

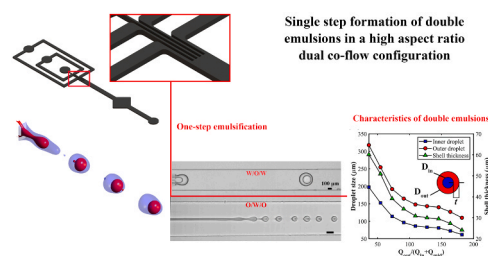
Microfluidic preparation of double emulsions using a high aspect ratio double co-flow device

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GRAPHICAL ABSTRACT



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ABSTRACT

An innovative microfluidic device for one-step production of W/O/W and O/W/O double emulsions is introduced. The proposed geometry inspired by a combination of single and two-step methods consists of two same-level co-flow configurations with a high aspect ratio of height to the channel's width. The designed geometry offers a mechanism to generate double-emulsion drops without requiring regular partial surface modification methods. It offers a simple, robust, and permanent method to fabricate compound droplets in a profoundly controlled manner. Due to the high aspect ratio of the designed geometry, the inner phase jet stream remains enclosed to the middle phase jet, which prevents it from encountering microchannel walls. Hence, the wettability of the channels' surface does not influence the core droplet, implying the double emulsion formation can be achieved without requiring partial wettability treatment. The effects of continuous phase flow rate on the double emulsion size and formation frequency are experimentally investigated. The proposed microfluidic device is able to fabricate relatively high monodispersed and high throughput double emulsions successfully, i.e., the generation frequency can be reached up to 350 Hz while the monodispersity remains below 6%.

1. Introduction

The liquid in a liquid structure commonly named a double emulsion [1] was first reported in 1925 [2]. Encapsulation of core material inside an unsolvable shell and generation of core/shell microcapsules has

attracted a lot of curiosity due to the ability of the shell to act as a temporary or permanent block and protecting layer for the core material [3,4]. Both oil-in-water in-oil (O/W/O) and water-in-oil-in-water (W/O/W) structures have possible applications in controlled drug-delivery [5], food science [6], living cell encapsulations [7],

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cosmetics industries [8], and pharmaceutical [9].

There are various methods categorized into two main one-step and two-step emulsification for the creation of double emulsions. Two distinct combinations of fundamental geometries, including cross-flow, flow-focusing, and co-flowing, are typically employed in the so-called two-step method. Two sequential T-junctions [10,11], flow-focusing [12,13], co-flowing [14,15], and various combinations of mentioned geometries [16–18] are the important successions of the so-called two-step methods. Generally speaking, in one-step method, the control on the formation of double emulsions is more facile, which results in the formation of a wider range of size and frequency of double emulsions [6]. Besides, the partial wettability of the surface is minimal in one-step methods, making them ideal for the long-term droplet generation [7].

The wettability patterning of the channel wall performs a vital role in the prospering generation of double emulsions in the two-step configuration. Regarding a proper material is essential for the production of droplets, i.e., hydrophobic materials are suited for the generation of aqueous droplets, while hydrophilic materials are appropriate for creating organic droplets [10]. For composing double emulsions, both types of surfaces are essential, and the microchannel walls must be partially manipulated to obtain the proper wettability configuration.

In a so-called one-step method, compound droplets are created in a single step. Ordinarily, innermost and intermediate phases are introduced through the same direction into a microcapillary tube. Simultaneously, the external fluid is injected into the outer coaxial zone from the opposing direction [20]. The compound droplets are formed by implementing proper shear forces from intermediate and outer phases to the innermost and outermost interfaces, respectively [21].

In the one-step method, the interface of the jet is unstable based on the Rayleigh-Plateau instability, following in the breakup of the liquid filament into drops [22]. The instability can be succeeded by restricting the interface close to the channel surface while strengthening the effect of the inertial forces compared to the interfacial forces [23]. Therefore, jets can be produced in a core-sheath type and preserved in a microfluidic channel [24].

Generally, one-step double emulsion preparation requires a minimal surface modification compared to two-step emulsification. Nevertheless, in all capillary-based one-step devices, hydrophobic wall treatment for the external face of the microcapillary injecting inner fluid is essential for the succeeding formation of W/O/W emulsions [20,25,26]. This is due to the prevention of the innermost aqueous fluid from adhering to the external side of the capillary. OTS [21] and OTMS [27] are two common materials for making glass capillaries hydrophobic. However, the main disadvantage of this method is the relatively small hydrophobic duration of the coated surface. Thus, this procedure should be replicated after each set of tests, requiring additional effort to remove and replace glass capillaries.

Almost all microfluidic devices for the preparation of single or multiple emulsions have a relatively small microchannel height compared to the width of it. For example, references [1–5], which are among the most famous works in the field of double emulsion preparation clearly prove this claim. Due to the smaller size of the height of the microchannel compared to the width of it, droplets will have contact with the upper and lower walls of the microchannel during the process of droplet formation. So, in order to have aqueous droplets, the walls should be hydrophobic, while for the fabrication of oil droplets, the channels should be treated in a way to be hydrophilic. Hence, one needs to treat the walls partially to achieve the desired combination of hydrophobic and hydrophilic combinations. This is a relatively complicated procedure and should be replicated periodically since after some times, the wall treatment effect is diminished.

In this research, inspiring by the precise and convenient fabrication procedure of soft lithography technique and minimal need to the surface wettability modification of single-step methods, we propose a novel double co-flow channel-based geometry to produce O/W/O double emulsions without requiring any usual surface modification. We also

generated W/O/W emulsions employing the PVA deposition procedure for making the whole channel hydrophilic. This indicates that the proposed device can be fabricated using hydrophobic substrates like PDMS to produce O/W/O and hydrophilic surfaces like glass to produce W/O/W emulsions without requiring any surface modification. We also explored the impacts of outer phase flow rate on the morphology and characteristics of double emulsions.

2. Geometric model

The schematic view of the existing microfluidic device geometry consists of two same-level co-flow rectangular channels is demonstrated in Fig. 1a. The presented geometry comprises three same distinct axes rectangular microchannel. Channels correspond to the introduction of inner and middle phases have a 40 μm fixed width, those correspond to the injection of continuous phase have a 60 μm fixed width, and the fabricated device has a 120 μm constant height, which provides a high aspect ratio of five for the central channel, making the jet of the innermost phase enclosed to the forming jet of the intermediate phase and prevents adhesion to the wall of the microchannel.

To eliminate the effects of outlet on the generation of double emulsions, the channel length is considered to be around 10,000 μm . A lozenge shape with dimensions of 1360 \times 1360 μm was placed downstream of the channel at a distance of 4800 μm for the accumulation of formed double emulsions. All inlet and outlet ponds are considered circular with an 1100 μm average diameter. A detailed sketch of the designed microchannel along with dimensions is depicted in Fig. 1b.

For evaluating the shape of the fabricated microchannel, especially at the dual co-flow junctions, we have utilized a surface profilometer device (Profilom3D, Filmetrics). A sight of the measuring procedure is shown in Fig. 1c. The resultant data reveals an acceptable depth and almost perfect space within channels (Fig. 1d).

3. Experimental procedure

3.1. Material

For the production of O/W/O emulsions, the internal phase consists of a mixture of 0.25% (w/w) Span 80 (Sigma-Aldrich) in silicone oil (10cSt, China National BlueStar, (Group) Co. Ltd). The middle aqueous phase is a mixture of 10% (w/w) polyvinyl alcohol (PVA, 87–89% hydrolyzed, Sigma-Aldrich) and 25% (w/w) Glycerol (Merck) in distilled water. The outer oil phase is a composite of 2.5% (w/w) Span 80 in silicone oil (100cSt, China National BlueStar, (Group) Co. Ltd).

For the production of W/O/W droplets, 1.5% (wt) Sodium alginate (19–40 kDa) is utilized as the inner fluid. The middle fluid consists of a mixture of 0.25% (w/w) Span 80 in silicone oil (10cSt, China National BlueStar, (Group) Co. Ltd). The outer aqueous phase is a mixture of 5% (w/w) polyvinyl alcohol and 25% (w/w) Glycerol in deionized water.

PVA is a surfactant for water-based solutions and is widely used in microfluidic droplet systems to prevent merging the generated drops in the reservoir. Glycerol is a very viscous material that can increase the viscosity of water-based solutions. We add glycerol to the media to increase the viscosity of the continuous phase. Hence, the more viscous the fluid, the more shear stress is exposed to the system and facilitates droplet formation.

Sodium alginate is a common material widely used for cell encapsulation and making scaffolds in biological systems, so the inner phase is decided to be this material to mimic the applications we seek to perform in our future works.

3.2. Microfabrication of PDMS device and wall treatment

The microfabrication process is based on the well-known soft lithography technique presented in numerous research works [32–35]. We have followed the rules provided by MicroChem Corp [36] for the

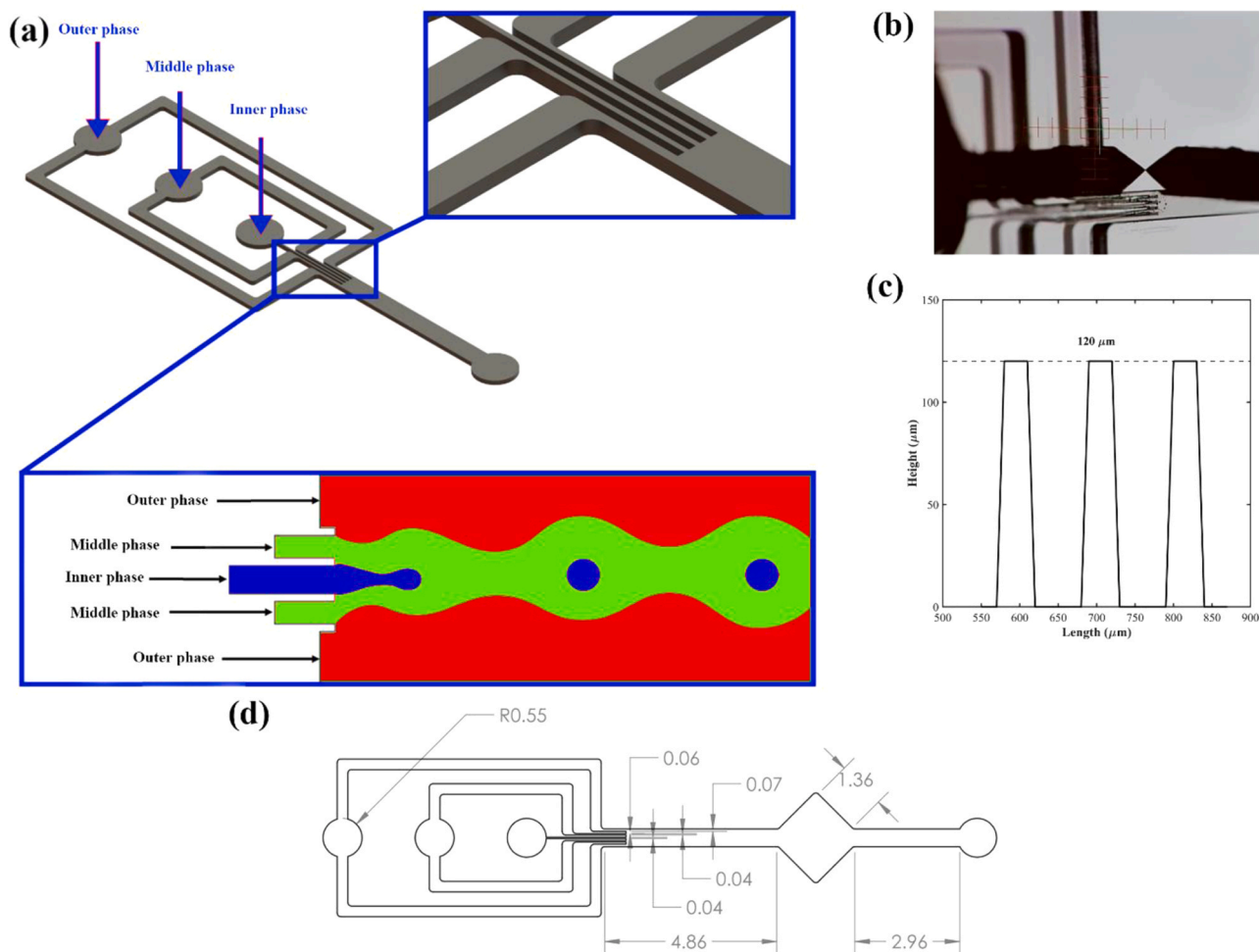


Fig. 1. (a) Schematic view of the designed double co-flow geometry, (b) a view of the surface profilometer device, (c) the resultant profile from the surface profilometer device, and (d) major dimensions (All dimensions are in mm).

fabrication of the desired microfluidic device.

Wall treatment of the microchannel for the production of W/O/W emulsions is conducted using the PVA deposition technique [37]. The hydrophilic treatment of the PDMS device is performed shortly after plasma treatment with 20 sccm oxygen flow and 0.67 mbar pressure. The PVA solution (1% (w/w) in deionized water) is injected into all channels through the outlet junction immediately after the bonding for 10 min. Then the parts are blown dry by pressurized air and are heated at 110 °C for 15 min on a hotplate. This procedure is replicated three times to ensure that all surfaces of the PDMS microchannel are transformed to the hydrophilic surface.

Fig. 2a and b show the contact angle of an untreated and treated PDMS surface, respectively. Five microliters of deionized water were poured on the surface of the PDMS and using a digital microscope,

images were captured. By employing ImageJ software, the contact angles of droplets were measured. The results show that a hydrophobic PDMS surface ($\theta = 111.5^\circ$) was transformed into a hydrophilic surface ($\theta = 21^\circ$) by the so-called PVA deposition technique.

3.3. Double emulsion generation

Fig. 3 illustrates the experimental apparatus utilized in this research. The setup consists of three injection pumps (SAMA Instruments, Iran), a biological microscope (Zeiss, Germany) connected to a high frame rate camera (XIMEA, Germany), the microfabricated PDMS device, data acquisition, and control unit for gathering videos and send data to the injection pumps. Videos are captured at a 2000 Hz frequency rate and processed using Droplet morphometry and velocimetry (DMV) software

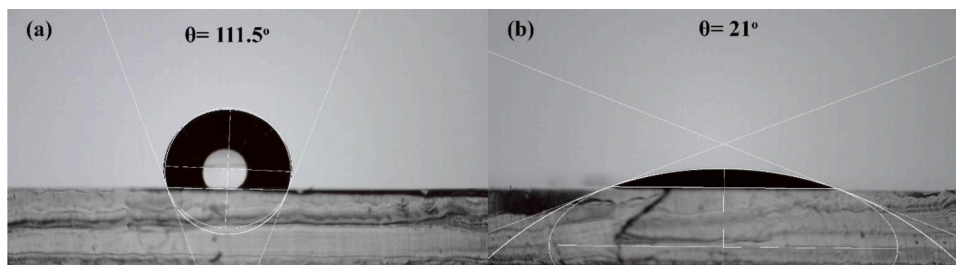


Fig. 2. (a) Contact angle for untreated PDMS before plasma PVA deposition, (b) contact angle for treated PDMS after plasma PVA deposition.

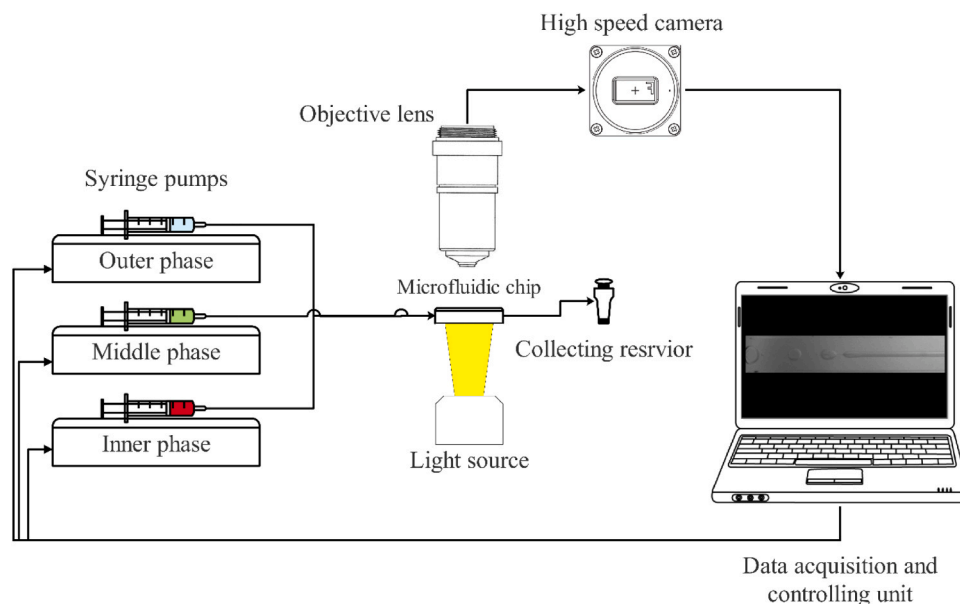


Fig. 3. Schematic view of the computational domain (not to scale) for double emulsion generation.

[38].

4. Results and discussion

Fig. 4a demonstrates a schematic view of the W/O/W droplet generation in the wall-treated dual co-flowing microfluidic device. The creation of W/O/W droplets occurs in a single step. The innermost aqueous phase enters the jet of the middle oil phase. Through dripping instability followed by the imposed shear rate of the external stream to the interface of the outer jet, both internal and intermediate phases break up, and double emulsion forms downstream of the channel.

The influences of the outer phase flow rate ratio to the total flow rate of inner and intermediate phases, $Q_i + Q_m$, on the final size of double emulsions and their thickness are illustrated in Fig. 3b. In all experiments for the creation of W/O/W droplets, the flow rates of internal and intermediate fluids were kept constant at 50 $\mu\text{l/h}$ and 500 $\mu\text{l/h}$, respectively, and the outer phase flow rate varies between 20,000 and 100,000 $\mu\text{l/h}$. Our previous investigations reveal that the continuous fluid flow rate influences the formation procedure and double emulsion characteristics more significantly [14].

We have previously performed a comprehensive numerical study on the influence of various parameters, including all phase flow rates and physical properties of each phase [8]. The local sensitivity analysis proved that the outer phase parameters have the most substantial influence on double emulsion formation and characteristics [8]. The results also revealed that the outer phase flow rate has the most significant influence on the double emulsion size and frequency of formation, which indicates that tuning size and frequency of double emulsions can be easily obtained by varying the outer phase flow rate. Because of the high flow rates needed for the outer phase and thus the limited time available for our experiments, we decided to only investigate the influence of the outer phase flow rate and prove that by tuning this parameter, a wide range of size of double emulsions can be obtained.

Also, our previous investigations [39–42] revealed that increasing inner phase flow rate results in the formation of bigger inner and outer droplets. This is while we have observed that increasing middle phase flow rate causes a larger outer droplet, while the size of the inner drops diminishes.

The sizes of both inner and outer droplets decrease remarkably by the outer phase flow rate increment. Besides, the outer phase flow rate has a more notable impact on the outer droplet size, D_o , than the interior

one, D_i ; thus, the shell thickness, $t = (D_o - D_i)/2$, reduces. The reduction in the size of both droplets can be explained by the fact that raising the outer phase flow rate leads to the more powerful shear rate exposed upon by the outer fluid on the external interface due to velocity gradient increment. Also, the intermediate phase jet diameter reduction creates a higher velocity gradient near the inner interface (the interface between internal and middle fluids), which leads to higher shear rates and smaller inner droplets.

Image sequences of W/O/W emulsions formation for dripping and jetting regimes are shown in Fig. 4c and d, corresponding to the $Q_o = 20,000 \mu\text{l/h}$ and $Q_o = 60,000 \mu\text{l/h}$, respectively. It is clear that increasing in continuous fluid flow rate leads to the transition phenomenon. Nevertheless, the formation of compound droplets happens in a single step in both flow regimes. Besides, a snapshot of the generated double emulsions passing through the lozenge shape, corresponding to the droplets of Fig. 4c, is demonstrated in Fig. 4e. As can be seen, produced double emulsions have a highly monodispersed size distribution and are stable in relatively high shear rates at the entrance of the expanded channel.

Analyzing outer droplet size for evaluating monodispersity of the designed device was performed frame by frame for each compound droplet after formation. The results corresponding to the previous image sequences are demonstrated in Fig. 4f and g. In the so-called dripping regime, the coefficient of variation (CV) is 2.64%, while for the jetting regime, the CV was measured to be 5.19%. Both values propose an acceptable monodispersity for almost all applications while maintaining the dripping regime offers higher monodispersed droplets.

The same procedure and findings were observed in the creation of O/W/O droplets. The process of encapsulation is quite similar, i.e., the internal jet enters the moving jet of the intermediate fluid, and as a consequence of dripping instability, both jets break up simultaneously, and the double emulsions produce. Both dripping and jetting regimes can be observed in this configuration. Still, we demonstrated two short-length (Fig. 5a, corresponding to $Q_o = 36000 \mu\text{l/h}$) and long-length jetting (Fig. 4b, corresponding to $Q_o = 60000 \mu\text{l/h}$) to examine the influence of jet length on the monodispersity of double emulsions. In all experiments, the flow rates of inner and intermediate fluids were kept constant at $Q_i = 300 \mu\text{l/h}$ and $Q_m = 6000 \mu\text{l/h}$, while the outer phase flow rate varies between 20,000 and 100,000 $\mu\text{l/h}$.

As can be inferred from Fig. 5c and d, the increment in jet length results in a decrement in monodispersity of double emulsions (from

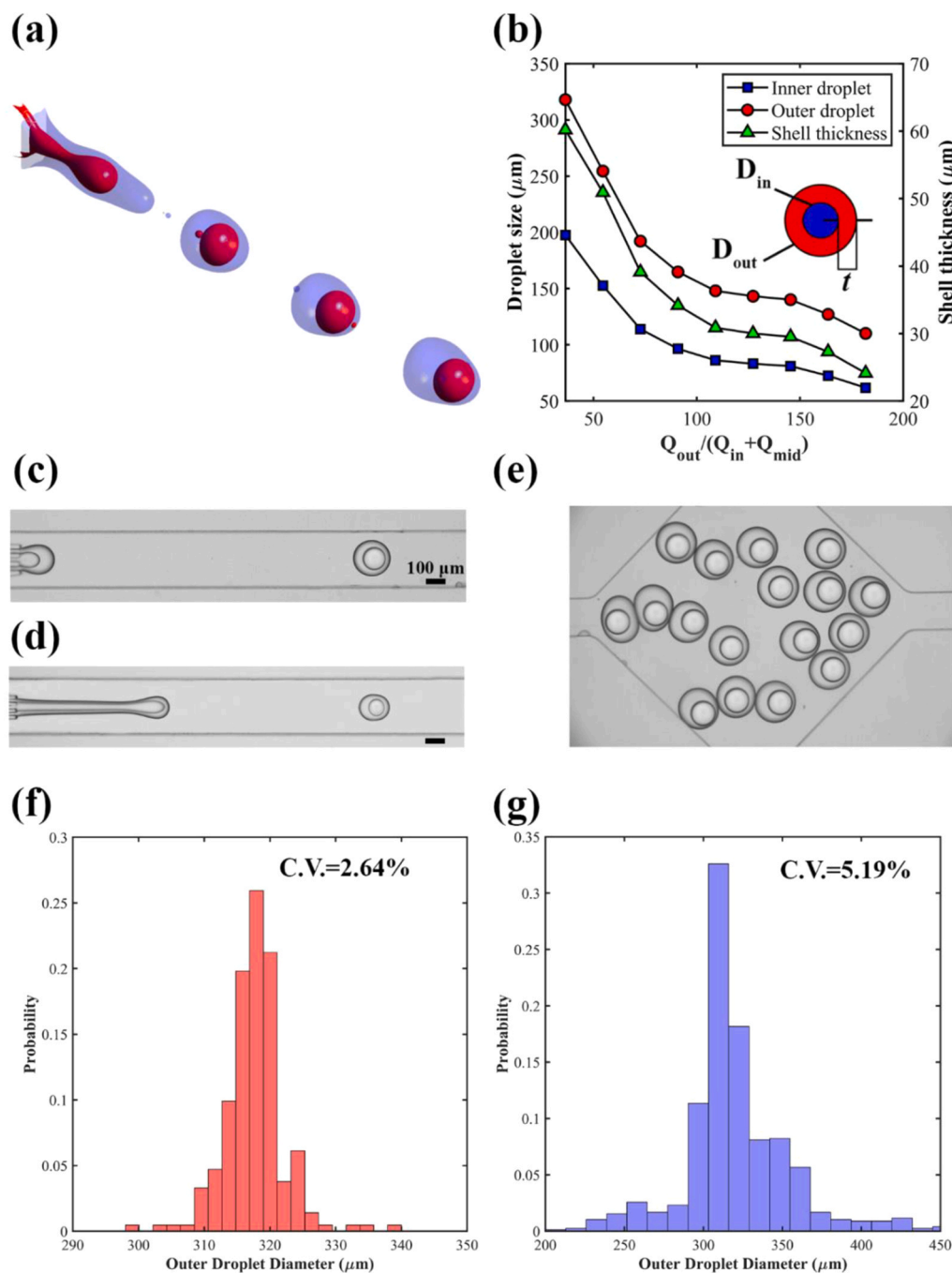


Fig. 4. (a) Schematic diagram of the double co-flow device for generating compound droplets. The internal aqueous fluid is injected from the central channel, penetrates the forming jet of the intermediate oil phase. The external aqueous phase is injected from the external channels, and the thread produced by coflowing internal and intermediate phases break up into droplets due to the Rayleigh–Plateau instability. (b) A plot of the inner droplet diameter, D_i , outer droplet diameter, D_o , and double emulsion shell thickness, $t = (D_o - D_i)/2$, against ratio of outer phase flow rate to the total flow rate of inner and middle phases. Image sequences of W/O/W double emulsion formation in (c) dripping regime ($Q_o = 20000 \mu\text{l/hr}$), and (d) jetting regime ($Q_o = 60000 \mu\text{l/hr}$). (e) A sequence of the double emulsions passing through the lozenge shape section. The outer diameter distribution of double emulsions measured during the formation process for (f) dripping regime and (g) jetting regime, corresponding to the provided image sequences. The flow rates of the internal and intermediate phases were kept constant during the experiments at $Q_i = 50 \mu\text{l/hr}$, and $Q_m = 500 \mu\text{l/hr}$.

3.78% to 5.47%). However, in both cases, the coefficient of variation is in an adequate range for most microfluidics applications.

The influences of the ratio of the external phase flow rate to the total flow rate of inner and intermediate phases on the size and thickness of droplets are depicted in Fig. 5e. The size of both droplets reduces dramatically by raising the outer phase flow rate. Moreover, the outer phase flow rate has a more notable influence on the outer droplet diameter than the inner one, resulting in a reduction in the shell thickness. The decrease in the size of both droplets can be justified by the fact that increasing the outer phase flow rate results in the more powerful shear rate exposed upon by the external phase on the outer interface due to the increase in velocity gradient. Also, the middle phase jet diameter contraction produces a more powerful velocity gradient near the inner interface, leading to higher shear rates and smaller inner droplets.

In different regions of the parameter space, liquid jets give a wide

diversity of breaking patterns. When capillary forces are dominant over other forces, the system exhibits a regime of periodic drop emission at the nozzle. Dripping is a phenomenon that follows in monodisperse drips whose size is regularly determined by the nozzle size. The system shifts to a regime characterized by the production of a long jet as inertial or viscous forces become comparable to capillary forces. Its radius pulsates, and it disintegrates into droplets far downstream of the nozzle. This is referred to as jetting, and it typically ends in a lot of drop size dispersion.

The formation rate of a microfluidic device represents the throughput of the device and plays a vital role in large-scale generation in many applications. The double emulsion generation frequency in W/O/W and O/W/O configurations is demonstrated in Fig. 6a and b, respectively. The formation rate increases dramatically as the flow rate ratio rises in both structures, which is due to the dramatic reduction in

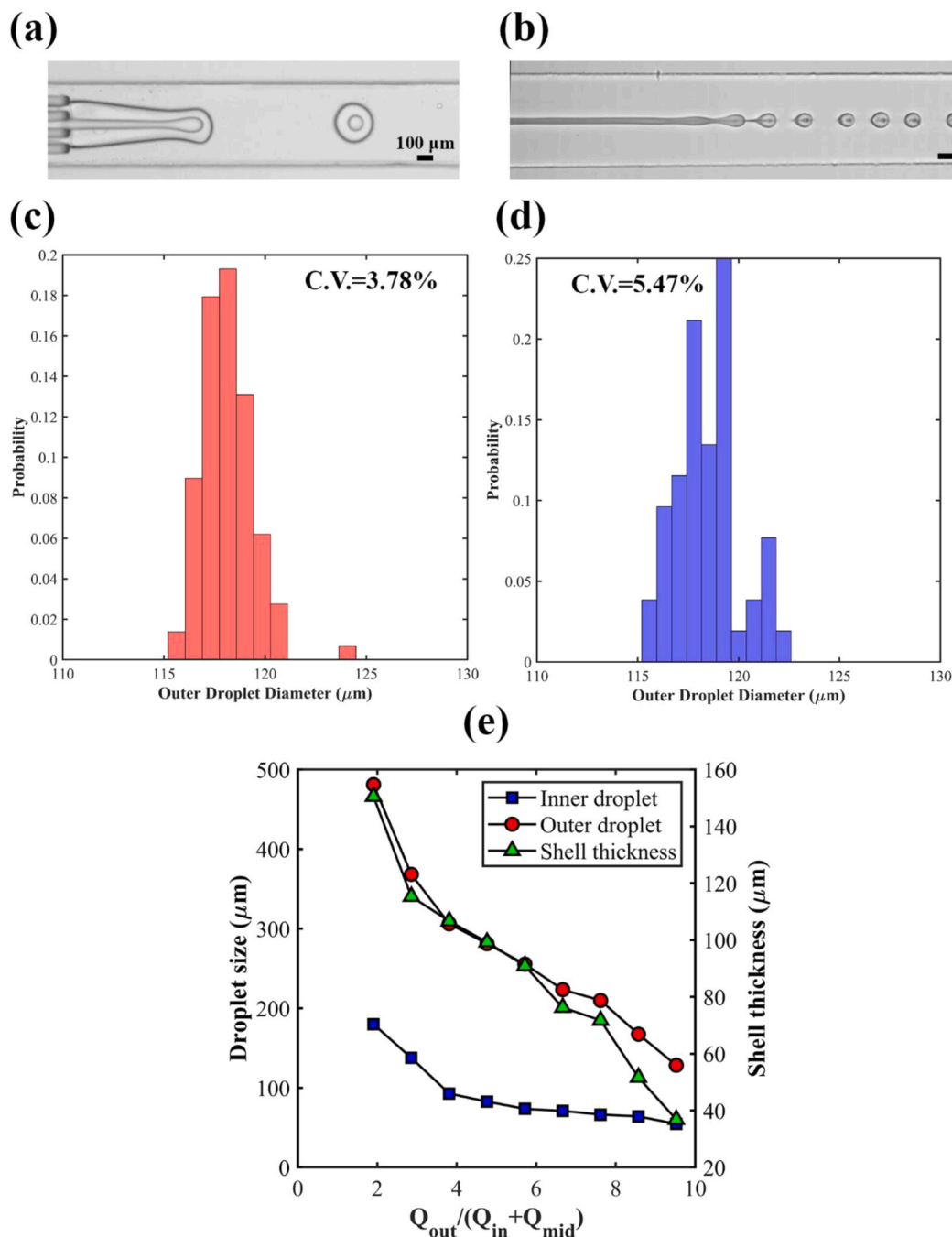


Fig. 5. Image sequences of O/W/O emulsion formation in (a) dripping regime ($Q_o = 36000 \mu\text{l/hr}$), and (b) jetting regime ($Q_o = 60000 \mu\text{l/hr}$). The outer diameter distribution of double emulsions measured during the formation process for (c) dripping regime and (d) jetting regime, corresponding to the provided image sequences. (e) A plot of the internal droplet diameter, D_i , outer droplet diameter, D_o , and double emulsion's shell thickness, $t = (D_o - D_i)/2$, against ratio of outer phase flow rate to the total flow rate of inner and middle phases. The flow rates of the internal and intermediate phases were kept constant during the experiments at $Q_i = 300 \mu\text{l/hr}$, and $Q_m = 6000 \mu\text{l/hr}$.

droplet sizes (Figs. 4b and 5e). The values of formation frequency show a relatively high throughput compared to the other microfluidic geometries [1].

We have also observed two typical dripping and jetting regimes and the transition criteria as a function of flow rate ratios. The transition from dripping to jetting in the W/O/W structure was observed at $Q_o/(Q_i + Q_m) = 100$, while for O/W/O configuration, it has occurred at $Q_o/(Q_i + Q_m) = 3$.

The transition between dripping and jetting regimes depends on both physical properties and flow rate of phases. When the configuration changes from W/O/W to the O/W/O, the physical properties of the

inner, middle, and outer phases vary significantly, i.e., the silicone oil utilized in this study has approximately 10 times more viscosity than the aqueous phase. So, it is predictable that the transition criteria would be considerably different among the two configurations.

For choosing the most appropriate conditions for a specific application, one should trade-off between the throughput and the monodispersity, i.e., the jetting regime has a higher generation rate of double emulsions while it suffers from a relatively poor monodispersity. In contrast, highly monodispersed double emulsions can be obtained with a much lower formation rate employing a dripping regime.

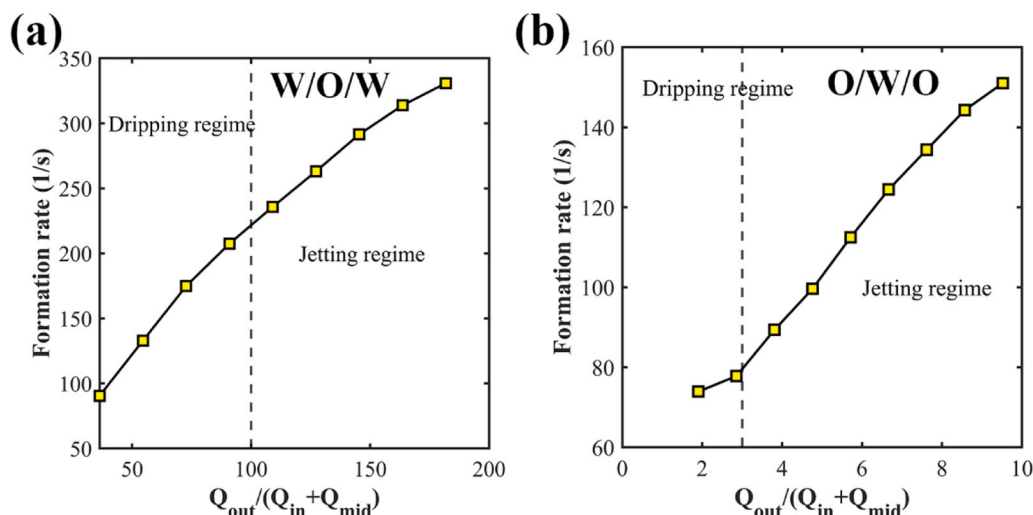


Fig. 6. Formation frequency along with the regime of double emulsion formation for (a) W/O/W and (b) O/W/O emulsions. The flow rates of the inner and middle phases were kept constant during the experiments at $Q_i = 50 \mu\text{l/hr}$, and $Q_m = 500 \mu\text{l/hr}$ for W/O/W and $Q_i = 300 \mu\text{l/hr}$, and $Q_m = 6000 \mu\text{l/hr}$ for O/W/O double emulsions.

5. Conclusion

To solve the problem of partial wettability treatment of microchannels for the fabrication of double emulsions, we have proposed a high aspect ratio of height to the width of the inner phase microchannel. This high aspect ratio results in the formation of the inner phase jet at the middle of the main channel without contacting with upper, lower, and side walls. By this approach, we have eliminated the need for partial wall treatment of microchannels for the fabrication of double emulsions, which is the main novelty and superiority of our work compared to the previous studies.

In summary, we proposed a dual co-flowing PDMS-based device with a high aspect ratio of height to the width of the microchannel for the single-step fabrication of O/W/O emulsions without the requirement for any wall treatment and fabrication of W/O/W emulsions with a single step PVA deposition technique for making the whole device hydrophilic. We successfully produced relatively high monodispersed and high throughput double emulsions employing this geometry without needing the common partial wettability patterning techniques.

Unlike double-emulsion drops fabricated by the standard one-step and two-step methods, our channel-based one-step approach presents a means to produce double-emulsion drops without requiring typical partial surface modification methods; offers a facile, robust, and permanent technique for the fabrication of double emulsions in a profoundly controlled manner, acceptable monodispersity, and sizeable throughput.

The introduced technology can be employed for microencapsulation of a variety of biomolecules and cells for different purposes, such as protecting them from the harsh environment and building desired scaffolds. Also, this droplet generation microchip can be used for providing drug capsules using in drug delivery systems. Such research will be the subject of our future studies.

CRediT authorship contribution statement

Amirmohammad Sattari: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Pedram Hanafizadeh:** Conceptualization, Investigation, Project administration, Supervision, Writing – review & editing. **Mohsen Mashhadi Keshitban:** Data curation, Investigation, Formal analysis, Methodology, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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