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Large microchannel emulsification device for mass producing uniformly sized droplets on a liter per hour scale

Abstract: We report the mass production of uniformly sized droplets on a liter per hour scale using a large microchannel (MC) emulsification device developed in this study. This MC emulsification device includes a newly designed 40×40-mm silicon MC array chip with 24,772 asymmetric MCs, each consisting of a circular microhole (17-μm diameter and 200-μm depth) and a microslot (17×119-μm cross-section and 60-μm depth). The oil-in-water (O/W) system was composed of *n*-tetradecane as the dispersed phase and a Milli-Q water solution containing 2.0 wt% Tween-20 as the continuous phase. The MC emulsification results demonstrated the stable mass production of uniformly sized oil droplets with average diameters of 87 μm and coefficients of variation below 2% over a wide range of volumetric flow rates of the dispersed phase up to 1.4 l/h. Analyses of shear stress at the chip surface and droplet generation via an asymmetric MC verified that the resultant droplet size and size distribution was not influenced by the volumetric flow rate of each phase. The large MC emulsification device has a potential droplet productivity exceeding several tons per year, which could satisfy a minimum industrial-scale production of monodisperse microdispersions containing emulsion droplets, microparticles, and microcapsules.

Keywords: asymmetric microchannel; droplet generation; mass production; microchannel emulsification; monodisperse emulsion.

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Nomenclature

A_{ch}	cross-sectional area of upper channel (m^2)
A_{MCA}	total area of MC arrays (m^2)
CV	coefficient of variation (-)
d	droplet diameter (m)
d_{av}	average droplet diameter (m)
$d_{eq,ch}$	equivalent diameter of upper channel (m)
f_{chip}	droplet generation frequency per MC array chip (s^{-1})
f_{MC}	droplet generation frequency per MC (s^{-1})
h_{ch}	height of upper channel (m)
h_{slot}	depth of microslot (m)
J_d	flux of dispersed phase [l/(m^2 h)]
L_{ch}	wetted perimeter of upper channel (m)
Q_c	flow rate of continuous phase (l/h)
Q_d	flow rate of dispersed phase (l/h)
Re_c	Reynolds number of cross-flowing continuous phase (-)
U_c	average velocity of continuous phase (m/s)
w_{ch}	width of upper channel (m)
$w_{s,slot}$	narrow side length of microslot (m)
V_{av}	average droplet volume (m^3)

Greek symbols

η_c	viscosity of continuous phase (Pa s)
η_d	viscosity of dispersed phase (Pa s)
ρ_c	density of continuous phase (kg/m^3)
σ	standard deviation (m)
τ_s	shear stress at chip surface (N)
ϕ_d	volume fraction of dispersed phase (%)

1 Introduction

Emulsification technology using microfabricated devices has been the focus of much attention in various fields over the past decade. Microfabricated emulsification devices include micromixer devices [1, 2], microfluidic emulsification devices [3–9], and microchannel (MC) emulsification devices [9–11]. Micromixer devices have demonstrated the mass production of emulsion droplets on a liter scale, while slightly polydisperse emulsions were obtained [1, 2]. Other microfabricated emulsification devices are capable of producing monodisperse emulsions containing uniformly sized droplets with a coefficient of variation (CV, defined in section 3.2) below 5% and precisely controlling the droplet size [9]. These monodisperse emulsions have potential applications for biomedicals, chemicals, cosmetics, and foods. In addition, they have been used as templates for manufacturing monodisperse microparticles and microcapsules whose size, shape, and composition are precisely controlled [5, 9, 12–17]. Industrial-scale production of these monodisperse micromaterials requires the mass production of uniformly sized droplets with a productivity of at least several tons per year (t/year), i.e., liters per hour (l/h).

Numerous research studies have been carried out using microfluidic chips with geometric designs such as T, Y, and cross junctions [3, 18, 19] and flow focusing of quasi-two and three dimensions [4, 5, 20, 21]. Microfluidic chips normally have only one droplet generation unit, resulting in a very low droplet productivity of typically $<10^{-3}$ l/h. This droplet productivity is determined by the volumetric flow rate of the dispersed phase (Q_d). Droplet generation for microfluidic emulsification requires forced flow of the continuous phase and is influenced by the flow of both phases [22]. The resultant droplet size can be varied using the same microfluidic chip but is sensitive to the flow of each phase. To improve the droplet productivity of microfluidic emulsification, several research groups have proposed large microfluidic chips, each consisting of parallelized droplet generation units [19, 23–26]. Nishisako and Torii [19] produced uniformly sized monomer droplets at a maximum Q_d of 0.32 l/h using a microfluidic chip with 128 cross junctions, i.e., 256 droplet generation units. However, successful long-term emulsification using large microfluidic chips is not straightforward, because it is necessary to maintain an equal flow of each phase at all of the droplet generation units, as well as to prevent clogging at each droplet generation unit due to the presence of tiny debris or bubbles. Cleaning these large microfluidic chips is also difficult, as they are chemically bonded with a flat plate prior to the first use.

The authors' research group has developed MC emulsification chips, each with at least one MC array composed of parallel microgrooves [10] or compactly arranged straight through-holes [11, 27]. MC arrays of asymmetric structure (Figure 1) are preferable for stably generating uniformly sized droplets whose size is mainly controlled by the MC dimensions [27, 28]. MC array chips have numerous

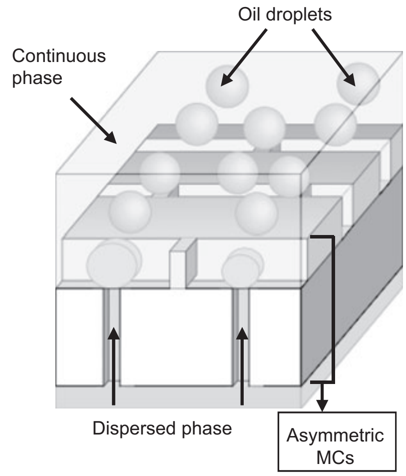

Figure 1 Three-dimensional schematic drawing of the generation of O/W emulsion droplets via asymmetric MCs.

droplet generation units [9], as each asymmetric MC corresponds to one droplet generation unit. In MC emulsification, droplets are generated by spontaneous transformation of the dispersed phase that has passed through the MCs, driven by the Laplace pressure difference [29]. This robust droplet generation has the major practical advantage that the resultant droplet size is insensitive to the flow of each phase below a critical value [30–32]. Moreover, each MC array chip physically attaches to a transparent plate or a thin spacer in the module, indicating that the chips can be readily cleaned when necessary. MC emulsification is, in principle, similar to membrane emulsification using micro-porous membranes [9, 33]. In membrane emulsification, relatively uniformly sized droplets with the smallest CV of ~10% are generated by forcing the dispersed phase through membrane pores in the continuous phase. Although membrane emulsification can generate droplets in the absence of the cross-flowing continuous phase at low production scales [34, 35], shear stress caused by the cross-flowing continuous phase is usually applied in this technique [36]. Real-time monitoring of droplet generation by membrane emulsification is normally difficult. Industrial-scale membrane emulsification devices were previously used for commercial production of a low-fat spread [33].

The use of MC array chips consisting of microgrooves resulted in low droplet productivity of up to 1.5×10^{-3} l/h [37]. Asymmetric MC arrays consisting of straight through-holes can accommodate $>10^4$ MCs per 1 cm^2 [11, 32], which is two orders of magnitudes greater than the typical number of microgrooves per 1 cm^2. Vladisavljević et al. [32] demonstrated the production of uniformly sized droplets at a maximum Q_d of 0.27 l/h using a previously designed 24×24-mm asymmetric MC array chip. Ideally, the maximum droplet productivity per unit area of an asymmetric MC array is constant, regardless of the MC size [38]. To satisfy the minimum droplet productivity needed for industrial-scale production, the MC emulsification device, including the preceding asymmetric MC array chip, must be scaled up. Therefore, in this study we developed a large MC emulsification device including a newly designed asymmetric MC array chip to realize the mass production of uniformly sized droplets on a liter per hour scale. We also investigated the shear stress at the MC array chip surface, the droplet generation characteristics via an asymmetric MC, and the influence of Q_d on the droplet size and droplet size distribution.

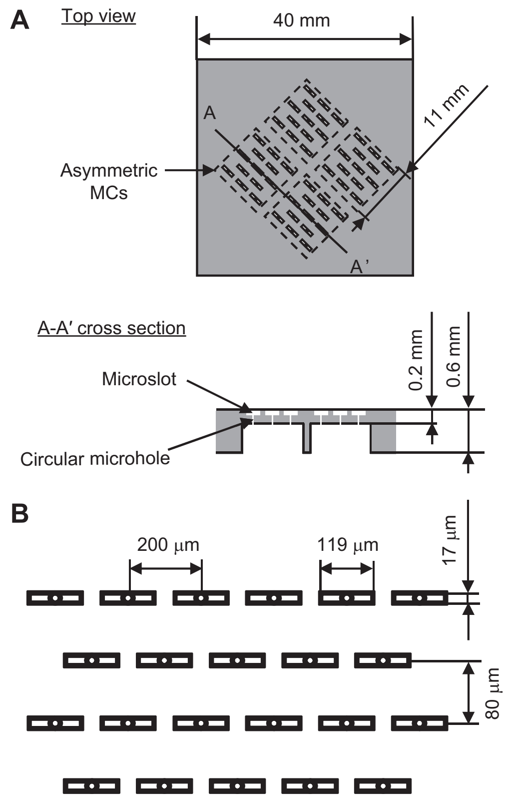

Figure 2 (A) Schematic representation of the WMS10 chip. (B) Schematic diagram of asymmetric MCs on the top side of the plate.

2 Development of a large microchannel emulsification device

2.1 Asymmetric microchannel array chip

We designed a 40×40-mm MC array chip (Model WMS10) consisting of four 11×11-mm asymmetric MC arrays (Figure 2A). The total area of these asymmetric MC arrays was approximately five times larger than that of a standard-sized asymmetric MC array chip [11]. In total, 6193 MCs were arranged in each asymmetric MC array (Figure 2B); this plate had 24,772 MCs. Each MC consisted of a circular microhole (17-μm diameter and 200-μm depth) located on the inlet side and a microslot (17×119-μm cross-section and 60-μm depth) located on the outlet side. The aspect ratio of 7:1 at the slot outlet is high enough to generate uniformly sized droplets [39]. The distance between two adjacent MCs in the horizontal and vertical rows (Figure 2B) was determined by considering the estimated droplet size and movement. The slot direction was vertical, parallel to the cross-flowing continuous phase over the slot outlets. A crossed support structure was fixed to the bottom side of the chip to reinforce asymmetric MC arrays with a 260-μm thickness.

WMS10 chips were fabricated via repeated photolithography and deep reactive ion etching (DRIE) on a 5-in. (127-mm) diameter, 600-μm thick silicon-on-insulator (SOI) wafer. The SOI wafer was composed from top and bottom single-crystal silicon (Si) layers and a thin, middle silicon dioxide (SiO_2) layer (Figure 2A). In brief, the first (second) DRIE on the top Si layer fabricated the microslots (circular microholes). Afterwards, a third DRIE on the bottom Si layer fabricated the deep wells as well as the crossed support structure, followed by the removal of the middle SiO_2 layer by reactive ion etching (RIE) to connect the microholes and the wells. Finally, the fabricated wafer was diced into individual asymmetric MC array chips. The fabricated microslots and microholes were highly uniform, satisfying a necessary criterion for obtaining monodisperse emulsions by MC emulsification [11].

2.2 Module and peripherals

The large MC emulsification device developed in this study is schematically presented in Figure 3A. We designed a module that can perform MC emulsification using a WMS10 chip. Figure 3B depicts top and bottom views of this 125-mm diameter, 42-mm height module. The main parts of the module are a bottom lid, a middle holder, a top lid, and two quartz glass plates that enable directly observing the flow of the two phases. The lids and holder were made of stainless steel (Japanese Industrial Standard, SUS 304). Wide upper and lower channels for separately directing two phases towards the WMS10 chip were formed by attaching two fluoro-rubber spacers inside the module. The WMS10 chip was sandwiched by two

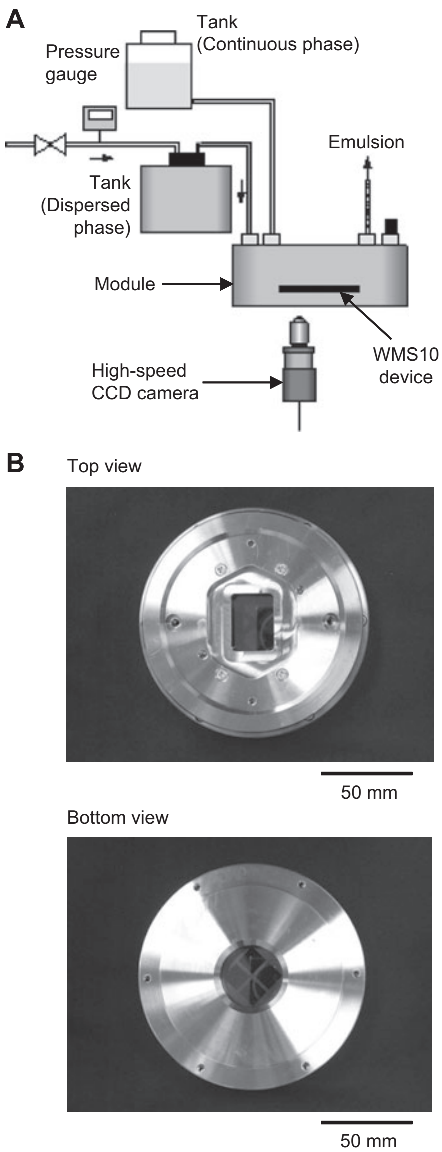

Figure 3 (A) Simplified schematic drawing of the large MC emulsification device developed in this study. (B) Top and bottom views of the module.

0.5-mm thick fluoro-rubber spacers, which is intended to appropriately separate the two phases. Two inlet through-holes and two outlet through-holes were fabricated on the middle holder (Figure 3B). To simplify the MC emulsification, each phase can be introduced into a wide channel via an inlet through-hole. One of the outlet through-holes is available for collecting the emulsion product.

In addition to the module, the large MC emulsification device also included a 10-l plastic vessel filled with a continuous phase, a 5-l pressure vessel (DV-5-A; Advantec Toyo Kaisha, Ltd., Tokyo, Japan) filled with a dispersed phase, and a custom-made microscope video system. The pressure vessel is connected to a nitrogen gas cylinder. The microscope video system consisted of a frame equipped with a precision XY stage, a metallographic microscope (MS-511B, Seiwa Optical Co., Tokyo, Japan), and a high-speed camera (Fastcam Ultima 1024R2; Photron Ltd., Tokyo, Japan). This system enables direct microscopic observation of droplet generation on the top surface of the WMS10 chip at a precisely adjusted position. Long-term MC emulsification could be performed by continuously adding the continuous phase to the vessel at a specified flow rate.

3 Materials and methods

3.1 Chemicals and solution preparation and properties

n-Tetradecane and polyoxyethylene (20) sorbitan monolaurate (Tween 20) were purchased from Wako Pure Chemical Ind. (Osaka, Japan). These reagents were used for our experiments as received. The dispersed phase was *n*-tetradecane with a viscosity of 2.7 mPa s and a density of 763 kg/m^3 at 25°C [40]. The continuous phase was prepared by dissolving Tween-20 in Milli-Q water at a concentration of 2.0 wt%. The continuous phase had a viscosity of 1.1 mPa s and a density of 1006 kg/m^3 at 25°C. Interfacial tension was measured at 25°C with a pendant drop interfacial tensiometer (PD-W; Kyowa Interface Science Co. Ltd., Saitama, Japan). The equilibrium interfacial tension between the two phases was 7.4 mN/m. The interfacial tension between *n*-tetradecane and pure water was 50 mN/m [40].

3.2 Emulsification procedure

Prior to the first use, the WMS10 chip surfaces were oxidized in a plasma reactor (PR500; Yamato Science Co. Ltd., Tokyo, Japan) to render them hydrophilic. The contact angle of a water drop on the plate top surface was less than 10°. Successful production of oil-in-water (O/W) emulsions by MC emulsification is normally achieved when an MC array chip is sufficiently hydrophilic to prevent wetting of the dispersed phase on the chip surfaces [41]. Each emulsification experiment started with degassing of a WMS10 chip soaked in the continuous phase under ultrasonication at 100 kHz for 20 min. During module assembly, the degassed WMS10 chip was mounted in a module compartment filled with the continuous phase, and two wide channels with a 0.5-mm depth were formed above and beneath the WMS10 chip.

The dispersed phase was supplied to the module by applying N_2 gas pressure to the liquid in the pressure vessel. The continuous phase was supplied to the module from an elevated vessel containing the liquid. The weight of each liquid phase was measured with a precision balance (PG12001-S; Mettler Toledo, Greifensee, Switzerland) placed beneath its vessel. The volumetric flow rate of each liquid phase was calculated from the weight data acquired at a time interval of 60 s. The tip of the collection tube was fixed to suppress the variation in the apparent pressures applied to the two phases during emulsion production. We captured microscopic images of droplet generation from the slot outlets using a high-speed camera (see section 2.2) at a frame rate of 1000 s^{-1}. The droplet generation rate from the slot outlets was estimated from the captured images. After each experiment, the WMS10 chip taken out from the disassembled module was subjected to a cleaning procedure using a 100-kHz ultrasonic bath [42]. The cleaned WMS10 chip was soaked in Milli-Q water containing 0.02 wt% sodium azide for the next experiment.

3.3 Determining average droplet size and droplet size distribution

The microscopic images captured with the high-speed camera were used to measure droplet size. The diameters of the resultant droplets were measured manually using WinRoof software (Mitani Co., Ltd., Fukui, Japan). The number-average droplet diameter (d_{av}) was determined by the following equation:

$$d_{av} = \sum_{i=1}^{n} d_i / n \tag{1}$$

where d_i is the diameter of the ith droplet and n is the number of the droplets measured ($n = 100$). The droplet size distribution was expressed in terms of CV, defined as:

$$\mathrm{CV} = (\sigma/d_{av}) \times 100 \tag{2}$$

where σ is the standard deviation.

4 Results and discussion

4.1 Shear stress at the MC array chip surface

The volumetric flow rate of the continuous phase (Q_c) applied in this study ranged from 1.2 to 10.8 l/h, depending on Q_d. To evaluate the flow state of the continuous phase in the upper channel, we calculated its Reynolds number (Re_c) defined as:

$$Re_c = \rho_c U_c d_{eq,u.c.}/\eta_c = \rho_c U_c (4A_{u.c.}/L_{u.c.})/\eta_c \tag{3}$$

where ρ_c is the density of the continuous phase, U_c is the average velocity of the continuous phase in the upper channel, $d_{eq,u.c.}$ is the equivalent diameter of the upper channel, $A_{u.c.}$ is the cross-sectional area of the upper channel, $L_{u.c.}$ is the wetted perimeter of the upper channel, and η_c is the viscosity of the continuous phase. The estimated U_c ranged between 21 and 178 mm/s. The calculated Re_c of 20 to 173 demonstrates that the cross-flowing continuous phase was in a laminar state. The shear stress (τ_c) caused by laminar cross-flow of the continuous phase at the MC array chip surface can be calculated by:

$$\tau_c = 3Q_c\eta_c/(2h_{u.c.}^2 w_{u.c.}) \tag{4}$$

where $h_{u.c.}$ is the depth of the upper channel and $w_{u.c.}$ is the width of the upper channel. The calculated τ_c ranged between 0.07 and 0.6 Pa and was less than the shear stress at the membrane surface (typically 1–30 Pa) applied during membrane emulsification [36]. The τ_c values at the plate surface strongly suggest that droplet detachment from the slot outlets (Figure 4) is not influenced by the shear stress caused by the cross-flowing continuous phase.

4.2 Droplet generation via an asymmetric MC

The micrographs in Figure 4 present a typical droplet detachment from a slot outlet at the lowest Q_d of 0.15 l/h and at a Q_c of 1.2 l/h. Although droplet generation via an asymmetric MC involves expansion and detachment processes [38], there is a difficulty in observing the expansion process that occurs in a microslot during experiments. During the detachment process, the dispersed phase that has reached the slot outlet starts to expand into the upper channel in the presence of the cross-flowing continuous phase. The starting point of the detachment process is defined as the moment when the tip of the dispersed phase reaches the slot outlet. The movement of the dispersed phase expanding in the upper channel cannot be observed until the expanding dispersed phase becomes wider than the narrow side of the slot outlet (Figure 4A,B). Our previous computational fluid dynamics (CFD) results demonstrated that this period usually takes up less than 10% of the total detachment time [38]. The dispersed phase rapidly expanded within 10 ms (Figure 4B–E), followed by instantaneous pinch-off of the neck formed in the slot, terminating the detachment process. Droplet generation, including the detachment process, was repeated

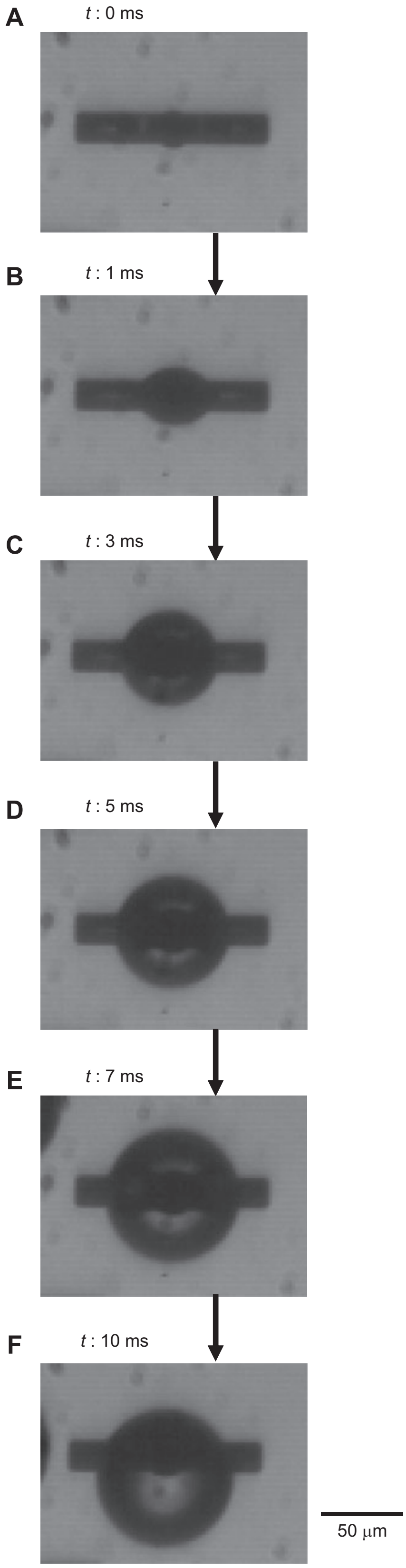

Figure 4 Sequential micrographs of the droplet detachment process from a slot outlet. *t* denotes time. The continuous phase flows from top to bottom in the micrographs.

periodically. A generated droplet with a diameter of approximately 85 µm immediately moved away from the slot outlet, unlike the weak adhesion to the plate surface of freshly generated soybean oil droplets stabilized by Tween-20 with a similar diameter [31]. This difference is attributable to the *n*-tetradecane being more hydrophobic and the *n*-tetradecane-containing system having a density difference between the two phases approximately three times greater than the soybean oil-containing system.

4.3 Influence of the volumetric flow rate of the dispersed phase

To investigate the influence of Q_d on emulsion production using the WMS10 chip, we applied Q_d over the range of 0.15 to 1.4 l/h. The Q_d/Q_d ratio was fixed at 0.13; the volume fraction of the dispersed phase (ϕ_d) was 11%. A typical micrograph of oil droplet generation from the slot outlets at the lowest Q_d of 0.15 l/h is presented in Figure 5A. Each active asymmetric MC generated uniformly sized droplets throughout four asymmetric MC arrays. The generated droplets had a d_{av} of 86.8 µm and a CV of 1.2% (Figure 5B), demonstrating high monodispersity of the resultant O/W emulsion. In MC emulsification, the resultant droplet size depends primarily on the narrow-side length ($w_{n,slot}$) of the slot as well as depending somewhat on the ratio of the slot depth (h_{slot}) to $w_{n,slot}$ [28]. Typical $d_{av}/w_{n,slot}$ values are between 3 and 4 [11, 31], depending on the slot dimensions. The $d_{av}/w_{n,slot}$ values increase when the viscosity ratio, defined as η_d/η_c, is below a critical value of ~10 for symmetric MCs [40] and 3–4 for asymmetric MCs [43]. The η_d/η_c value was 2.7 in this study, and the droplet/slot size ratio ($d_{av}/w_{n,slot}$) obtained using the WMS10 plate was 5.1. We thus consider that the d_{av} value of the generated oil droplets is reasonable.

The influence of Q_d on the d_{av} and CV of the O/W emulsions produced using the WMS10 chip is presented in Figure 6A. Their d_{av} values (87 µm) hardly depend on Q_d, and their CV was < 2% over the Q_d range applied here. This demonstrates that the asymmetric MC array chip developed in this study is capable of producing monodisperse emulsions at droplet productivities over 1 l/h, which has not yet been achieved by other microfluidic emulsification devices. Further increases in Q_d caused droplet plugging near the outlet of the upper channel. The influence of Q_d on the droplet generation frequency per MC array chip (*f*) is also presented in Figure 6B. *f* can be estimated by:

$$f = Q_d / V_{av} = 6Q_d / \pi d_{av}^3 \quad (5)$$

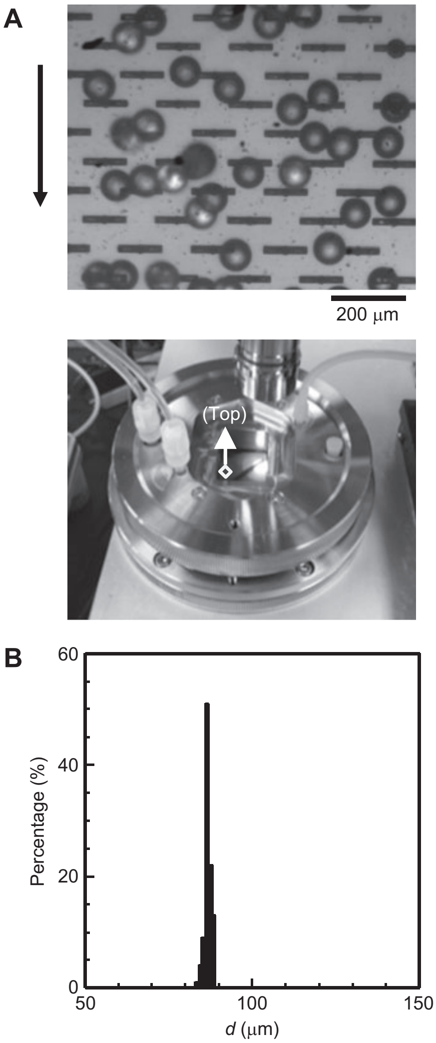

Figure 5 (A) Typical droplet generation result at a dispersed phase volumetric flow rate (Q_d) of 0.15 l/h. (Top) Optical micrograph of the generation of oil droplets via asymmetric MCs. The arrow denotes the direction of the cross-flowing continuous phase. (Bottom) Top view of the module during MC emulsification. (B) Size distribution of the oil droplets generated using the WMS10 chip.

where V_{av} is the average droplet volume. f increased almost linearly with increasing Q_d, achieving a maximum value of 3.8×10^9 h^{-1} (1.1×10^6 s^{-1}). If droplets were generated from all of the asymmetric MCs, the droplet generation frequency per asymmetric MC (f_{MC}) could be simply calculated as 42.8 s^{-1}. During MC emulsification, we observed that all of the asymmetric MCs generated uniformly sized oil droplets with f_{MC} of approximately 40 s^{-1}. The preceding comparison regarding f_{MC} proves that our experimental result is valid. The dispersed-phase flux (J_d) is a useful indicator of droplet productivity via MC arrays as well as microporous membranes. J_d is defined as:

$$J_d = Q_d / A_{MCA} \quad (6)$$

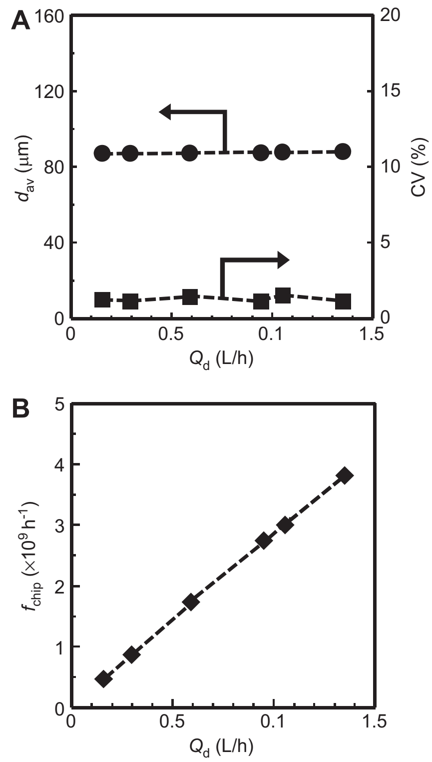

Figure 6 (A) Influence of Q_d on the average droplet diameter (d_{av}) and coefficient of variation (CV) of the O/W emulsions produced using the WMS10 chip. (B) Influence of Q_d on the droplet generation frequency per chip (f).

where A_{MCA} is the total area of the MC arrays. The maximum Q_d of 1.4 l/h is equivalent to J_d of 2800 l/(m² h). The maximum J_d applied in this study was similar to the critical J_d [2700 l/(m² h)] for producing uniformly sized *n*-tetradecane oil droplets with d_{av} of around 30 μm using a standard size asymmetric MC array chip (WMS1-3) [32].

As presented in this section, we realized the mass production of uniformly sized droplets at a maximum Q_d of 1.4 l/h by MC emulsification. The maximum productivity of monodisperse emulsions in this study was 11.2 l/h. This droplet productivity corresponds to a droplet throughput capacity of 12.2 t/year. Actual droplet productivity per year may become somewhat lower owing to the necessity of regularly cleaning the module and WMS10 chip. This droplet production scale is considered to permit a minimum industrial-scale production of monodisperse emulsions as a template for monodisperse high-tech micro-materials (e.g., highly functional polymer microparticles). Some important industrial applications require the mass production of uniformly sized droplets with several microns. We expect that development of large MC emulsification chips consisting of smaller asymmetric MCs could achieve production scales of these droplets higher than the current MC emulsification chips [37]. Droplet productivity could be easily increased by parallelizing the modules, equipping each with a WMS10 chip. In a large MC emulsification device (Figure 3), both liquid phases are delivered from vessels, not from syringes, thereby indicating that only one vessel is needed to deliver a liquid phase to multiple modules over a long period of time. An alternative approach for increasing droplet productivity is to further scale up the asymmetric MC array chip. As mentioned in an earlier section, a 5-in. (127-mm) diameter wafer was used for fabricating the WMS10 chip. The fabrication of an asymmetric MC array wafer could realize the production of uniformly sized droplets at Q_d over 10 l/h and monodisperse emulsions with a throughput of over 100 l/h.

5 Conclusion

The large MC emulsification device developed in this study realized the mass production of uniformly sized droplets with d_{av} of 87 μm and CV below 2% with a productivity exceeding 1 l/h. Droplet generation via asymmetric MCs was not influenced by the cross-flowing continuous phase because of low shear stress at the chip surface and remarkably rapid droplet detachment. The *n*-tetradecane droplets generated could readily move away from the slot outlets, differing from the motion of the soybean oil droplets stabilized by the same surfactant [31]. This difference is attributable to the higher hydrophobicity of *n*-tetradecane and the higher density difference of the O/W system containing *n*-tetradecane. Use of the large MC emulsification device also demonstrated the practical advantage of mass producing uniformly sized droplets whose d_{av} and CV barely depend on Q_d. Successful MC emulsification using large vessels for supplying both phases suggests the feasibility of long-term mass production of uniformly sized droplets. Large MC emulsification devices with liter-scale droplet productivity per hour are expected to find application in the industrial-scale production of monodisperse dispersions containing droplets, microparticles, and microcapsules.

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