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SHORT COMMUNICATION

Microchannel emulsification for mass production of uniform fine droplets: integration of microchannel arrays on a chip

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Abstract We present a novel microchannel emulsification (MCE) system for mass-producing uniform fine droplets. A 60 × 60-mm MCE chip made of single-crystal silicon has 14 microchannel (MC) arrays and 1.2×10^4 MCs, and each MC array consists of many parallel MCs and a terrace. A holder with two inlet through-holes and one outlet through-hole was also developed for simply infusing each liquid and collecting emulsion products. The MCE chip was sealed well by physically attaching it to a flat glass plate in the holder during emulsification. Uniform fine droplets of soybean oil with an average diameter of 10 μm were reliably generated from all the MC arrays. The size of the resultant fine droplets was almost independent of the dispersed-phase flow rate below a critical value. The continuous-phase flow rate was unimportant for both the droplet generation and the droplet size. The MCE chip enabled mass-producing uniform fine droplets at 1.5 ml h^{-1} and 1.9×10^9 h^{-1}, which could be further increased using a dispersed phase of low viscosity.

Keywords Microchannel emulsification · Fine droplet · Microchannel array · Scale up · Silicon chip

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1 Introduction

Novel microfluidic techniques for producing emulsions have been proposed over the last decade. Major advantages of microfluidic techniques include the generation of uniform emulsion droplets with a coefficient of variation (CV) of typically less than 5% and the precise control of droplet size and monodispersity. Typical geometric designs of microfluidic droplet-generation chips are microchannel (MC) arrays with a terrace (Kawakatsu et al. 1997, 1999), T- and Y-junctions (Thorsen et al. 2001; Nishisako et al. 2002; Steegmans et al. 2009), flow-focusing geometries (Anna et al. 2003; Takeuchi et al. 2005; Yobas et al. 2006), and co-flowing systems (Utada et al. 2005, 2008). The microfluidic technique using MC arrays with a terrace is called microchannel emulsification (MCE). In an MCE chip, part of the dispersed phase with a flat shape in a terrace expands into a deep channel; the dispersed phase in the channel then spontaneously transforms into a droplet, which is driven by the Laplace pressure difference (Sugiura et al. 2001a). Droplet generation for MCE is controlled by only the dispersed-phase flow, since the gentle continuous-phase flow used to collect the resultant droplets is negligible in such droplet generation. Moreover, the size and monodispersity of droplets generated by MCE are not sensitive to the dispersed-phase velocity below the critical value (Sugiura et al. 2002a), which is suitable for readily performing emulsification. The current MCE chips enable generating uniform (fine) droplets of 1–100 μm (Sugiura et al. 2002b; Kobayashi et al. 2007). In the other microfluidic techniques, droplet generation is basically driven by the rapidly flowing continuous phase, indicating that the flow of both phases has to be precisely controlled to successfully performing emulsification. Uniform droplets generated using these microfluidic techniques are typically 10–500 μm.

Uniform droplets generated by microfluidic techniques are useful templates for producing uniform microspheres and microcapsules (Sugiura et al. 2001b; Nakagawa et al. 2004; Utada et al. 2005; Li et al. 2008). In particular, typical applications of uniform fine droplets include fine microspheres as packings for chromatography columns (Nakashima et al. 2000) and fine microspheres and microcapsules as carriers for drug-delivery systems (Wei et al. 2008a, b). However, microfluidic chips usually have a very low throughput in terms of the volume flow rate of the dispersed phase (Q_d), since droplets are usually generated from one pair of short MC arrays for MCE or a single MC for the other microfluidic techniques. For instance, uniform fine (10 μm) droplets of triglyceride oil are generated using a current microfluidic chip at Q_d of $<10^{-2}$ ml h^{-1} ($<10^3$ droplets s^{-1}) for a flow-focusing geometry (Xu and Nakajima 2004) and of $<10^{-1}$ mL h^{-1} for an existing MCE chip. This throughput would be difficult to satisfy even in laboratory-scale production. Thus, the scaling up of microfluidic emulsification systems is vital for increasing the number of MCs, although a few research groups have reported on mass production of droplets by microfluidic techniques over the last half decade (Kawai et al. 2003; Kobayashi et al. 2005; Nishisako and Torii 2008). Although the large microfluidic emulsification systems enabled mass production of uniform droplets with an average size of 30 μm (MCE) or 95 μm (cross-junctions), large microfluidic emulsification systems for uniform fine droplets have not yet reported. In principle, smaller cross-junctions can be parallelized for producing uniform fine droplet. However, it is expected that it becomes difficult to precisely control the flows of the two phases and to prevent the clogging by small debris as the MC characteristic size decreases. In MCE, MCE chips consisting of microfabricated asymmetric through-holes (Kobayashi et al. 2005) are the most promising for mass-producing uniform droplets. The asymmetric through-holes must be miniaturized to produce fine droplets. However, it is not easy to precisely fabricate asymmetric through-holes with a cross-sectional size of <5 μm, even using cutting-edge microfabrication technology. Even if MCE chips with the fine asymmetric through-holes were obtained, they would not be tolerable enough to handle during MCE.

Here we present a new MCE chip consisting of integrated MC arrays, which is intended for reliably mass-producing uniform fine droplets. The MC geometry selected here is an MC array consisting of parallel microgrooves and a terrace. We also investigated droplet generation in the new MCE chip and the throughput capacity of uniform fine droplets for such a chip. The silicon MCE chip consisting of shallow microgrooves and terraces and deep channels is strong enough for handling. A new holder with two inlet through-holes and one outlet through-hole was also designed and used for simple MCE operation. Since an MCE chip only physically attaches to a transparent plate in the module without chemical bonding, the chip can be detached from the plate when necessary. This feature is practically advantageous when tiny particles that have entered the MCE chip disrupts droplet generation.

2 Experimental

2.1 Chip and module for MCE

A 60 × 60-mm MCE chip containing 14 MC arrays was designed for this study (Fig. 1a). Each parallel MC array (length 34 mm) consisted of 850 MCs and terraces positioned at the inlet and outlet (Fig. 1b); 11,900 MCs were positioned on the chip. The steps depicted in Fig. 1b were designed to be much deeper than MCs to enhance the dispersibility of the generated droplets. A channel with two through-holes was located at the outlet side of each MC array (Fig. 1a). In this channel, a continuous phase was infused from the inlet through-hole, and an emulsion was collected from the outlet through-hole. A channel for supplying a dispersed phase was located at the inlet side of each MC array (Fig. 1a). All the channels were connected at side edges of the chip, which opened to channels outside the chip. This geometry also contributes to reducing the chip size, since the channel formed outside the chip enables forming a laminar dispersed-phase flow. As a result, the MCE chip designed here increased the number of MCs by 17 times that of the previous crossflow-type MCE chip (Kawakatsu et al. 1999).

MC arrays and deeper channels were fabricated on a single-crystal silicon substrate with a thickness of 0.5 mm via two steps of anisotropic wet etching (Kikuchi et al. 1992). Through-holes with a diameter of 1.0 mm were fabricated in an MCE chip by sandblast etching. The MC cross section and terrace length in the fabricated MC arrays were highly uniform, which is essential for generating uniform droplets by MCE. The fabricated long MCs had a depth of 2 μm, a width of 10 μm, and a length of 104 μm; the terraces fabricated at the MC outlets had a depth of 2 μm and a length of 19 μm. These MC and terrace dimensions were determined to stably generate uniform fine droplets (Sugiura et al. 2002b, c). The step depth was 100 μm.

An MCE module designed for this study is schematically presented in Fig. 2. This module has a diameter of 15 cm and a height of 2.4 cm. The holder consists of a bottom lid, an artificial quartz glass plate, and an upper cover plate. The bottom lid and upper cover plate were made of stainless steel (Japanese Industrial Standard, SUS 304) and were fabricated by conventional milling. Fluoro-

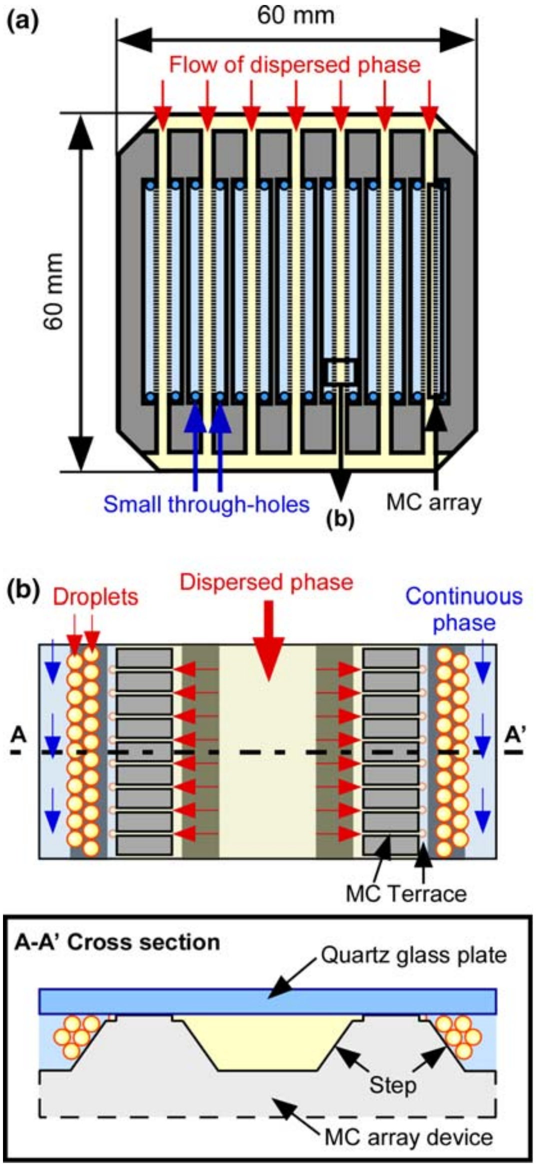

Fig. 1 Chip geometries for mass producing uniform fine droplets. **a** Schematic top view of an MCE chip consisting of 14 MC arrays. *Solid circles* denote the inlet through-holes for the continuous-phase liquid and the outlet through-holes for the emulsion product. **b** Schematic top and cross-sectional views of droplet generation via MC arrays on the chip

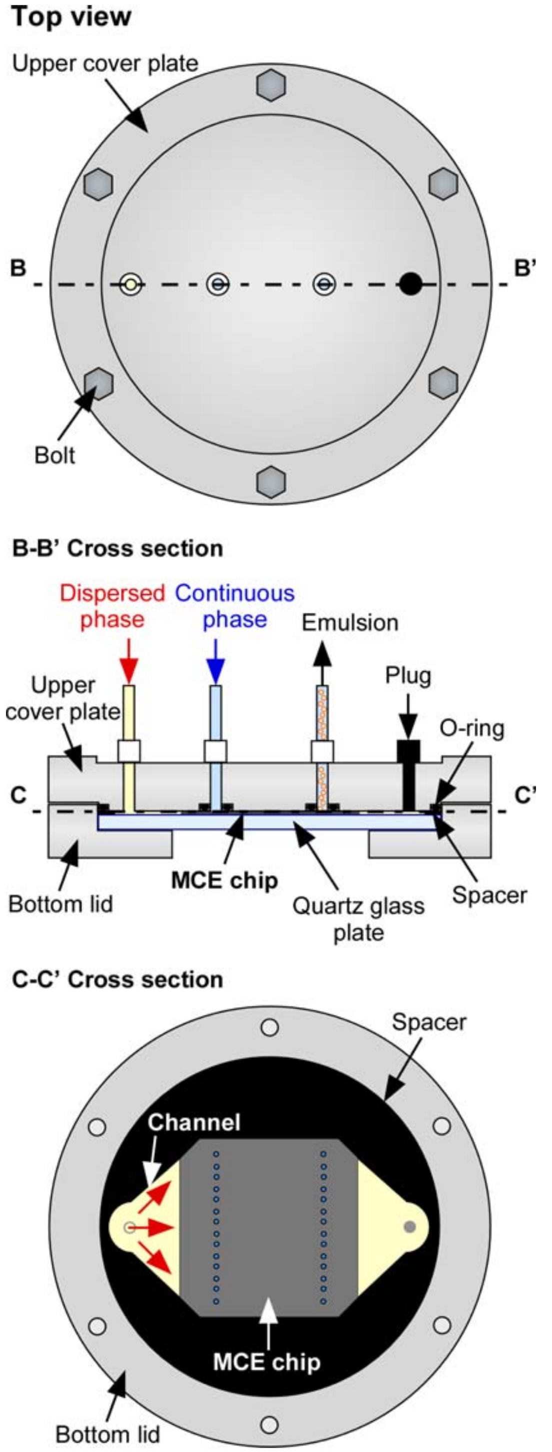

Fig. 2 An MCE module for mass producing uniform fine droplets. *Top*: Schematic top view of the module equipped with the MCE chip. *Middle*: Schematic cross-sectional view of the module (B–B′ cross section). *Bottom*: Schematic top view of a planar geometry with the chip and channels for the dispersed phase (C–C′ cross section)

rubber o-rings and a spacer are also attached inside the holder for appropriate separation of two liquids. The bottom lid, equipped with the glass plate and the spacer, forms a reservoir where an MCE chip is mounted. The large through-hole in the bottom lid also allows direct microscopic observations of the liquid flow inside and near the MC arrays. The upper cover plate has two inside through-holes and two outside through-holes (middle of Fig. 2), which are used for infusing two liquids and for collecting the resultant emulsion. A dispersed phase is infused from one of the outside through-holes and reaches a channel outside the chip (bottom of Fig. 2). The liquid then advances through the channel and reaches the side edge of a channel inside the chip. A continuous phase is infused from one of the inside through-holes and reaches the inlet through-holes on the chip. An emulsion product comes out from the outlet through-holes on the chip and reaches the outlet of another inside through-hole. It is important to note that each fluid is simply supplied to the module using only a tube and a pump, and that only three tubes are required for conducting MCE using the module.

2.2 Materials

We chose an oil-in-water (O/W) emulsion system, which has been used as the model for MCE (Kobayashi et al. 2007, 2008). The model system is advantageous in that droplet productivity for the MCE chip developed here easily compares with that of the previous MCE chips. Refined soybean oil (Wako Pure Chemical Ind., Osaka, Japan; dynamic viscosity $\eta = 50.4$ mPa s at 298 K) was used as the dispersed phase. A Milli-Q water solution containing 1.0 wt% sodium dodecyl sulfate (Wako Pure Chemical Ind.; $\eta = 0.98$ mPa s) was used as the continuous phase. The equilibrium interfacial tension between the two phases was 4.5 mN m^{-1}.

2.3 Emulsification procedure and analysis

Hydrophilic MC arrays are suitable for generating uniform O/W emulsion droplets in MCE (Kawakatsu et al. 1997; Kobayashi et al. 2008). The MCE chip and the glass plate were subjected to plasma oxidation in a plasma reactor (PR41, Yamato Science Co. Ltd., Tokyo, Japan) to form a hydrophilic silicon dioxide layer on their surfaces before the first usage. The assembled module (Fig. 2a), which was filled with the continuous phase, was mounted on the stage of a custom-made frame. The two liquids were supplied to the module using two syringe pumps (Model 11, Harvard Apparatus Inc., MA, USA). Each liquid filled a glass syringe mounted on the syringe pump. During MCE operation, Q_d was controlled from 0.5 to 2.0 ml h^{-1}, and the flow rate of the continuous phase (Q_c) was fixed at 10.0 ml h^{-1}. The Reynolds number of the continuous phase (Re_c) that flows in each channel was calculated to be 0.19, suggesting a laminar flow of the continuous phase. It is necessary to mention that the back pressure from collection parts was kept constant during the operation. The outlet of a collection tube was fixed to be the same height as the MCE chip mounted in the module. The top surface of an emulsion collected in a vessel was also kept lower than the tube outlet. Droplet generation via an MC array was monitored using a metallographic microscope (MS-511B, Seiwa Kougaku Seisakusho Ltd., Tokyo, Japan) equipped with the frame and a CCD camera (KP-C550, Hitachi, Ltd., Tokyo, Japan) connected to the microscope. The MCE chip separated from the glass plate was cleaned by the procedure reported in the literature (Kobayashi et al. 2008) and then stored in 0.1 M nitric acid before the next usage. The size distribution of the emulsion droplets was determined using a laser diffraction particle size analyzer (Coulter LS 13 320, Beckman Coulter Ltd., CA, USA). The reported droplet-size distributions were calculated from the average of at least two measurements.

3 Results and discussion

We first investigated the flow characteristics of two liquids on an MCE chip developed in this study. Figure 3a–d depicts the typical droplet generation behaviors using the MCE chip. At an initial Q_d of 0.5 ml h^{-1}, the dispersed phase entered seven parallel channels (between each two MC arrays) from the side edge of the chip. Next, the oil–water interface advanced through the channels until they were filled with the dispersed phase. The dispersed phase that reached the inlet of each MC array passed through MCs and expanded in a terrace with a disklike shape (Fig. 3a). The dispersed phase that passed through the outlet of the MC array transformed into droplets. This transformation was dominated by the difference in Laplace pressures of the oil–water interface between the terrace and the deep channel (Sugiura et al. 2001a). The droplet generation process took place periodically, and uniform oil droplets were generated via each MC array (Fig. 3a). The droplets were swept away from the outlet of each MC array by the cross-flowing continuous phase. Figure 3e demonstrates that emulsions were produced from all the MC arrays and flowed toward the outlet through-holes. As demonstrated above, the flow of the two phases and the droplet generation process were appropriately controlled during MCE using the chip consisting of integrated MC arrays.

Figure 4a (top) depicts the effect of Q_d on the Sauter diameter ($d_{3,2}$) of the generated droplets and the span of their size distribution (span $= d_{50}/(d_{90} - d_{10})$). At the lowest Q_d of 0.5 ml h^{-1}, the resultant droplets had a $d_{3,2}$ of 10.6 μm, a span of 0.165, and a coefficient of variation of <5% (estimated by image analysis using WinRoof software ver. 5.6, Mitani Co., Fukui, Japan). They also had a monomodal and very narrow size distribution (Fig. 4b). These results demonstrate that an emulsion with uniform fine droplets was obtained using the MCE chip. When Q_d was increased stepwise, monodisperse emulsions with spans of 0.165–0.200 were produced at Q_d of 1.5 ml h^{-1} or less. In this Q_d range, $d_{3,2}$ of the resultant droplets ranged from 10.6 to 11.6 μm and slightly increased with increasing Q_d. Additionally, microscopic observations during MCE confirmed that the resultant droplet size hardly changed between Q_c of 0 and 10.0 ml h^{-1}, corresponding

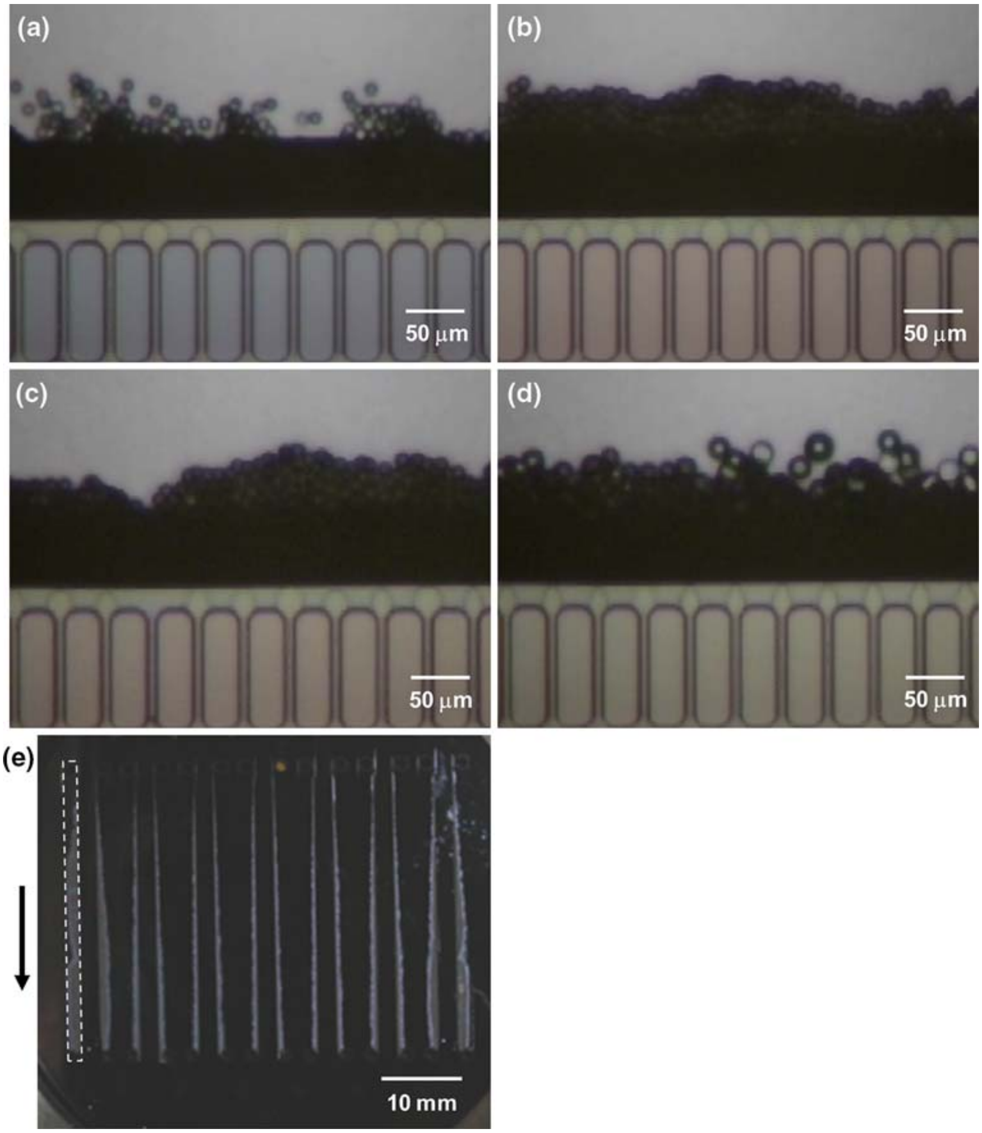

Fig. 3 Mass production of uniform fine emulsion droplets using the MCE chip. **a–d** Optical micrographs of generating fine oil droplets at the flow rates of the dispersed phase (Q_d) of 0.5 m; h^{-1} (**a**), 1.0 ml h^{-1} (**b**), 1.5 ml h^{-1} (**c**), and 2.0 ml h^{-1} (**d**). **e** Photograph of mass-producing an O/W emulsion with uniform fine droplets using an MCE chip with 14 MC arrays. Q_d was 0.5 ml h^{-1} in this case

to Re_c of 0 and 0.19. Kawakatsu et al. (1999) reported the size of the droplets with an average diameter of about 15 μm generated by MCE was independent of Q_c in a Re_c range of 0–16, supporting the preceding result. In contrast, at Q_d of 1.75 and 2.0 ml h^{-1}, the span value dramatically increased to 0.607 and the droplet size distribution became wider, especially toward the large droplet size area (Fig. 3c, d). The $d_{3,2}$ value also greatly increased at Q_d of 2.0 ml h^{-1}. As a result, the MCE chip developed in this study enabled the production of O/W emulsions with uniform fine droplets at a critical Q_d of 1.5 ml h^{-1}, which considerably exceeds a maximum Q_d (5×10^{-3} ml h^{-1}) for the previously designed MCE chip (Kawakatsu et al. 2000). The new MCE chip can effectively reduce the operation time necessary to obtain the required amount of emulsion products, which is advantageous for unstable emulsion droplets and emulsions containing sensitive components. In principle, the MCE chip is also applicable to mass production of W/O emulsions with uniform fine droplets by the surface modification of silicon MC arrays.

The droplet production rate (v_{chip}) of the MCE chip is also indicated in Fig. 4a (bottom). The v_{chip} increased with increasing Q_d in the range of 1.5 ml h^{-1} or less, whereas a further increase in Q_d lowered the v_{chip}. Uniform fine droplets were generated at a maximum v_{chip} of 1.86×10^9 h^{-1}, which corresponds to 5.17×10^5 s^{-1}. The v_{chip} values below the critical Q_d were fitted well by the following equation.

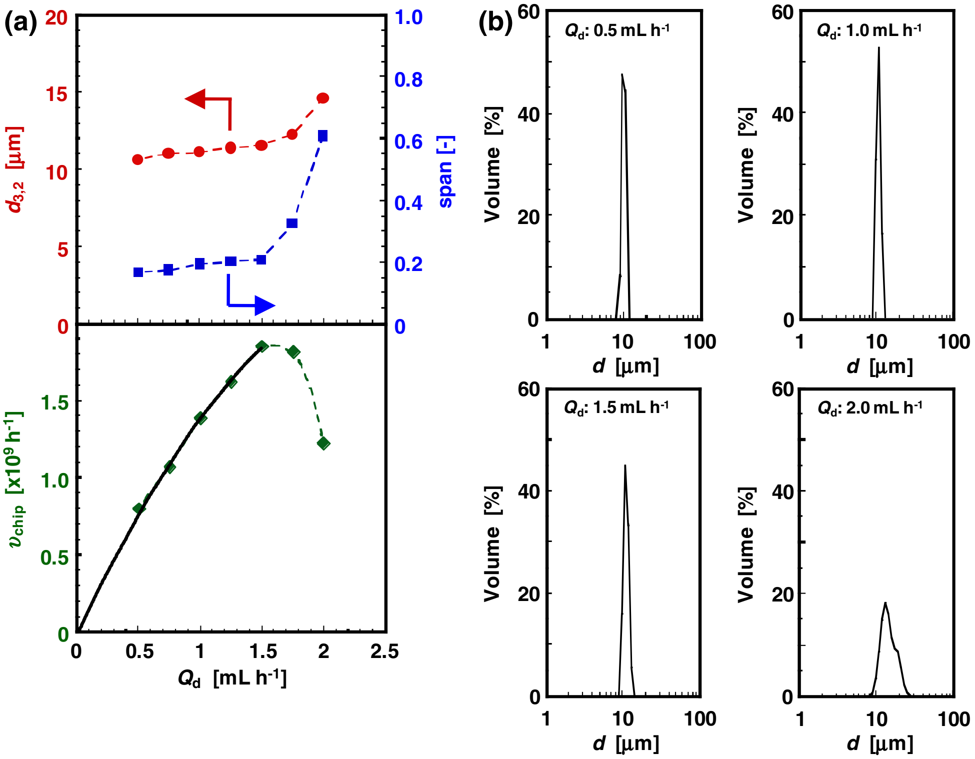

Fig. 4 **a** Effect of Q_d on the Sauter droplet diameter ($d_{3,2}$), the span of the droplet diameters, and the droplet production rate of the MCE chip (v_{chip}). The *solid curve* in the bottom graph is expressed by Eq. 2 ($R^2 = 0.9973$). **b** Size distributions of the fine oil droplets generated using the MCE chip. Here, d is the droplet diameter

$$v_{chip} = 2 \times 10^9 Q_d - 6 \times 10^8 Q_d^2 \qquad (1)$$

Since almost all the MCs generated uniform fine droplets at Q_d of 1.5 ml h^{-1} where v_{chip} reached the maximum value, the droplet generation production rate from each MC (v_{MC}) was calculated to be 43.4 s^{-1}. Xu and Nakajima reported that a microfluidic chip with one flow-focusing geometry had the capacity to generate uniform fine droplets of soybean oil at a maximum v_{chip} of 200 s^{-1} (Xu and Nakajima 2004). Thus, the MCE chip with integrated MC arrays was demonstrated to be a high-performance microfluidic chip for mass-producing uniform fine droplets. We also note that the maximum v_{chip} for the MCE chip depends greatly on dispersed-phase viscosity and can be further increased using a dispersed phase of low viscosity (e.g., alkanes) by at least one order of magnitude.

Over the critical Q_d, some of the dispersed phase that passed through an MC array remarkably expanded instead of successfully generating droplets, suggesting that the flow state of the dispersed phase was affected by the dispersed-phase velocity inside the MC. Sugiura et al. revealed that the droplet generation characteristics are relevant to the capillary number of the dispersed phase that flows inside an MC. The capillary number, defined as the balance between viscous force and interfacial force, can be estimated using the following equation:

$$Ca = \frac{\eta_d U_d}{\gamma} = \frac{\eta_d}{\gamma} \cdot \frac{2.8 \times 10^{-10} Q_d}{A} \qquad (2)$$

where η_d is the dynamic viscosity of the dispersed phase (Pa s), U_d is the characteristic velocity of the dispersed phase (m s^{-1}), A is the total cross-sectional area of MCs (m^2), and γ is the interfacial tension between the two phases (N m^{-1}). Ca at the critical Q_d of 1.5 ml h^{-1} was 0.019, which is reasonable since it is the same order of magnitude as the critical Ca obtained using the previous MCE chip for generating fine droplets (Sugiura et al. 2002a). Interfacial force is dominant below the critical Ca, allowing the generation of uniform fine droplets based on spontaneous transformation of the oil–water interface due to the Laplace pressure difference. In contrast, the effect of viscous force becomes significant over the critical Ca, causing the generation of non-uniform larger droplets due to the quasi-laminar flow of the dispersed phase. Analysis of the flow state of the dispersed phase using a dimensionless number demonstrated that droplet productivity for each MC was successfully maintained even after integrating MC arrays on a chip.

The MCE chip developed here has a sufficient capacity for mass-producing uniform fine droplets on a laboratory scale, whereas their production scale must be increased further to attain practical-scale production. Additionally, increasing the number of MCs on an MCE chip can be achieved using larger substrates. The MCE chip used in this study was fabricated on a 3-inch silicon substrate. If an MCE chip is fabricated on a larger silicon substrate (e.g., 5-inch in diameter), 32 MC arrays and 5.8 × 10^4 MCs can be integrated on a 100 × 100-mm chip while maintaining the dimensions of the MC arrays except for their length. Key points of successful emulsification using this MCE chip are uniform attachment of the large chip onto a glass plate and precise control of the flow of each phase inside a module. Although piling up MCE chips is also a possible scaling-up approach, a major drawback of this approach is the difficulty in monitoring MCs in each piled-up chip. Parallelization of MCE chips would be preferable as a further scaling-up approach.

4 Conclusion

This article has demonstrated a simple and reliable technique for mass-producing uniform fine emulsion droplets using a new MCE chip consisting of integrated MC arrays, fabricated by a commonly used etching technique. Simple operation of MCE was realized using a new holder, which needs only one tube and one pump for each liquid. The MCE module developed here also enabled the stable control of the flow of the two phases on the MCE chip. The MCE chip was capable of producing monodisperse emulsions with fine droplets of soybean oil with $d_{3,2}$ of 10 μm at a Q_{d} of 1.5 ml h^{-1}, achieving a sufficient throughput to mass-produce uniform fine droplets at least on a laboratory scale. The emulsification technique using the MCE chip is also considered promising from a practical point of view because the $d_{3,2}$ and span values of the resultant droplets were not so sensitive to Q_{d} below a critical value. Although the MCE module must be further scaled up for practical-scale production, MCE is believed to be a versatile technique for mass-producing uniform fine dispersions including emulsion droplets, microparticles, and microcapsules.

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