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High-Throughput Generation of Emulsions and Microgels in Parallelized Microfluidic Drop-Makers Prepared by Rapid Prototyping

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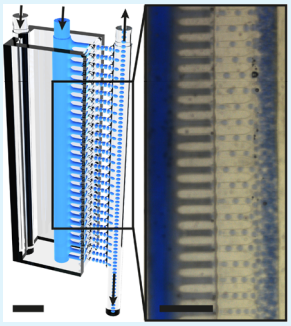
Supporting Information

ABSTRACT: We describe the preparation of rapid prototyped parallelized microfluidic drop-maker devices. The manufacturing technique facilitates stacking of the drop-makers vertically on top of each other allowing for a reduced footprint and minimized dead-volume through efficient design of the distribution channels. We showcase the potential of the additive manufacturing technique for microfluidics and the performance of the parallelized device by producing large amounts of microgels with a diameter of ca. 500 μm, a size that is inaccessible using traditional synthetic approaches.



KEYWORDS: *microfluidics, microgel, upscaling, parallelization, 3D printing, rapid prototyping, additive manufacturing*

1. INTRODUCTION

Monodisperse soft particles represent a versatile class of materials with manifold applications across disciplines. Small representatives of such particles in the nano- and micrometer regime can be produced using heterogeneous polymerization processes, such as emulsion and dispersion polymerization.[1,2] Large uniform particles can only be prepared using microfluidic drop-makers, where the droplets act as templates for polymer particles with diameters ranging from micrometers to the millimeter scale.[3−5] As the particles are generated one-by-one at a channel intersection inside of the drop-maker, the throughput of such devices is low and the yield of particles over time is poor. Several approaches have been pursued to parallelize drop-makers and increase the rate of droplet- and therefore particle generation. In *ladder*-type parallelization, the in- and outlets of a row of drop-makers are connected with distribution channels, extending the device geometry to a second layer for simple emulsions.[6−8] This has been accomplished by carefully aligning and mating several layers of PDMS on top of each other. The rows of distribution channels can be connected in a third layer to further increase the amount of drop-makers per device. Using this technique, large amounts of double emulsions could be generated.[6] By contrast, *branched*-channel devices rely on fluid distribution in the same layer as the channel intersection where the droplets are generated. Only the distribution of the dispersed phase is moved into the second layer, thus minimizing problems with alignment compared to *ladder*-type devices.[9] Another way to minimize alignment processes and distribution channels is in *circular* drop-maker arrangements.[10,11] Also combinations of these techniques have been applied with multiple circular arrangements connected with distribution channels, leading to the greatest number of paralellized drop-makers and highest throughput to date.[12]

All of these parallelization approaches exhibit a relatively large footprint, as all of the drop-makers are arranged in one layer. The two-dimensional layout entails large dead-volumes resulting from long distribution channels. The need for precise alignment of individual fluid-channel layers further obviates application of parallelized drop-makers in industrial processes.[13] Stacking of drop-makers on top of each other while connecting the in- and outlets in the vertical direction would allow for a high density of microfluidic drop-makers per area and volume, while reducing the complexity of the device structure and minimizing dead volume. Current fabrication techniques for drop-maker parallelization, such as soft-lithography and micromachining, limit the structures to two-dimensional, obviating widespread use of parallelized devices.[8,14]

Rapid prototyping based on additive fabrication principles enables the production of three-dimensional structures of nearly any desired shape or architecture.[15−17] Different principles such as stereolithography, fused deposition molding, selective laser sintering or selective laser melting have been applied to generate microreactors for chemical synthesis.[14,18−20] Direct rapid prototyping of microfluidic channel

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devices has recently been proposed, culminating in a modular system for plug-and-play microfludics.[14,21−23] Direct rapid prototyping has become an important production technique because of its short design-to-device time, low cost, and full freedom of design.[24]

Here we report the fabrication of a parallelized microfluidic flow-focusing device using digital light processing, a rapid prototyping technique that allows stacking of individual drop-makers on top of each other, minimizing the device footprint and distribution channel length. We showcase the applicability of our device by preparing monodisperse microgels with a diameter of ∼500 μm, which are inaccessible via standard emulsion or precipitation polymerization protocols.

2. RESULTS AND DISCUSSION

We start with designing the desired device architecture in a commercial CAD program. From the in- and outlets, fluid distribution channels extend into the device perpendicularly to the base area. The channel intersections at which droplets are generated are stacked vertically along the distribution channels, as depicted in Figure 1a, b (see also CAD files in the Supporting Information). To achieve monodisperse droplet formation at all parallelized intersections, we need to pay special attention to pressure control inside of the device.[25] The device layout is predetermined by minimizing pressure variation along the different drop-maker intersections by designing the distribution channels with a much larger diameter than at the channel intersection, see Figure 1a. The channels leading to these intersections are circular with a radius of 375 μm.

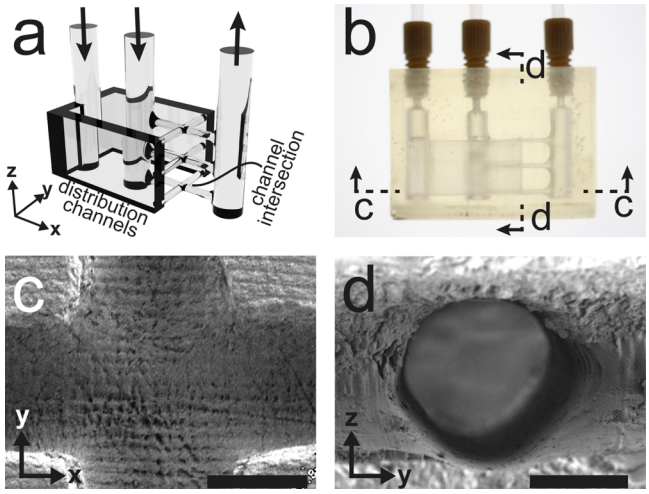

Figure 1. (a) Artistic rendering of the channel structure with inlets for continuous and dispersed phase and an outlet for the emulsion. (b) Photograph of prototyped device with tube connectors and dotted lines indicating the sectioning planes applied to image the SEM channel crossections in c and d. (c) Scanning electron micrograph of cross-section of the gold sputtered device allowing insight onto the channel contours showing voxels from micromirror array fabrication. The scale bar represents 500 μm. (d) Close up on the channel intersection showing matching design and fabricated channel sizes. The scale bar represents 300 μm.

The 3D channel CAD architecture is fabricated by rapid prototyping, which builds up the structure layer-by-layer (Perfactory Mini-multilense from EnvisionTEC). Each layer contributes to the structure with a defined voxel-height, while the features within each layers are produced using a 180 W mercury vapor lamp, which is reflected off a micromirror array, illuminating 1400 × 1050 pixels.[26−29] We apply a hydrophobic methacrylate based photoresist (eShell600) with appropriate wetting properties and excellent solvent resistance for generating aqueous droplets in mineral oil. The methacrylate photoresist is exposed at 100 mW/dm^2 for 8 s in defined areas cross-linking the resist and hence producing the resulting structure at a resolution of 32 × 32 × 30 μm in x-y-z-directions. Depending on the aspect ratio, we can achieve a maximum resolution of 200 μm for the channel width.[27,28] The unexposed resist is removed subsequently using solvent treatment.[28] A cut through the device close to the channel intersection enables microscopic inspection of the indicated sectioning planes, as depicted in Figure 1b, c. The channels are accessible for the liquids and exhibit a voxel pattern in the x−y-plane, resulting from the micromirror lithography (see Figure 1c, d). The fabricated channel dimensions in fact match the design values (cf. CAD files in the Supporting Information).

We use Upchurch M-660 connections to guide the liquids to and away from the chip. Threads for access to the channel architecture are designed as part of the device manufacturing process. For the continuous phase we use a (50:50) mixture of mineral oil and heptane to obtain a suitable viscosity and we add Span 80 as a surfactant. As dispersed phase we use deionized water colored with blue ink (see video in the Supporting Information). Flow rates of the disperse and continuous phase as well as their ratios are known to influence the drop formation mechanism. We map out the droplet formation regimes for one of the drop-makers to explore the flow rates required to obtain monodisperse droplets. We obtain monodisperse droplets in the plug-flow and dripping regimes, see Figure 2a. Moving along Q_c^{100} for Q_c/Q_d = 100 we obtain a clear decrease in droplet size as we move from the plug-flow regime into the dripping regime and the aspect ratio (AR) approaches unity above 1100 μL/min, see Figure 2b.

To verify that all three channel junctions produce droplets of the same size, we collected more than 100 droplets and performed image analysis, resulting in a standard deviation of 4.8% for the droplet diameter. Furthermore, the hexagonal arrangement of the collected droplets indicates monodispersity, see Figure 2c, d.

To showcase facile scalability of our concept, we prepared a device with 28 parallel cross-sections, as shown in Figure 3a. The previously described channel design with one inlet for the dispersed and continuous phase is extended by an additional outlet for the emulsion to compensate for varying pressure differences at individual junctions. The photograph image in Figure 3b demonstrates monodispersity of blue dyed water in oil droplets. The device easily produces droplet emulsions at rates of 3 L/h, suggesting utilization for industrial applications.

To demonstrate the applicability and superior performance of the prototyped parallel drop-maker device, we apply it to emulsify a microgel precursor together with a water-soluble photoinitiator (see the Supporting Information for details on synthesis). Subsequently, we perform a photochemical cross-linking reaction to generate monodisperse ∼500 μm microgels. Monodisperse microgels of such sizes are impossible to produce by standard heterogeneous polymerization techniques, as secondary processes give rise to bidisperse or polydisperse samples.[2] Here, a water-soluble six-armed star-shaped PEG precursor with a molecular weight of M_n = 18 kDa carrying acrylate groups at the terminus of each arm can be cross-linked photochemically. To cross-link the precursor inside of the

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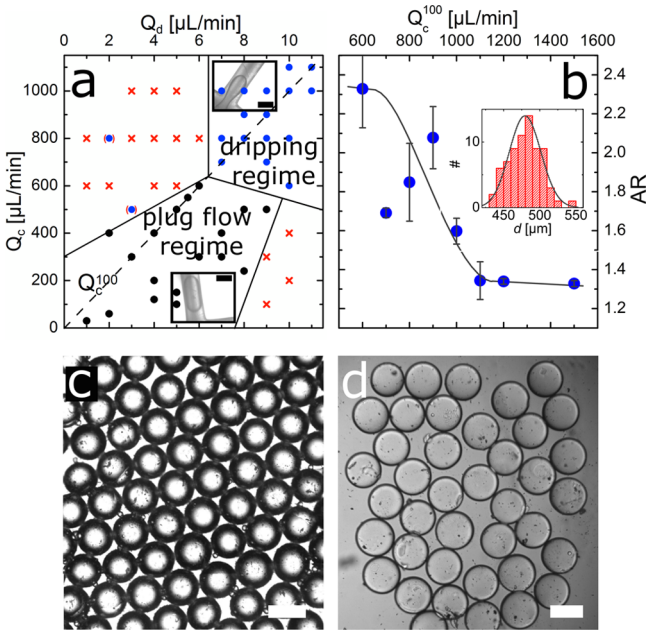

Figure 2. (a) Droplet formation map for the various conditions and different droplet formation regimes. The flow of the continuous phase Q_c versus the dispersed phase Q_d; black circles: plug flow regime, blue circles: dripping regime, red crosses: no droplet formation. The blue circles with red parentheses represent conditions where droplets are formed sporadically. The inset micrographs display representative conditions at the channel intersection for the different regimes. (b) Droplet aspect ratio *AR* versus the flow of the continuous phase Q_c^{100} for $Q_c/Q_d = 100$. The inset shows the particle size distribution for the droplets in c. (c) Monodisperse water droplets in oil produced using the parallelized microfluidic device assemble in a hexagonal lattice indicating monodispersity. (d) Micrograph of microgels in aqueous medium. All scale bars represent 500 μm.

microfluidically emulsified droplets the added radical photoinitiator is exposed to UV light with λ_{max} = 380 nm.[30] The resulting microgels are large with dimensions similar to the droplets generated in the same device, see Figure 2d. This is the first example of high-throughput generation of microfluidically produced microgels. These unprecedented results substantiate the quality as well as versatility of our design and rapid prototyping technique.

3. CONCLUSION

The fabrication technique and parallelization concept presented here can be easily extended and adopted to other materials and other drop-maker geometries. The device is printed from a cross-linkable methacrylate, which exhibits excellent resistance toward polar and nonpolar solvents. The device geometry is compatible with techniques to further passivate the channel geometry using for example gas-phase deposition methods.[5] The specific device architecture presented here facilitates the production of large droplets, which can act as reaction containers for chemical conversion, encapsulation or particle formation. In the future the challenge will lie in decreasing the channel diameters to generate smaller droplets and particles and achieve even higher drop-maker densities per chip. One potential way to conquer this demand could be the application of two-photon 3D lithography. However, also the high-throughput production of large diameter microgels, as presented here, is of special interest for several applications. These range from selective extraction and purification, to biomedical application in oral drug delivery or toxin uptake in the gastrointestinal passage. For these applications, it is crucial to control the microgel dispersity, while generating large amounts at the same time. The approach presented here will help to achieve these demanding requirements.

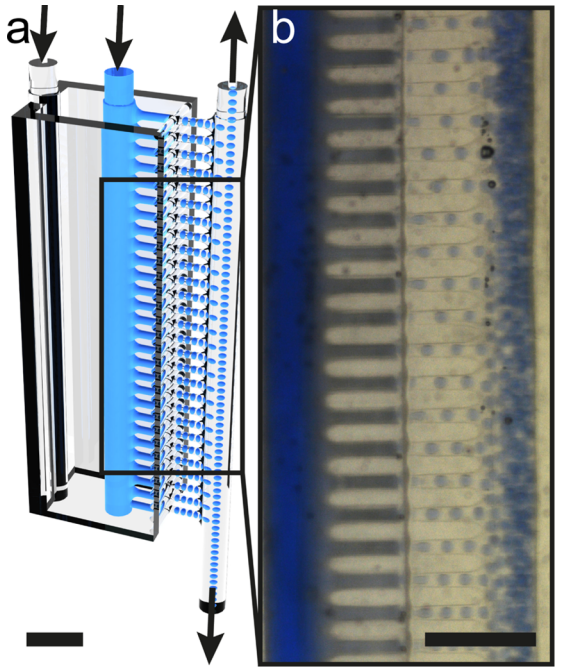

Figure 3. Parallelized drop-maker with 28 channel intersections. (a) Artistic rendering of an up-scaled parallel drop-maker with inlets for the dispersed and continuous phase and two outlets for the produced emulsion. (b) Micrograph of the running device producing blue dyed water droplets in oil. The scale bars represent 5 mm.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimentals on the microfluidic emulsification and microgel preparation and video of the emulsification process in a parallelized triple drop-maker device. CAD files of the parallel triple and 28 dropmaker devices. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.5b03969.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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