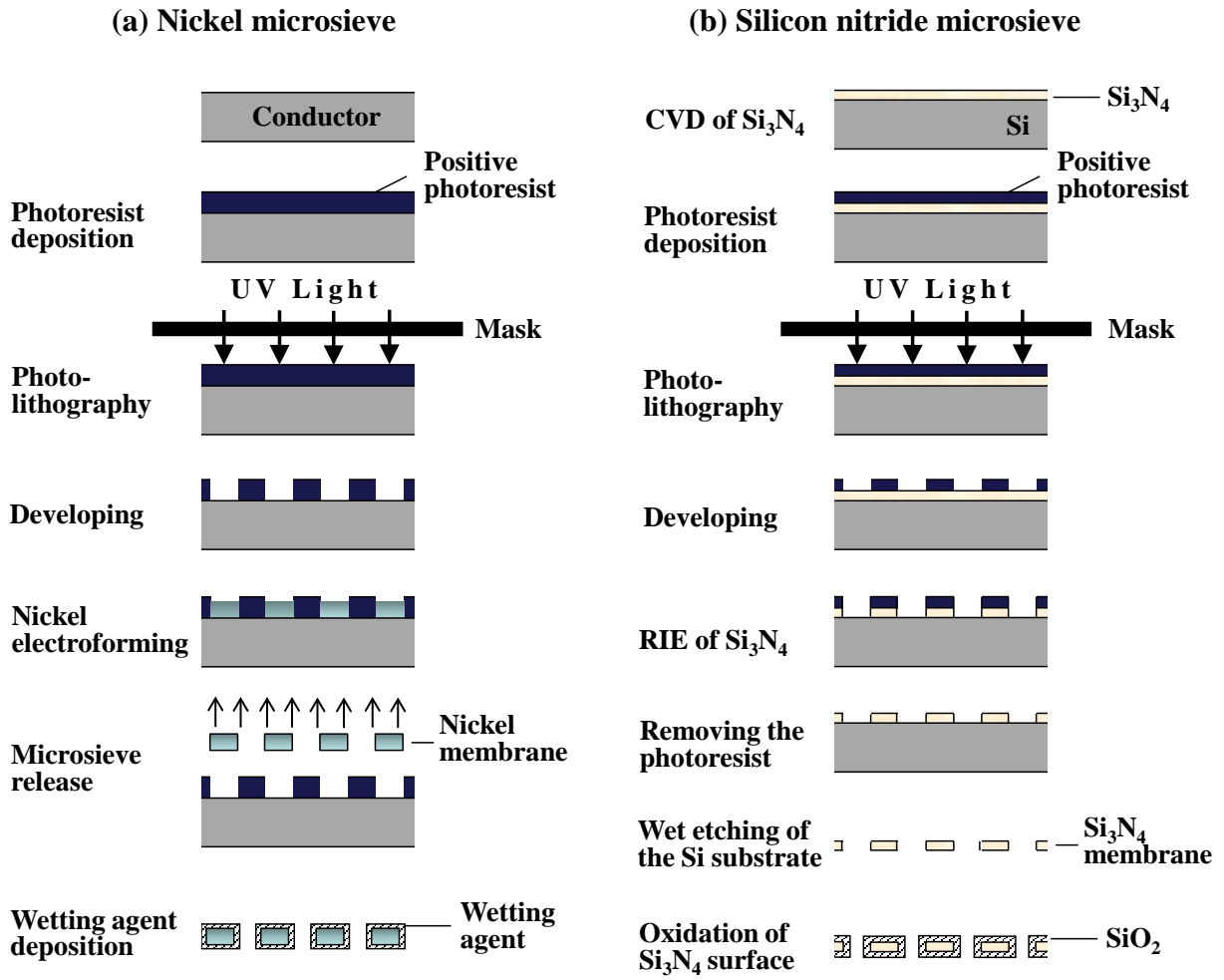
Stationary cone

rotating membrane

Figure 2

Figure 3

(a) Nickel microsieve

(b) Silicon nitride microsieve

Conductor

Positive
photoresist

**Photoresist
deposition**

CVD of Si₃N₄ — Si_3N_4

Si

Positive
photoresist

**Photoresist
deposition**

UV Light

Mask

**Photo-
lithography**

UV Light

Mask

**Photo-
lithography**

Developing

Developing

**Nickel
electroforming**

RIE of Si₃N₄

Nickel
membrane

**Microsieve
release**

**Removing the
photoresist**

Wet etching of
the Si substrate — Si_3N_4
membrane

**Wetting agent
deposition**

Wetting
agent

**Oxidation of
Si₃N₄ surface** — SiO_2

Figure 4

58

(a) Soft lithography

Si wafer

Photoresist deposition — Si, Negative photoresist

UV exposure — UV Light, Mask

Developing

Casting — PDMS prepolymer

Thermal curing — ~70–120°C, PDMS elastomer

Peeling off — PDMS replica

Bonding — PDMS, Transparent plate

(b) Hot embossing lithography

Heating — Mold, PMMA

Pressing

Cooling and separating

Bonding — Transparent plate, PMMA

Figure 5

(a)
Dispersed phase
Continuous phase
Droplets

(b)
Large droplets
Small droplets
Small droplets

(c)
Reagent solution
Merged droplet

(d)
Polymer solution
Crosslinking solution
Micro-gel
Continuous phase

(e)
Reagent 1
Buffer
Reagent 2
Continuous phase

(f)
Dispersed phase
Continuous phase
Continuous phase

(g)
Continuous phase
Dispersed Phase 1
Dispersed Phase 2

(h)
Dispersed phase
Continuous phase

(i)
Liquid 1
Liquid 2

Figure 6

Figure 7

(a) Microgrooves

**Polished
Si wafer**

**Thermal
oxidation** — SiO_2

Si

**Photoresist
deposition** — Positive photoresist

UV Light

Mask

UV exposure

Developing

Etching SiO_2

**Removing the
photoresist**

**Etching the Si
microstructure**

(b) Straight-through channels

**Aluminium
vapour
deposition** — Al

Si

**Photoresist
deposition** — Positive photoresist

UV Light

Mask

**Photo-
lithography**

Developing

Etching Al

**Removing the
photoresist**

**Etching the Si
microstructure**

**Removing Al
and oxidation** — SiO_2

Figure 8

(a) Dead end MC module　　　**(b) Cross flow MC module**

terrace

Disperse phase

Continuous phase

Glass plate

MC

Stagnant continuous phase

Glass plate

Oil

Continuous phase

Oil

Figure 9

Figure 10

SF$_6$ etch   **Polymer deposition**   **SF$_6$ etch**
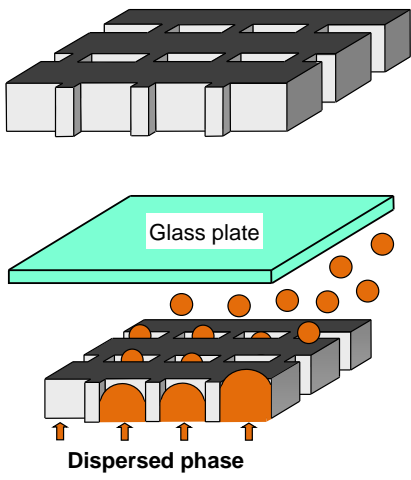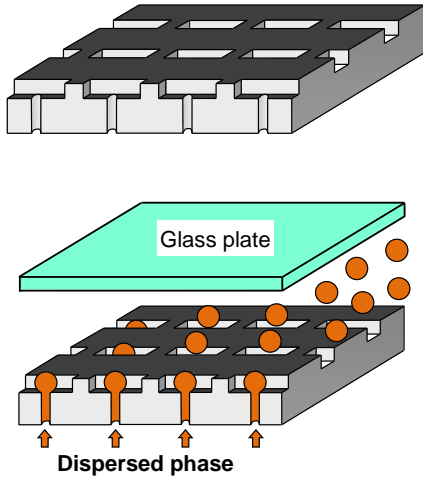
Figure 11

(a) Symmetric MC plate **(b) Asymmetric MC plate** **(c) Symmetric MN plate**

Glass plate

Glass plate

Glass plate

Dispersed phase

Dispersed phase

Dispersed phase

Figure 12

dispersed phase

plateau

continuous phase

Figure 13

(a)

1. Exposing insulated optical fiber

Exposed part

Insulation

2. Pouring PDMS and curing

3. Removing fiber

4. Inserting glass capillaries

Glass
capillary

Glass
capillary

(b)

Inner
phase

Middle
phase

Middle
phase

Orifice

Outer
phase

Outer
phase

Figure 14

(a)

Continuous phase

Dispersed phase

(b)

Dispersed phase

Continuous phase

(c)

Middle fluid

Outer fluid

Inner fluid

(d)

Middle fluid

Outer fluid

Inner fluid

(e)

Middle fluid

Outer fluid

Inner fluid 1

Inner fluid 2

Figure 15

(a) Pulling a capillary

Heat

Force ⇐ ⇩⇧ ⇒ Force

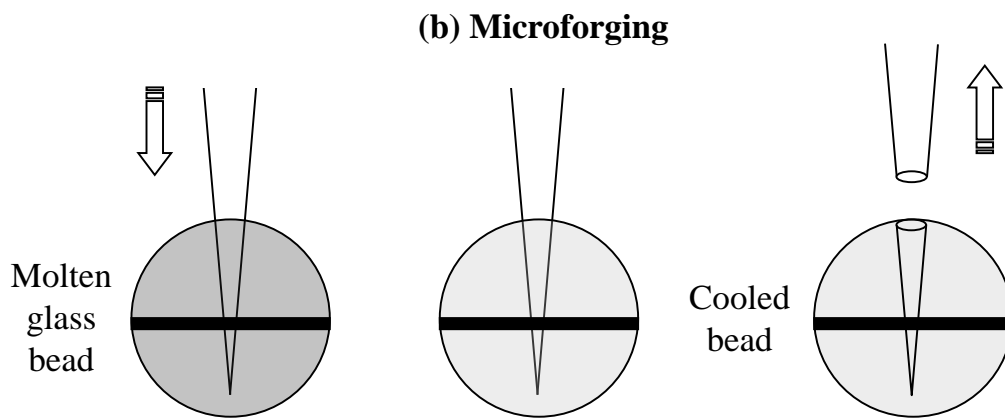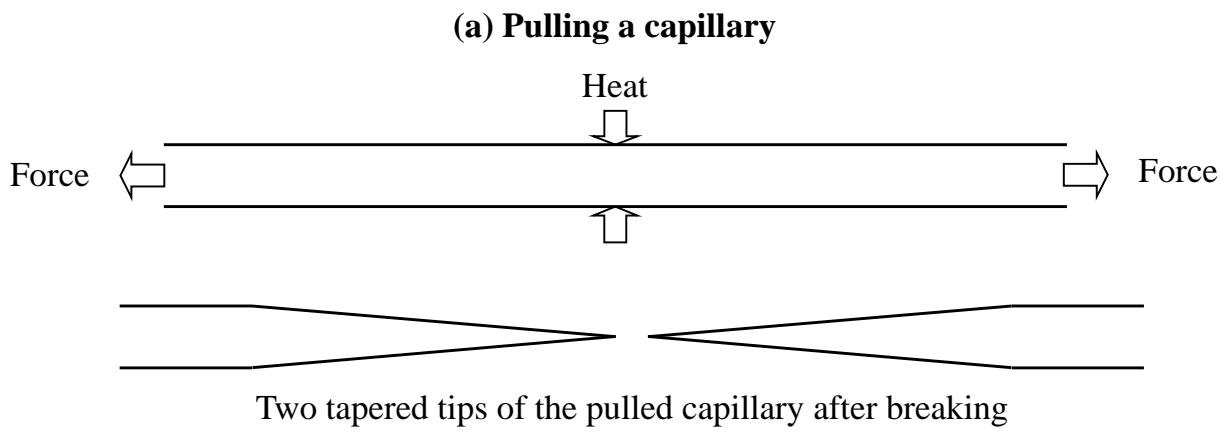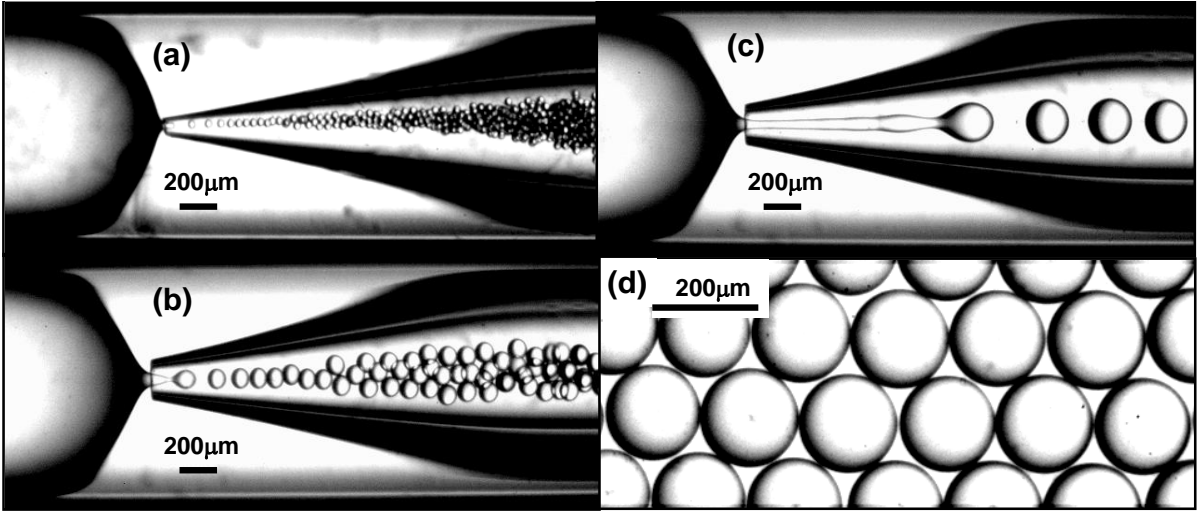Two tapered tips of the pulled capillary after breaking

(b) Microforging

Molten
glass
bead

Cooled
bead

Figure 16

Figure 17

Figure 18

(a)

(b)

RIE of silicon
(~10 μm)

DRIE of silicon
(~170 μm)

Oxidation and
DRIE of silicon
from backside

SiO₂

Fusion
bonding

Al

Al sputtering
and RIE of
silicon

H

Magnified portion

Emulsion

Continuous
phase

Continuous
phase

Dispersed
phase

Figure 19