DIY 3D Microparticle Generation from Next Generation Optofluidic Fabrication

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Engineered microparticles with nonspherical shapes have attracted increased attention recently due to different shape-dependent functionalities that emerge from specific particle geometries. [1] Examples of these shape-dependent functionalities are seen in biology where the shape and surface area of drug carrier particles can alter cellular uptake,[2] and the shape of implanted hydroxyapatite particles can change the body's inflammatory response.[3] Additionally, complex double-cone particles have allowed for programmable release of multiple active ingredients for therapeutic applications.[4] Besides for bioinspired applications, nonspherical particles can self-align in a confined flow[5] or change the rheological properties of a solution.[6] Also, particles with interlocking shapes can create low-density loadbearing structures from particle jamming.[7]

Although, it remains challenging to create complex 3D-shaped particles to meet new emerging demands. Microfluidic methods such as stop flow lithography (SFL)[8] and optofluidic maskless lithography (OFML)[9] have shown great potential for producing complex-shaped particles, however, the approach mostly resulted in 2D extrusion shapes with uniform side profiles. By modifying the SFL process, we previously demonstrated the creation of 3D-shaped particles with a fabrication scheme called optofluidic fabrication.[10] Optofluidic fabrication creates an infinite set of complex 3D-shaped particles simply by varying inertial flow[11] and light conditions. However, our 3D particles generated from the use of this method have been mainly on the mm scale because of large mm scale channels used to lower pressure drops, limiting the method's potential usage. Similar particle fabrication methods termed optical transient liquid molding (TLM)[12] and Dean flow-based optofluidic fabrication[13] were reported generating 3D-shaped particles with overall sizes of hundreds of micrometers. These methods created sub-millimeter particles by using smaller channel molds, even though their dimensions are still large for potential applicability in numerous biotechnological applications.[14] Here, we present a novel method termed next generation optofluidic fabrication (NG-OF) for creating 3D-shaped microparticles an order of magnitude smaller than our previously demonstrated particles, while still utilizing primarily mm scale channels for ease of fabrication and low pressure drops.

As shown in Figure 1a, NG-OF uses multiscale channels where the inertial flow shaping is achieved in a mm scale channel upstream,[10] and passes a tapered reduction section while keeping its flow shape. The flow is then rapidly stopped, ultraviolet (UV) polymerization is initiated in the reduction section (Figure 1b; and Figure S1, Supporting Information), and a 3D microparticle(s) is generated (Figure 1c–e). Furthermore, we present a new rapid channel fabrication scheme to effectively create fluidic channels with custom pillar configurations. When a new particle shape is needed, a new channel with a different pillar configuration is required. Thus, instead of preparing new channels either by photolithography or 3D printing,[10,15] NG-OF uses an on-the-fly approach that creates pillars at a desired channel location by local UV polymerization (see Figure 4a and more details below) that is used for creating 3D-shaped microparticles.

As mentioned, NG-OF is based on inertial flow shaping from our previous optofluidic fabrication.[10] Figure 1a shows...
Figure 1. Operating principles of next generation optofluidic fabrication: a) The flow cross-section of inert (i and iii) and UV-reactive streams (ii) are shaped by fluid inertia as they flow past pillars at Re = 5. The flow cross-sections at slices S0 and S6 are shown at the inlet and after passing six pillars. After inertial flow shaping, fluid streams enter a tapered reduction zone that reduces the channel area 100-fold, scaling down the flow cross-section to the µm scale. b) After inertial flow shaping, the flow is quickly stopped, and patterned UV light is illuminated on the channel reduction section creating a 3D microparticle. c) A rendering of a microparticle resulting from a T-shaped UV light pattern with an E-shaped flow cross-section. d) Experimental setup showing the microparticle polymerization process. From left to right: Far-field view of UV illumination on the mm scale channels, inertial flow shaping can occur under reasonable pressure drops while maintaining the flow cross-section through the tapering zone. The flow is then rapidly stopped, and a 3D particle is generated by illuminating patterned UV light at the reduction section (labeled "R"), as shown in Figure 1b–e.

To generate a well-defined particle, the flow needs to be stopped fully to allow sufficient UV exposure and minimize diffusion between UV-curable and inert fluids. The stopping time relies on two timescales: 1) hydraulic capacitance and 2) viscous dissipation. First, the hydraulic capacitance timescale is dominated by the flexible channel walls which inhibits fast changes in pressures due to expansion and relaxation of the PDMS channel walls under pressure. When the input pressure is lowered to stop the flow, the channel relaxes and induces unwanted squeeze flow. We address this issue by using stiffer thermally cured PDMS channels, however, more curing agent or other rigid oxygen permeable materials can further reduce this hydraulic capacitance timescale. Second, the viscous dissipation timescale is determined by viscous diffusion of momentum, proportional to $D_k/\nu$, where $\nu$ is the kinematic viscosity. This implies that smaller channels will result in faster viscous dissipation leading to shorter flow stopping time. However, the higher pressures required by smaller channels often become too high for conventional PDMS-glass channels to withstand. As a solution, NG-OF utilizes the tapered reduction design where the channel cross-sectional area decreases by a factor of 100. This allows a moderate input pressure of 1200 mbar to still generate sufficient inertial secondary flows at Re = 5 (where Re is the Reynolds number and see Note S1 (Supporting Information) for detailed definitions of all associated parameters) with stop times less than 400 ms (see Figure S2, Supporting Information).

For NG-OF microparticle generation, we first prepared a channel mold using a 3D printer (photocurable inkjet printer) since photolithography is not practical for creating multiscale channels with a vertical tapering design. To understand and characterize the inertial flow in our channel, entire channels were simulated using COMSOL Multiphysics. Note that the 3D printed mold displayed a rounded cross-sectional channel shape in the reduction section due to resolution limits of the 3D printer (Figure S3, Supporting Information), and this feature was taken into consideration for simulations. Simulation details can be found elsewhere, but briefly, the steady-state incompressible Navier–Stokes and convection-diffusion equations were solved simultaneously with each model containing $8.9 \times 10^6$ degrees of freedom. Normalized concentration slices of photoinitiator concentration are presented in Figure 2a–c where three channels with different pillar configurations are modeled: A channel with six pairs of half-cylindrical pillars located along the side-walls (Figure 2a), six pillars located along the center (Figure 2b), and pillars that create an “E”-shape flow cross-section (Figure 2c). Channel top views are also presented for an x–y slice 5 µm above the channel bottom, and more slices can be found in Figure S4.
The z–y slices S0-S6 show the flow shape evolution, and the final reduction slice labeled “R” is shown with the area scaled up 100 times for easier visual inspection.

These simulation concentration slices were compared with experiments. The simulation concentration slices were thresholded similar to our previous work [15] using the upper local 50% concentration range to compare with the experimental particle shapes. For experiments, a thin slit of UV light was illuminated at locations S6 and R across the entire width of the channel, generating a particle whose shape represents the flow cross-section. Simulation and experimental cross-sections for the three channel designs are shown in Figure 2d, and more particle images can be seen in Figure S5 (Supporting Information). Channel heights were normalized between S6 and R (Figure S6, Supporting Information) to allow direct comparison between cross-sectional area measurements, and a detailed comparison is plotted in Figure 2e. Although general cross-sectional area trends matched, slight cross-sectional area differences were seen. These cross-sectional area differences were smaller for experimental cases compared to simulations cases. Since the steady state simulation results do not take into account the flow stopping step, diffusion occurring during flow stoppage creates a larger experimental particle shape, especially in the channel reduction where particle sizes approach relevant diffusion scales. One interesting feature was seen in the center-pillar case (Figure 2b) where the experimental area was increased while the simulation predicted a decrease. This may be because the numerical prediction does not include particle polymerization or oxygen inhibition. For the center-pillar channel, the flow shape is isolated from the side walls, preventing loss of polymerization from oxygen-inhibition near the side walls,[18] allowing the full uninhibited flow shape to polymerize. Also, it was assumed that the main channel was perfectly rectangular. Under internal pressure, PDMS channels bulge, leading to shape discrepancies which could be corrected with more accurate geometry modeling.

With the channel design validated as a method to miniaturize the inertially shaped flow, the same three channels were used to create 3D-shaped microparticles as shown in Figure 3. The full 3D particle shape could be adjusted by simply changing the light pattern or changing the location the light pattern was illuminated. In Figure 3a, UV light was illuminated off-center, and 3D microparticles with overall dimensions of width × depth × height approximately equal to 70 × 70 × 104 µm³ are generated. By using the center-pillar channel in Figure 3b, the UV-reactive stream is directed away from the channel walls, allowing for a smaller 3D particle. Although the flow cross-section is not as intricate from this pillar configuration, overall particle dimensions are as small as 30 × 50 × 35 µm³. To demonstrate increased particle shape complexity, the E-channel was used (Figure 3c) that created particles with dimensions of ≈ 70 × 70 × 104 µm³. Note that since the photomasks were aligned manually, some shape discrepancies can be seen from the particle side-views. However, these mask alignment discrepancies could be fixed completely with a digital micro-mirror device (DMD) UV system to accurately control the location of UV illumination.[9b] These 3D microparticles can

![Figure 2. Numerical versus experimental analysis of inertial flow shaping with reduction channels. a) Normalized concentration plots of inertial flow shaping from a channel with half-cylindrical pillars located along the side walls. The x–y view shows the concentration 5 µm above the channel bottom. z–y slices at S0-S6 show the flow shaping achieved upstream. After the reduction section, slice R shows the miniaturized flow cross-section with the area scaled up 100 times for easier visual inspection. b) Similar concentration plots are shown for a channel with pillars located along the central axis and c) for a complex pillar configuration that results in an “E” shape flow profile. d) Thin particles are polymerized and flipped on their sides at locations S6 and R to reveal flow shape changes. Scale bars for row S6 represent 1 mm, while scale bars for row R represent 100 µm. Simulation cross sections at similar locations as d) are shown using an upper 50% concentration threshold. e) To compare cross-sectional shapes pre- and postreduction, the reduction cross-sections were scaled up. Error bars represent standard deviation from 15 particles created in 3 different channels.](image-url)
potentially be made smaller and finer by overcoming challenges with diffusion between coflowing fluid streams. As particle sizes become smaller, diffusion length scales can approach particle sizes, either requiring faster flow stopping to limit diffusion or particles with less intricate shapes. With the experimentally tested conditions of $Re = 5$, the average transit time through the main channel section is $2.2 \text{ s}$, leading to a total diffusion time of $\approx 2.6 \text{ s}$, including flow stopping. The theoretical particle resolution can be inferred by calculating the diffusion length $L_D$ from Equation (1) below

$$L_D = \sqrt{D_IP_D t_D} \tag{1}$$

where $D_P$ is the diffusivity of photoinitiator and $t_D$ is the total diffusion time. With the DMPA diffusivity of $4 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$\textsuperscript{[15]} in polyethylene glycol diacrylate (PEG-DA) and a diffusion time of $2.6 \text{ s}$, an isometric diffusion length of $\approx 10 \text{ µm}$ is expected, representing the particle resolution limit. By incorporating a rigid channel\textsuperscript{[19]} higher allowable pressures and flow rates could reduce transit and stop times, leading to finer particle features. For example, a Reynolds number of 20 reduces the transit time fourfold to $0.55 \text{ s}$. Assuming a faster stop time of $<100 \text{ ms}$ from a rigid channel, the diffusion length could be reduced to $L_D = 5 \text{ µm}$, allowing for particle features half the size.

It should be mentioned that to fabricate a new particle shape, a specific pillar configuration should be determined. For this task, two open-source programs, Flowsculpt\textsuperscript{[20]} and uFlow,\textsuperscript{[21]} can be used to easily design a new channel. Flowsculpt calculates the necessary pillar configuration to achieve a desired flow shape, and uFlow quickly displays the flow shape from user inputted pillars. Although these tools are not designed specifically for the NG-OF process due to the interpillar distance difference, they still provide quick and very close approximations to flow shapes and channel designs that greatly aid in the design process. Then, a specific channel can be prepared using a 3D printer; however, the 3D printing preparation process can be costly and time-consuming whenever new channels are required. Therefore, instead of printing new channels, a simple method is hereby presented by creating custom pillars in blank channels via UV polymerization. As shown in Figure 4a–c, a blank channel is first filled with UV-reactive fluid. Then a circular pattern of UV light is illuminated to create a pillar (Note S2, Supporting Information) at a desired location. By using a programmable motorized microscope stage (Movie S1 and Figure S7, Supporting Information), multiple pillars were created sequentially with high precision in a fully automated manner. We refer to this custom UV-polymerization pillar scheme as “Do-it-yourself” (DIY) pillars. Although a blank channel mold originally needs to be printed, any pillar configuration (size, location, and spacing) can be prepared from this single blank channel mold.

Note that under normal UV polymerization conditions, the DIY pillars will not remain fixed during flow due to the oxygen permeable layer. Thus, we overexpose UV light and use a slight channel modification made during the channel preparation step. An oxygen diffusion barrier is added on top of the channels by simply inserting a conventional glass slide into the liquid PDMS during the curing process. This glass slide becomes embedded within the PDMS channel structure.

Figure 3. Examples of 3D-shaped microparticles created using NG-OF. a) The top-view, side-view, and 3D-view of experimentally fabricated 3D microparticles are shown by combining three different UV light patterns with part of the “I”-shaped flow cross-section. b) The center-pillar design creates a smaller UV-reactive flow shape. c) The E-pillar channel demonstrates more complex 3D-shaped microparticles. Renderings of the 3D particles are shown below. The position of UV illumination is also illustrated with the UV light path intersecting the channel cross section. Particles are false-colored to enhance contrast with background. Scale bars represent 75 µm.
and controls oxygen diffusion into the channel. Using the DIY-pillar generation scheme, we created the same channel layout as the E-channel used in Figures 2 and 3 (Movie S1, Supporting Information). The lateral location and diameter of the six sequential pillars were analyzed (Figure S8, Supporting Information) and plotted in Figure 4e,f. Both the original 3D printed channel molds and the DIY channels were compared. For both the original channels and the DIY channels, the lateral positions of the pillars and errors in diameter were compared (Figure 4e,f), and resulted in less than 3% error, showing a high precision pillar fabrication scheme.

Simulation and experimental areas were analyzed (Figure 4g) at S6 and R for the DIY channel and compared with the E-channel data from Figure 2d. The E-shape is stretching relatively more during inertial flow shaping and also shows slight asymmetry in the middle “tip.” This stretched inertial flow shaping may be caused from the more rigid DIY pillar channels since the embedded glass diffusion barrier does not allow as much channel expansion during flow. The different E-particle shapes might also be caused from slight concave shape (Figure S9, Supporting Information) of DIY pillars due to the numerical aperture (NA) of the 2.5× objective (NA = 0.085). The experimental cross-sectional areas were plotted.
Keywords

3D microparticles, inertial microfluidics, optofluidic fabrication, optofluidics

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[1] a) A. Choi, K. D. Seo, D. W. Kim, B. C. Kim, D. S. Kim, Lab Chip 2017, 17, 591; b) K. D. Seo, D. S. Kim, S. Sanchez, Lab Chip 2015, 15, 3622; c) M. Li, N. Hakimi, R. Perez, S. Waldman, J. A. Kozinski, D. K. Hwang, Adv. Mater. 2015, 27, 1880.

[2] a) H. Y. Geng, W. Y. Chen, Z. P. Xu, G. R. Qian, J. An, H. J. Zhang, Chem. – Eur. J. 2017, 23, 10878; b) X. Y. Wang, L. Lin, R. F. Liu, M. Chen, B. L. Chen, B. He, B. He, X. L. Liang, W. B. Dai, H. Zhang, X. Q. Wang, Y. G. Wang, Z. F. Dai, Q. Zhang, Adv. Funct. Mater. 2017, 27, 1700406; c) J. A. Champion, S. Mitragotri, Proc. Natl. Acad. Sci. USA 2006, 103, 4930.

[3] F. Lebre, R. Sridharan, M. J. Sawkins, D. J. Kelly, F. J. O’Brien, E. C. Lavelle, Sci. Rep. 2017, 7, 2922.

[4] K. Je, J. H. Kim, T. S. Shim, M. Ku, J. Yang, S.-H. Kim, Adv. Mater. Interfaces 2018, 5, 1701163.

[5] W. E. Uspal, H. B. Eral, P. S. Doyle, Nat. Commun. 2013, 4, 2666.

[6] E. J. Hinch, L. G. Leal, J. Fluid Mech. 1972, 52, 683.

[7] a) K. A. Murphy, N. Reiser, D. Choksy, C. E. Singer, H. M. Jaeger, Granular Matter 2016, 18, 26; b) H. M. Jaeger, Soft Matter 2015, 11, 12.

[8] D. Dendukuri, S. S. Gu, D. C. Pregibon, T. A. Hatton, P. S. Doyle, Lab Chip 2007, 7, 818.

[9] a) S. E. Chung, W. Park, S. Shin, S. A. Lee, S. Kwon, Nat. Mater. 2008, 7, 581; b) S. E. Chung, W. Park, H. Park, K. Yu, N. Park, S. Kwon, Appl. Phys. Lett. 2007, 91, 041106.

[10] K. S. Paulsen, D. Di Carlo, A. J. Chung, Nat. Commun. 2015, 6, 6976.

[11] H. Amini, E. Sollier, M. Masaelli, Y. Xie, B. Ganapathysubramanian, H. A. Stone, D. Di Carlo, Nat. Commun. 2013, 4, 1826.

[12] a) S.-H. Kim, Z. F. Dai, Adv. Mater. 2015, 27, 2970.

[13] K. S. Paulsen, A. J. Chung, presented at the Int. Conf. Miniaturized Systems for Chemistry and Life Sciences (MicroTAS 2016), Dublin, Ireland, October 2016.

[14] G. C. Le Goff, R. L. Srinivas, W. A. Hill, P. S. Doyle, Eur. Polym. J. 2015, 72, 386.

[15] K. S. Paulsen, A. J. Chung, Lab Chip 2016, 16, 2987.

[16] P. Panda, K. P. Yuet, D. Dendukuri, T. A. Hatton, P. S. Doyle, New J. Phys. 2009, 11, 115001.

[17] L. C. Hsiao, A. Z. M. Badruddoza, L. C. Cheng, P. S. Doyle, Soft Matter 2017, 13, 921.

[18] D. Dendukuri, P. Panda, R. Haghgooie, J. M. Kim, T. A. Hatton, P. S. Doyle, Macromolecules 2008, 41, 8547.

[19] K. W. Bong, J. Xu, J.-H. Kim, S. C. Chapin, M. S. Strano, K. K. Gleason, P. S. Doyle, Nat. Commun. 2012, 3, 805.

[20] a) D. Stoecklein, C.-Y. Wu, D. Kim, D. Di Carlo, B. Ganapathysubramanian, Phys. Fluids 2016, 28, 012003; b) D. Stoecklein, M. Davies, N. Wubshet, J. A. Stone, B. Ganapathysubramanian, ASME J. Fluids Eng. 2017, 139, 031402.

[21] a) J. K. Nunes, C. Y. Wu, H. Amini, K. Owsley, D. Di Carlo, J. A. Stone, Adv. Mater. 2014, 26, 3712; b) D. Stoecklein, C.-Y. Wu, K. Owsley, Y. Xie, D. Di Carlo, B. Ganapathysubramanian, Lab Chip 2014, 14, 4197.

[22] a) N. W. Choi, J. Kim, S. C. Chapin, T. Duong, E. Donohue, P. Pandey, W. Broom, W. A. Hill, P. S. Doyle, Anal. Chem. 2012, 84, 9370; b) B. Li, M. He, L. Ramirez, J. George, J. Wang, ACS Appl. Mater. Interfaces 2016, 8, 4158.