

High-Throughput Step Emulsification for the Production of Functional Materials Using a Glass Microfluidic Device

Alessandro Ofner, David G. Moore, Patrick A. Rühs,* Pascal Schwendimann, Maximilian Eggersdorfer, Esther Amstad, David A. Weitz, André R. Studart*

High-volume production of monodisperse droplets is of importance for industrial applications due to increased emulsion stability, precise control over droplet volumes, and the formation of periodic arranged structures. So far, parallelized microfluidic devices are limited by either their complicated channel geometry or by their chemically or thermally unstable embedding material. This study shows a scalable microfluidic step emulsification chip that enables production of monodisperse emulsions at a throughput of up to 25 mL h⁻¹ in a glass device with 364 linearly parallelized droplet makers. The chemical and thermal stability of such a glass device allows for the preparation of a broad variety of functional particles and microdroplets by using any desired solvent together with nanoparticles, polymers, and hydrogels. Moreover, the microfluidic device can be stringently cleaned for nearly unlimited use and permits the

alternating production of oil-in-water and water-in-oil emulsions. The combined high throughput, chemical and thermal stability offered by our device enables production of monodisperse functional materials for large-scale applications.



1. Introduction

Microfluidics provides precise control of fluids and enables unparalleled encapsulation opportunities in the fields of diagnostics,^[1] pharmaceutics,^[2] cosmetics,^[3] and

A. Ofner, D. G. Moore, Dr. P. A. Rühs, P. Schwendimann, Prof. A. R. Studart Complex Materials Department of Materials ETH Zurich, 8093 Zurich, Switzerland E-mail: patrick.ruehs@mat.ethz.ch; andre.studart@mat.ethz.ch Dr. M. Eggersdorfer, Prof. D. A. Weitz Department of Physics and School of Engineering and Applied Sciences Harvard University Cambridge, MA 02138, USA Prof. E. Amstad Institute of Materials EPF Lausanne, 1015 Lausanne, Switzerland food science.^[4] Microcapsules and microparticles made of hydrogels,^[5] functional polymers,^[6] and stimuli-responsive particles^[7] have been developed using microfluidic droplets as templates. These functional particles, however, can only be produced in small quantities if conventional microfluidic techniques are applied.^[8] By contrast, bulk methods have a high throughput but lack the control over droplet size and monodispersity enabled by microfluidics.^[9] Thus, there is a need in scientific studies and industrial applications for a droplet production method that combines the large production volumes of bulk processes with the fine control of microfluidic techniques.

One strategy to increase the throughput of microfluidic devices is the parallelization of droplet makers such as T-junctions^[10] and flow-focusing nozzles.^[11] Because drop pinch-off in both T-junctions and flowfocusing geometries is induced by shear forces of the outer fluid, inevitable pressure fluctuations in such designs result in shear force variations that lead to

polydisperse droplets.^[12] Furthermore, parallelization of such droplet makers requires complex multilayer structures with various numbers of inlets and channels in order to distribute the liquids to the droplet makers or to collect them after emulsification. Such devices are difficult to fabricate and reproduce due to their complex 3D structure.^[13-15]

A promising approach to simplify the microfluidic design and to circumvent the undesired polydispersity arising from pressure fluctuations is to utilize the concept of step emulsification.^[16] In step emulsification, also referred to as microchannel or edge-based droplet generation emulsification,^[17] droplets are formed when a fluid is pushed through a long shallow channel into a large deep reservoir. In contrast to T-junctions and flowfocusing approaches, droplets detach from the shallow channel into the "step" without the need of an external force. The driving force that fills the drops is the sudden drop in the Laplace pressure experienced by the disperse phase as it passes through the step.^[18] By adding a defined geometry to the end of the shallow channel, such as a constriction or a sudden enlargement, the flow rate of the fluid into the droplet is decoupled from the applied flow rates of the fluids.^[19] This independence enables a new hydrodynamic instability to be used to form the droplet. Below a critical Capillary number, the droplet size becomes dependent on the geometry of the device and insensitive to fluctuations of the input disperse phase flow rate.^[20] This enables massive parallelization of the droplet makers since the droplet size is independent of the continuous phase flow rate.^[21] As opposed to flow focusing or T-junction systems, droplet makers in step emulsification can be linearly parallelized on one layer using only two inlets and one outlet.^[17] However, a drawback of step emulsification is the low droplet production per single droplet maker compared to flow focusing or T-junctions.^[22] Thus, a highly parallelized device with several hundreds of droplet makers is needed in order to compete with the throughputs achieved in flow focusing.^[23]

Recent work on highly parallelized droplet production focused on devices fabricated in polydimethylsiloxane (PDMS),^[13,23-25] an attractive material for rapid prototyping by soft-lithography.^[26] However, the choice of chemicals that can be used in such devices is very limited, as most solvents swell PDMS and damage the chip.^[27] Various methods to improve the chemical resistance of microfluidic droplet makers have been explored such as implementing glass-like coatings on PDMS with using sol–gel chemistry,^[28] or using more chemically resistant polymers such as poly(methyl methacrylate),^[14] fluoropolymers,^[29] and silicon.^[30] However, these methods need an additional fabrication step, lack the fabrication precision required for micron-sized droplets, are limited in the choice of chemicals or are not sufficiently transparent to enable microscopic analysis. A notable exception is a parallelized flow-focusing device fabricated in glas^[15] that, however, suffers from the drawbacks of flow focusing as discussed above. Overall, a simple and relatively fast technique to implement micrometer-sized channels in glass is far from standard. An ideal scaled-up device would require several hundred linearly parallelized step-emulsification droplet makers^[23] implemented in glass.^[15,17] Such a device would allow to use step emulsification not only for the production of liquid droplets but also for the production of functional materials.

Based on previous research on step-emulsification devices,^[31-33] we combine the scalability of step emulsification with the chemical and thermal stability of glass in a multichannel high-throughput microfluidic device that allows for a robust material production. Scale up is achieved through parallelization while keeping droplet production monodisperse due to the insensitivity of the droplet size to flow rates in step emulsification. In order to implement the step geometry in glass, we outline an etching method including photolithography, wet-etching, and thermal bonding, which allows fabrication of a parallelized, defect-free glass chip. The chemical compatibility of our glass device enables utilization of organic solvents that cannot be processed in polymer-based devices and enables reutilization of the chip, reducing the costs associated with device fabrication. Moreover, the stability of glass enables emulsification at higher temperatures, facilitating control of the viscosity of the fluids and the emulsification speed. Because of the chemical and thermal compatibility of glass, our microfluidic device enables the production of a broad variety of new materials at high throughput.

2. Experimental Section

2.1. Glass Chip Fabrication

Glass chips were fabricated using wet etching techniques. 1.0 mm thick Borofloat 33 wafers were annealed at 580 °C over night and then masked with 50 nm Cr, 25 nm Au, and 8 μ m AZ9260 photoresist. The AZ9260, gold, and chrome were sequentially templated using positive photolithography (1:4 AZ400k developer diluted with water), gold etchant (15% KI, 5% I₂ in water), and chrome etchant (20% ammonium cerium (IV) nitrate, 4.8% acetic acid, in water), respectively. A glass etch rate with 40% HF and Borofloat 33 was established using profilometry to be roughly 3.2 μ m min⁻¹. One wafer was etched shallow to a depth of 20 μ m and the other deep etched to 100 μ m. The etches were isotropic and the etch masks had strong enough adhesion to achieve 1:1 etch to underetch ratios. After etching, the masks were stripped sequentially using acetone, gold etchant, and chrome etchant.



The wafers were then diced into 15×60 mm chips and 0.7 mm inlets were drilled using a diamond-coated drill bit. The chips were thoroughly cleaned using sonication in acetone and ethanol solutions, followed by a surface activation in a piranha solution (1:1, sulfuric acid:hydrogen peroxide) and an RCA1 solution (1:1:5, ammonium hydroxide:hydrogen peroxide:water), and finally the wafers were thoroughly rinsed in water. The shallowetched and deep-etched chips were put into contact while still wet. The water held the wafers tightly together by capillary force during alignment, which was done by hand under a macroscope. Once aligned, the wafers were allowed to dry for several hours in the open, bringing the chips into a weakly bonded state. The chips were then thermally bonded in a vacuum wafer bonder at 10^{-5} mbar and 550 °C for 30 min with an applied force of 2.0 MPa. Finally, microfluidic chips were connected via a commercial four-way connector from Dolomite and polytetrafluoroethylene (PTFE) tubing to syringes mounted on syringe pumps (PHD ultra, Harvard Apparatus). When a hydrophobic device was desired, a solution of 5% octadecyltrimethoxysilane with 0.5% butyl amine in toluene was flowed through the device for 2 h.

2.2. Droplet Production

Before producing o/w droplets, the device was rinsed for 1 min with 1 ${}_{\rm M}$ aqueous NaOH. This setup was used for all experiments unless otherwise noted.

Toluene droplets were emulsified with anthracene in water with 2 wt% polyvinyl alcohol (PVA, M_W = 31 000–50 000) and illuminated using deep blue light (365 nm).

Polycaprolactone (PCL) ($M_W \approx 14\,000$) microcapsules were produced by dissolving 10 wt% in dichloromethane and emulsifying in water with 2 wt% PVA, showing a mean droplet diameter of 81 μ m (coefficient of variation, CV = 3.7%). The droplets were dried on a glass slide at room temperature.

Magnetically responsive droplets were prepared by dissolving dry iron oxide nanoparticles (FerroTec EMG 1400, 10 nm) in chloroform. The solution was emulsified in water with 2 wt% PVA, showing a mean droplet diameter of 93 μ m (CV = 4.6%).

Poly(*N*-isopropylacrylamide) (pNIPAm) microspheres were produced by emulsifying a aqueous solution containing 20 wt% of NIPAm with 2 wt% bisacrylamide as crosslinker, 0.1 wt% of ammonium persulfate as initiator, and 0.01 wt% of tetramethylethylenediamine as accelerator, within a hexadecane continuous phase with 5% of polyglycerol polyricinoleate (PGPR) as surfactant. The droplets showed a mean diameter of 97 μ m (CV = 4.6%).

Paraffin wax droplets were produced at 90 °C. Therefore, the microfluidic chip was connected via the four-way connector over PTFE tubes to heated centrifuge tubes, which were controlled by an elveflow pressure controller. The microfluidic chip, the PTFE tubes, and the centrifuge tubes were immersed in a heated water bath and paraffin wax was emulsified in water with 2 wt% Tween 80 at constant pressure rates of 100 mbar per inlet.

Intentional clogging experiment was performed by adding solid PCL microspheres, prepared as shown in Figure 3a, in a dispersion with hexadecane into a running device. After clogging, the device was cleaned with tetrahydrofuran, chloroform, water, sulfuric acid, aqueous 1 M sodium hydroxide solution, and ethanol, by applying vacuum with a vacuum pump and by heating the device to 600 $^\circ \! \text{C}.$

3. Results and Discussion

A schematic of the proposed parallelized microfluidic glass device is shown in Figure 1. The geometry of the up-scaled step-emulsification device consists of a central channel to carry the dispersed phase and two adjacent parallel channels that contain the continuous phase. These 120 μ m high channels are connected through an array of parallelized 20 μ m high nozzles with wedge-shaped droplet makers (Figure 1a).

In this design, droplets are formed at the step between each nozzle and the continuous-phase channel. At the beginning of the droplet break-up, the dispersed phase fluid is confined in the shallow channel with a rectangular cross section as an asymmetrical tongue. It is important that the dispersed phase does not wet the channel walls.^[16] For a channel of height *h*, the contact angle between the dispersed phase and the channel wall (α) determines the radius of curvature r ($r = h/(2\cos(\alpha))$) and thus the driving pressure gradient (Δp) for droplet formation. The high curvature of the dispersed phase in the shallow channel results in a large pressure drop at the interface between the dispersed and continuous phase: $\Delta p \approx \gamma/r$, with γ being the interfacial tension. Upon entering the deep continuous phase channel, the dispersed phase relaxes and expands into a symmetrical bulb. The pressure difference between the confined asymmetric thread and the symmetric bulb sucks the dispersed phase into the bulb. Hence, the bulb grows and the pressure gradient increases depleting the nozzle of dispersed phase. A neck forms between the thread and the bulb (Figure 1b).^[21,34] A Rayleigh–Plateau instability triggers the break-up of the bulb from the remaining dispersed phase in the nozzle and a droplet forms (see Video S1, Supporting Information). Interestingly, the instability is determined by the shape of the nozzle at the outlet^[32] and the droplet size is independent of dispersed phase flow rate, as long as the dispersed phase is depleted faster from the nozzle than it is refilled, the so-called dripping regime. Moreover, in that regime the droplet formation process is also independent of the continuous phase flow rate. At higher dispersed phase flow rates, the driving force for the droplet pinchoff is the shear rate of the continuous phase, the so-called jetting regime.^[23] Typically, it is desirable to operate the device in the dripping regime where the droplet size is determined by the smallest channel dimension and is independent of flow rates. The droplet size in the dripping regime is approximately four times the shallow channel height.^[18,35] The interfacial tension and





Figure 1. Layout, working principle, and wet-etch fabrication of a glass microfluidic device for multiple step emulsification. a) Schematic of a step-emulsification channel arranged with four parallelized droplet makers. The dispersed phase flows through shallow distribution channels to a wedge-shaped nozzle. The droplet breakup occurs at the step between the 20 μ m high nozzle and the 120 μ m high continuous phase channel. b) The step emulsification process involves (1) the inflow of the dispersed phase to the step, (2) the build up of a Laplace pressure difference between the fluids in the nozzle and in the continuous phase channel, which draws out the dispersed fluid, and (3) the formation of the final droplet caused by Rayleigh plateau instability. c) Layout of a parallelized microfluidic emulsification chip with 364 steps. The steps are at the end of the indicated red shallow channels (20 μ m). The device consists of three inlets, two for the continuous phase and one for the dispersed phase, and an outlet to collect the produced droplets. d) To produce the glass emulsification device a glass etching process consisting of (1) photolithography, (2) HF etching, (3) stripping, cleaning, and (4) thermal bonding. The top glass chip is isotropically etched to a depth of 20 μ m and the bottom chip to 100 μ m. Both parts combined form a 120 μ m deep continuous phase channel.

viscosities set the transition from the dripping to the jetting regime, which is typically captured by a critical Capillary number.^[16] This dimensionless ratio of viscous to surface tension forces is given by $Ca = \eta v/\gamma$, with η as the viscosity, v as the flow rate of the dispersed phase and, γ as the interfacial tension.

Combining multiple droplet makers while still achieving monodisperse droplets at high throughputs is a major challenge in flow-controlled devices due to unavoidable pressure fluctuations across adjacent channels. The flow rate independence of the droplet size in the dripping regime prevalent at the steps makes it possible to scale up an array of droplet makers while keeping size monodispersity. We take advantage of this to design a microfluidic device with 364 linearly parallelized droplet makers (Figure 1c). Another advantage of the step design is the simple setup of the emulsification device. Step emulsification is the only microfluidic technique that allows parallelization of droplet makers in a 2D array without an additional channel distribution layer or multiple inlets. Our microfluidic chip consists of three inlets, two for the continuous phase, and one for the dispersed phase. A single outlet is used to collect the generated droplets. Polytetrafluorethylene tubes connect the inlets to syringe pumps that feed liquids at constant flow rates while the outlet is connected to a collection vial. The simplicity of this setup allows a linear scale up of hundreds of droplet makers fed only by one inlet. Thus, it is possible to scale up the chip without multiple connection ports.^[10,13–15]

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The proposed parallelized design is implemented in a glass chip to combine the scalability offered by step emulsification with the chemical compatibility and thermal stability of glass. Microfluidic glass devices are produced using a simple and efficient technique comprising photolithographic, etching, and bonding steps (Figure 1d). In short, Borofloat 33 borosilicate glass wafers are first annealed at 580 °C and then coated with a chrome adhesion layer and an inert gold layer through electron beam physical vapor deposition. Then, a hydrophobic photoresist is deposited on the masked wafer through spin coating. The photoresist and metal films are then photolithographically patterned and hard-baked for an extended period to form a more hydrophobic barrier and prevent etching defects.^[36] To implement the step geometry, one wafer is etched shallow (20 µm) and another is etched deep (100 μm) using a 40% HF aqueous solution. After etching, the wafers are diced, inlets are drilled, and the wafers are stripped off the masks and cleaned before being contacted and aligned by hand. Chips are allowed to dry at room temperature, resulting in a weak, but stable pre-bond. Finally, the chips are bonded in a bonder aligner at 550 °C, resulting in an extremely robust, hermetically sealed covalent bond. This defect-free wet-etching process used to fabricate microstructured glass allows us to reproducibly manufacture 364 droplet makers with high geometrical accuracy.

Up-scaling the step-emulsification process in a glass device with 364 nozzles enables a robust and fast production of monodisperse droplets. An actively working device producing toluene-in-water droplets by step emulsification is shown in Figure 2a. In this process, droplets of the inner liquid phase are formed at the steps of the nozzles and dispersed in the continuous phase. The droplet makers are fed by an array of parallel nozzles, which are recognizable by the lower color intensity arising from the shallower channels (Figure 2a and Video S2, Supporting Information). The defect-free fabrication of the chip allows production of monodisperse droplets that readily form ordered 2D arrays (Figure 2b and Video S3, Supporting Information). For an average droplet diameter of 101 µm, the CV is as low as 2.5% for toluene-in-water droplets, whereas for hexadecane-in-water droplets, with an average diameter of 81 μ m, the CV is 2.8% (Figure 2c and Video S4, Supporting Information). This small variation is likely caused by different contact angles and viscosity ratios of the emulsified liquids.

Monodispersity of droplets increases the stability of emulsions against Ostwald ripening,^[37] enables tight control over volumes in multiple chemical or biological reactions, allows precise dosing in pharmaceutical applications, and can form ordered templates for the fabrication of periodic porous structures.^[38] The robustness of step emulsification enables long-term droplet production at constant droplet diameter. We produce emulsions of hexadecane-in-water for 10 h with constant monodispersity (Figure 2d). Because dripping is driven by the Laplace pressure difference rather than the flow of the immiscible phases, the obtained droplet size is insensitive to the applied flow rates of the inner phase (Figure 2e) and is determined primarily by the nozzle geometry.^[32] This condition is valid below a critical flow rate value, q_{max} , which defines the transition from dripping to jetting regime in our upscaled device.^[39] Under the dripping regime, slight variations in flow rates between adjacent nozzles do not compromise the monodispersity of the droplets generated. While in the dripping mode, the mean droplet size is insensitive to the flow rates of the continuous phase (Figure 2f). Beyond q_{max} , the flow of the dispersed phase changes from dripping to jetting mode and droplets are sheared by the continuous phase.^[17,30]

In addition to monodispersity and robustness, these parallelized devices operate at dispersed phase flow rates of up to 25 mL h⁻¹ or \approx 70 µL h⁻¹ per nozzle for 81 µm droplets of hexadecane in water. This overcomes the low throughput and inconsistent long-term droplet production of other microfluidic techniques, making microfluidics closer to being useful for the fabrication of monodisperse droplets for industrial applications and for scientific studies on model emulsions.

To demonstrate the chemical compatibility and thermal stability of our glass devices and the versatility of this new step-emulsification platform, we produce diverse functional materials, including biodegradable, magnetically and temperature-responsive monodisperse microdroplets and particles.

As opposed to polymeric microfluidic devices, the microstructured glass chip used in this work enables production of droplets of various fluids, such as hydrocarbons and even aggressive solvents such as chloroform, dichloromethane, or toluene. Having the freedom of solvent choice is highly attractive for the preparation of functional materials. For example, toluene and chloroform are often chosen as the dispersed phase of emulsions, since they can be used as a vehicle for a wide range of molecular species, monomers, and/or particles of interest for the creation of functional materials. Additionally, toluene and chloroform are common solvents for many unpolar and amphiphilic polymers, which allows glass microfluidics to significantly broaden the spectrum of materials that can be emulsified. These solvents would lead to rapid swelling and debonding if used in polymeric microfluidic chips.^[27]

As proof of concept examples, we produce microdroplets and functional particles by using a variety of solvents containing polymers, nanoparticles, and hydrogels. Taking dichloromethane as dispersed phase, biodegradable polycaprolactone microcapsules are successfully





Figure 2. Up-scaled step-emulsification device producing monodisperse droplets. a) Photograph of the entire microfluidic glass chip actively producing oil-in-water droplets. The chip is illuminated using UV-light (365 nm). Contrast is provided by anthracene added to the toluene oil phase, which leads to blue oil-in-water droplets. Scale bar is 1 cm. b) A photograph at higher magnification shows the detail of the parallelized droplet makers and crystalline-arranged, closely packed, and monodisperse oil droplets in water. Videos of running devices are shown in Videos S2 and S3 (Supporting Information). Scale bar is 500 μ m. c) Size distribution of hexadecane-in-water droplets with a mean size of 80.9 μ m and a coefficient of variation (CV) of 2.8%. d) Robustness of the microfluidic device producing monodisperse hexadecane-in-water emulsions for 10 h. e) Insensitivity of the droplet size distribution on the applied inner flow rate below a critical flow rate $q_{max} = 25$ mL h⁻¹. The boundary between dripping and jetting of the dispersed phase is defined as q_{max} . f) Insensitivity of the droplet size on the flow rate of the continuous phase even under static flow conditions.



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Figure 3. Functional emulsions and microparticles generated in chemically and thermally compatible microfluidic glass chips. a–d) Examples of functional materials produced with a parallelized step-emulsification device operated at flow rates up to 25 mL h⁻¹. a) Solution of dichloromethane and polycaprolactone (PCL) dispersed in water and a SEM picture of a dried PCL microsphere after solvent evaporation (inset). b) Chloroform droplets loaded with superparamagnetic iron oxide nanoparticles in water in the absence (top) or presence (bottom) of an external magnetic field (Video S5, Supporting Information). c) Temperature-responsive poly(*N*-isopropylacrylamide) (pNIPAm) hydrogels in hexadecane produced with a hydrophobized glass chip. d) Paraffin wax microspheres quenched at room temperature after droplet emulsion production at 90 °C. e) Effect of temperature on the maximal throughput production q_{max} of a 90% glycerol solution in water. Decreasing the viscosity^[44] of the dispersed phase by increasing temperature enables higher emulsification throughput.

prepared in an aqueous continuous medium (Figure 3a). These microcapsules can potentially be used as microspheres for drug release^[40] or as sacrificial templates for the generation of biological scaffolds and porous ceramic structures.^[38,41] Additionally, the freedom of chemical's choice allows for processing polymers in a broad variety of solvents, ranging from theta-solvents to bad solvents. This versatility might be of interest in polymer science, as it enables to process polymers at different states of coil expansion.

In another example, chloroform is used as a vehicle for superparamagnetic iron oxide nanoparticles (SPIONs)



to generate monodisperse magnetically responsive droplets in water. Placing an external magnet next to the outlet microfluidic channel confirmed the response of the SPION-loaded droplets to a magnetic field gradient (Figure 3b and Video S5, Supporting Information). In addition to spatial manipulation, such fields can potentially be used to mix the inner content of droplets through coalescence or could be exploited as an external trigger to release cargo.^[7]

By hydrophobizing the glass chip channels through silane functionalization, water-in-oil emulsions can also be produced. This enables, for example, preparation of pNIPAm hydrogel microspheres from monodisperse water droplets dispersed in hexadecane (Figure 3c). Such hydrogel microparticles have been proposed for example as materials for passive cooling of buildings and as smart materials for bioseparation.^[42,43]

Apart from the possibility of emulsifying nearly every chemical, the device is also compatible with a broad variety of surfactants used for droplet stabilization. As examples, we can stabilize droplets with anionic surfactants (sodium dodecyl sulfate, sodium dodecylbenzenesulfonate, commercial soap), nonionic surfactants ((PVA), PGPR, Tween, Span), particles (SiO₂), and proteins (β -lactoglobulin).

Besides its chemical inertness, glass is also thermally stable compared to materials used in other microfluidic devices. This allows production of emulsions at high temperatures, enabling droplet formation with materials that are solid at room temperature. The preparation of solid microspheres from emulsions often includes an additional fabrication step, such as, for example, volatile solvent evaporation or various polymerization techniques. By operating the glass chip at higher temperatures, we provide a new route for the one-step preparation of solid microspheres using high-throughput microfluidics. Thus functional microparticles can be formed from materials that are solid at room temperature using solvent-free emulsification followed by thermal quenching.

Microfluidic emulsification at 90 °C, for example, enables production of monodisperse paraffin wax droplets that solidify upon quenching to microspheres of 69.7 µm diameter (CV = 2.8%) (Figure 3d). The resulting solid microspheres may be used as sacrificial templates or serve as impenetrable solid shells if incorporated into the middle phase of double emulsions. Moreover, operating the device at higher temperatures decreases the viscosity of most chemical solutions, increasing the maximum achievable throughput rate before reaching the critical Capillary number $Ca_{crit} = \eta v/\gamma$. We illustrate this feature using, for example, a 90% glycerol solution in water emulsified in hexadecane (Figure 3e). With higher temperatures the viscosity η decreases by two orders of magnitude, allowing for an increase in the flow rate v while keeping the emulsification process in the dripping mode.^[44] Comparable reductions in viscosity upon temperature increase are also possible with a variety of other polymer solutions. Thus, emulsifying at high temperatures should also enable the production of microdroplets of highly concentrated polymeric solutions, which are too viscous to be processed at room temperature.^[45]

In addition to the creation of functional microcapsules and particles, the combined chemical and thermal compatibility of glass allows effective cleaning of the entire device by simple heating or using chemicals including solvents, acids, or bases. This provides a means to recover clogged devices. As dust particles, organic remainders or aggregates are almost unavoidable; clogging is a reoccurring problem that restricts polymer-based devices to multiple use. Although the step-emulsification process is insensitive to small pressure fluctuations between different droplet makers, clogging of multiple channels reduces the number of active nozzles and may ultimately lead to sufficient pressure differences that result in the transition from dripping to jetting in some nozzles, leading to droplet polydispersity. Additionally, adsorption of chemicals or proteins to the channel walls can change the surface chemistry and eventually destabilize the droplet formation mechanism due to wetting of the dispersed phase. All these issues decrease the amount of material produced and limit the lifetime of a microfluidic device.

To demonstrate the ability to stringently clean and renew our microfluidic device for repeated use (Figure 4), we simulate clogging events by intentionally adding PCL microspheres to the dispersed phase during emulsification (Figure 4a). The clogged device leads to more polydisperse droplets (Figure 4b) as blocked channels increase the flow rate through the remaining open channels. To unclog the device and recover the ability to generate monodisperse droplets, the device is cleaned repeatedly with chloroform, tetrahydrofuran, isopropyl alcohol, sulfuric acid, sodium hydroxide solution, and water, and by applying vacuum and by heating to 600 °C.

The hydrophobic silanization is removed by thermal treatment at 600 °C, offering a hydrophilic channel surface to produce w/o emulsions (Figure 4c). Thus we can alternate between o/w and w/o emulsification. In the example shown in Figure 4, the surface is remodified to produce o/w emulsions by covering the channels again with a hydrophobic surface coating using silanes (Figure 4d). In a last step, we show that the original configuration of the device can be restored through thermal removal of the surface functionalization at 600 °C, again enabling the preparation of o/w emulsions (Figure 4e). As a result, the same monodispersity as before the repeated cleaning steps is achieved. Besides the ability to effectively clean the device, the surface functionalization can





Figure 4. Clogging experiments that illustrate the ability to stringently clean and recycle the same microfluidic chip due to its thermal, chemical, and mechanical stability. To demonstrate device recovery, a hydrophobic functionalized microfluidic device is intentionally clogged after 20 min with PCL microspheres while producing w/o emulsions. a) 20 min after starting the intentional clogging, the device is still producing monodisperse droplets. With increasing amount of PCL microspheres, more droplet makers become clogged and the flow rate per remaining working droplet maker increases. b) This makes the device change its operation mode from dripping to jetting, resulting in the polydisperse droplets observed between 40 and 50 min. The completely clogged device is cleaned with chloroform, tetrahydrofuran, isopropyl alcohol, sulfuric acid, sodium hydroxide solution, and water. Between flushing with chloroform and tetrahydrofuran, the device is cleaned with vacuum treatment. Finally, the device is thermally treated for 4 h at 600 °C. c) The renewed hydrophilic device is used to produce monodisperse o/w emulsions for 1 h. d) Surface functionalization through silane treatment allows for a hydrophobic surface, which enables the production of w/o emulsions. e) Heating the same device to 600 °C for 2 h removes the organic compounds of the surface treatment, leaving a hydrophilic surface that allows for the preparation of o/w droplets again. Scale bars are 500 μ m and 100 μ m for the insets.

thus be reversibly changed multiple times. The thermal treatment not only allows for stringently cleaning or surface functionalization of the microfluidic chip but also permits one to autoclave the device for biomedical applications. This ability fulfills an important requirement toward industrial applications.

In summary, we demonstrate a highly parallelized microfluidic step-emulsification device that can be fabricated in silica glass using simple photolithography, wetetching, and thermal bonding. The very reproducible and defect-free etching technique allows fabrication of a robust microfluidic chip capable of producing monodisperse emulsions with a flow rate of up to 25 mL h⁻¹ for several hours. Given the flow rate insensitivity of the size of droplets made by step emulsification, such high flow rate can be achieved by parallelized droplet makers without compromising the droplet monodispersity. This allows us to successfully produce large quantities of polymer

microspheres, magnetically responsive emulsions, and hydrogel microspheres. The thermal stability provided by glass represents another major feature of this new device, since it enables the use of temperature to reduce the viscosity of the emulsifying fluids and thus increases significantly the throughput of the step-emulsification process for highly viscous solutions. Using such high temperature emulsification capability, we also demonstrate the preparation of microspheres by thermal quenching of molten emulsified phases, which would not be possible to produce otherwise. Moreover, the device can be stringently cleaned and recycled through chemical treatment or heating of the glass chip to 600 °C, enabling nearly unlimited use. These proof-of-concept examples illustrate the wide range of applications that can benefit from this scalable microfluidic technology. The parallelization potential of these devices and the unique long-term stability of glass brings microfluidics closer to industrial applications.



Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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