# Research Highlights

DOI: 10.1039/b606043a

## Microparticle synthesis by continuous-flow lithography

The broad usefulness of microsized hollow or solid particles, *e.g.* for microoptics, material sciences and biomedical applications, is well-documented. The key challenges of the fabrication of microparticles are the uniformity of size and shape, and the possibility of functionalizing the particles by encapsulation of, or coating with, chemicals. Microsized devices facilitate the production of microparticles as they provide inherently perfect control over the size rendering subsequent filtering procedures unnecessary. Typically, approaches for microparticle synthesis on microfluidic chips rely on the break-off of droplets in two-phase flows in T-shaped or crossed channel junctions, in which one particle per time can be created with axysymmetric shapes such as disks, spheres and cylinders.

Patrick S. Doyle and co-workers at MIT have developed a one-phase method that combines the advantages of microfluidics and microscope projection photolithography.[1] The fabrication process is performed in a PDMS microfluidic device positioned on an inverted microscope (Fig. 1). An acrylate oligomer stream containing a photosensitive initiator is pumped through the channels, and exposed to short pulses of ultraviolet light. Particle arrays are formed quickly by polymerization within less than 0.1 s.

The pattern and shape of the particles in the *x*–*y*-plane is determined by the pattern of the transparency mask that is inserted into the field-stop of the microscope. The smallest feature size that can be created by continuous flow lithography is limited by the optical resolution and the depth of field of the microscope objective (here 3 μm). The *z*-plane projection is mainly dependent on the height of the channels. In this context, the permeability of PDMS for oxygen is an important requirement for the fabrication process. The oxygen reacts with the initiator species to form chain-termination peroxide radicals, leaving a non-polymerized lubricating layer with a thickness of 2.5 μm near the PDMS walls. Hence, the formed particles are washed out directly by the unpolymerized oligomer stream. Thus, the method can be performed repeatedly; thereby arrays of particles are produced in a continuous manner with a throughput of nearly 100 particles per second, which makes this method superior to standard photolithography techniques.

Polymeric particles of various shapes are created, such as polygons, and non-symmetric or curved objects (Fig. 2). Exploiting the laminar flow in a Y-shaped channel, the authors are also able to synthesize bifunctional particles. As a proof of principle, they polymerize rectangular particles across the interface of two streams of oligomer, one of which contains a Rhodamine dye. The polymer particles that are formed at the interface are partly fluorescent, and partly non-fluorescent. Particles with different proportions of stained and pure polymer may be created simply by shifting the interface relative to the position where the particles are formed, which is realized by changing flow rates, or by moving the microscope stage.

The authors propose to synthesize morphological complex and multifunctional microparticles by continuous flow lithography, and to achieve a much higher throughput by increase of the area of the light source and further parallelization.

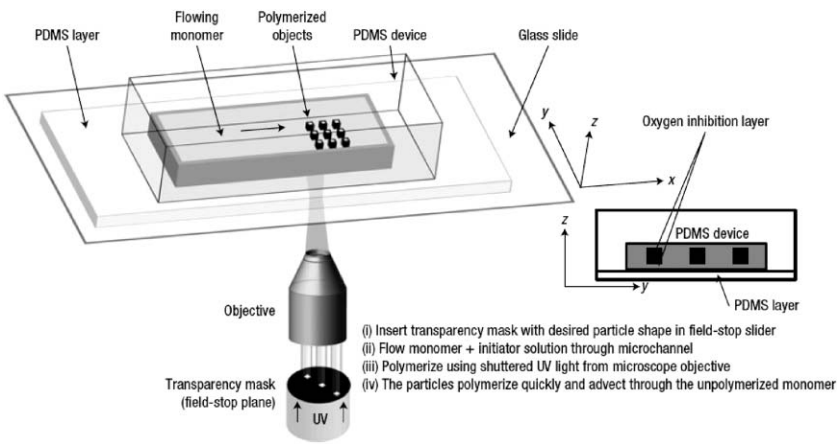


**Fig. 1** Scheme of the experimental setup used for continuous-flow lithography. (Adapted by permission from Macmillan Publishers Ltd, *Nature Materials*,[1] copyright 2006.)

## Viscous threads investigated in diverging channels

Highly viscous liquids are often found in daily life (*e.g.* honey or glue), and likewise, numerous industrial and biological liquids have widely different viscosities. Although the interesting fluid behaviour of high viscous solutions (*e.g.* pouring honey onto a slice of bread) is a familiar observation, the mechanism of these processes is not fully understood yet. Moreover, merging and mixing of liquids exhibiting different viscosities is a rather complex phenomenon due to the evolution of relative mobilities of the liquids as they are mixing.

Employing microfluidic chips, the flow phenomena of complex liquids can be easily studied in predefined channel geometries within the laminar flow regime. Recently, Thomas Cubaud and Thomas G. Mason investigated the deformation of a viscous thread on a microchip.[2] At first, the thread is formed by hydrodynamic focussing in a silicon–glass microchip comprising a crossed channel system (Fig. 3). A liquid with high viscosity (silicon oil) is injected with a defined flow rate into the central channel, and is focussed by a less-viscous liquid supplied by the side channels. Under the condition of large differences of viscosity of the liquids, the system

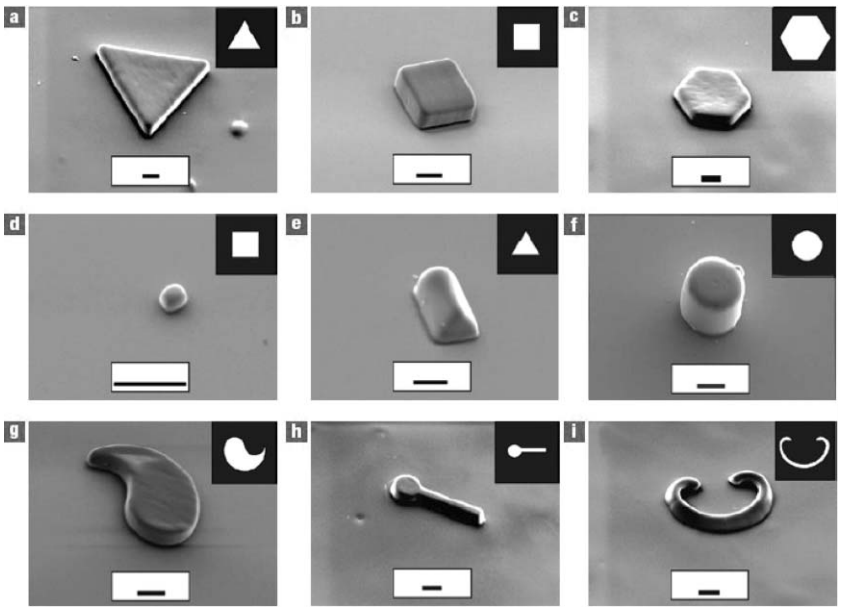

**Fig. 2** Scanning electron microscope images of polymer particles (scale bar: 10 μm). The inset in the figures shows the feature on the transparency mask that was used to form the particle. The pattern of the mask was projected into the microfluidic channel by a × 40 objective. The height of the particles was determined by the height of the used microchannels (a–c, g–i: 20 μm, d: 9.6 μm, e, f: 38 μm). (Adapted by permission from Macmillan Publishers Ltd, *Nature Materials*,[1] copyright 2006.)

minimizes viscous dissipation by forming a nearly cylindrical thread of the more viscous liquid in the centre, lubricated by the less viscous solution near the channel walls. Flowing downstream, the liquids enter a diverging channel. As this happens, the thread of the high viscous liquid is bending and folding rather than simply dilating, which is caused by extensional viscous stress. Along the diverging channel, periodic oscillations of the thread are observed with increasing amplitude and decreasing wavelength, while the thread thins. This folding instability can be observed, if the viscosity of the liquids differs by a factor of ~15. The morphologies are dependent on the flow rates of both high and low viscous liquid, and the angle of the diverging channel.

The observed viscous folding provides the ability to enhance mixing. In the diverging channel, the bent shape of the thread increases the interfacial area between the liquids. At the same time, the less viscous liquid is trapped between the folds that thin along the diverging channel section. Intermolecular diffusion occurs for low flow velocities, and is negligible for large velocities, where the thread boundary remains sharp (Fig. 4). For a large flow rate and high ratios of viscosity, the folding morphologies can become more complex and even more complex ''subfolding'' patterns appear.

This study by Cubaud and Mason could open up new directions for controlling liquid interfaces and exploiting viscous instabilities in (microfluidic) systems that are dominated by viscous forces.

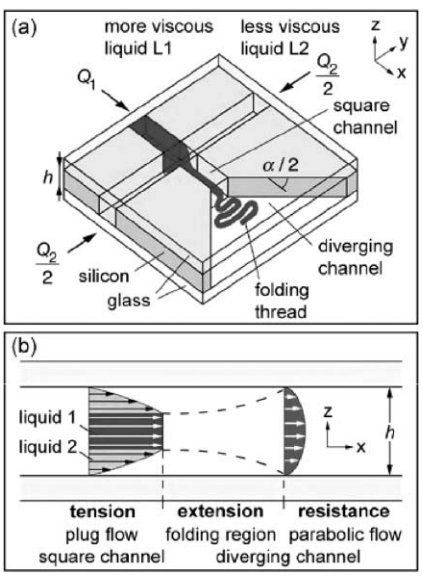


**Fig. 3** (a) A thread is formed when a viscous solution (L1) is hydrodynamically focused by a less viscous solution (L2). Folding of the thread is observed as it enters a diverging channel characterized by the angle α ($Q_1$, $Q_2$: volume flow rates of the liquids L1 and L2, respectively). (b) Flow profiles along the microchannel (side view). The arrows indicate velocities. (Adapted with permission, copyright 2006, The American Physical Society.)

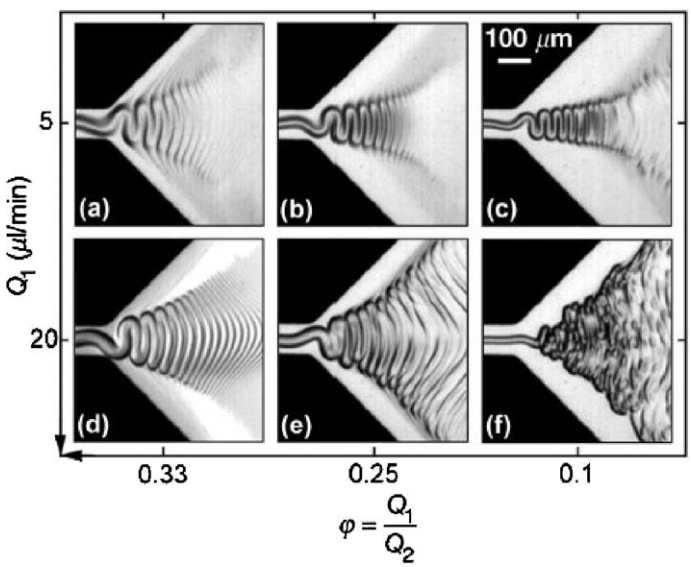


**Fig. 4** The folding morphologies of the viscous thread depend on the absolute flow rate of the viscous solution ($Q_1$), and the relative flow rate ($Q_1/Q_2$). Utilizing silicon oil with a very high difference in viscosity (500 cP and 0.5 cP, respectively), the crossover between mainly diffusive (a–c) and mainly convective (d–f) folding regimes can be observed. The striations at the boundary of the pile of folded threads in a–c are due to diffusive mixing. For larger velocities, the thread boundary remains sharp. Heterogeneous viscous mixtures with non-periodic viscous ripples are formed for large flow rates (f). (Adapted with permission, copyright 2006, The American Physical Society.)

 

## Addressable electrode arrays for DNA analysis

Issues associated with analysis and detection of minute sample quantities are challenging in the development of advanced miniaturized biosensors and bioassays. In particular for low concentrated sample, strategies are required to handle minute quantities of biomolecules, and to preconcentrate the sample to a detectable level. Addressing these demands, Faisal A. Shaikh and Victor M. Ugaz describe a microdevice that is capable of performing several functions on a single chip, *i.e.* sequential preconcentration of sample (DNA), focusing in a narrow zone, metering and injection into an analysis channel.[3] The device consists of three components: a glass chip with etched channels, a silicon chip (the channel bottom plate) patterned with several electrodes with equal distances of 225 μm, and a printed circuit to address the electrodes. DNA is injected into the assembled device. Upon applying a voltage, the DNA—being intrinsically polyanionic—migrates towards the nearest anode. Due to the small distance of the electrodes, high electrical fields are achieved with a minimal applied potential (1 V), while bubble formation due to hydrolysis reactions at the electrodes is prevented. Switching of the electrode array facilitates release, or capture of DNA at specific electrodes. In this way, the DNA is transported from one to the next electrode, and preconcentrated at the same time. The width of the zone of the preconcentrated DNA is determined by the size of the electrodes. It can be reduced by imposing a focusing scheme whereby a negative potential is applied to both electrodes located on either side of the capture electrode. In this way, significant increase in DNA concentration at the electrodes by a factor of 50 is achieved. Employing the electrode capture system, the authors show more functionalities of the device such as metering of DNA sample, and changing of the buffer solution by superimposing hydrodynamic flow.

The technique is broadly applicable to any kind of charged biomolecules, and represents an efficient mechanism for "digitally" collecting and metering precise sample quantities.

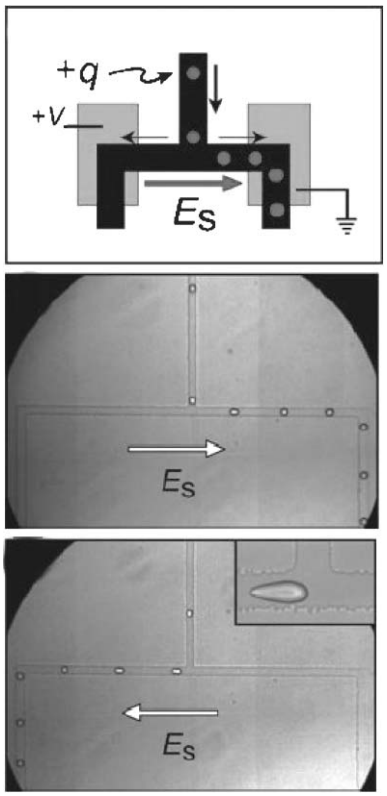


**Fig. 5** Sorting of charged microdroplets at a T-junction. Top: At the T-junction, the droplets enter either the right or the left branch (middle and bottom), depending on the direction of the applied electrical field. The distance of the droplets is reduced to half after the bifurcation, which indicates that the oil stream is evenly divided. The inset in the bottom image shows the deformation of a charged droplet in an electric field. (Adapted with permission, copyright 2006, Wiley-VCH.)

## Electrical control of microdroplets

Since the first demonstration in 2001,[4] droplet-based microfluidics has attracted broad interest. The tiny, finite volumes of typically several hundred pL to nL are generated by injection of an aqueous solution into a hydrophobic carrier, and enable rapid mixing and transport of reactants along the channel. A myriad of applications have been proposed and experimentally demonstrated, *e.g.* for conducting reactions, for protein crystallization, protein expression, cell analysis, and particle synthesis.

Darren R. Link *et al.* describe in a recently published article the concept of an electrically addressable microdroplet system.[5] A combination of electrostatic charge on the droplets and electrical fields on the devices facilitate the insertion of various functional modules to split, recombine, and sort the droplets. The device is fabricated in PDMS bonded onto a glass plate that is patterned with indium tin oxide (ITO) electrodes. Charging of the droplets is facilitated at the instant of generation. Additionally to the standard focusing techniques, a high voltage is applied, which capacitively charges the water/oil interface. This concept provides several advantages: First, at high voltages, the droplet diameter can be significantly decreased, and it is no longer restricted to the dimension of the used microchannel. Second, the electronic control enables precise synchronization of the production and arrival of individual droplets at specific locations. Third, it provides a further control level to guide droplets through the microchannels, additionally to flow rates and channel geometry. As an example, drop-by-drop sorting at a T-junction is demonstrated (Fig. 5). The authors discuss the benefit of such a microdroplet sorting system for high-throughput screening, combinatorial chemistry, and the search for rare biological function in libraries of biomolecules.

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## References

1 D. Dendukuri, D. C. Pregibon, J. Collins, T. A. Hatton and P. S. Doyle, Continuous-flow lithography for high-throughput microparticle synthesis, *Nat. Mater.*, 2006, **5**, 365–369.
2 T. Cubaud and T. G. Mason, Folding of Viscous Threads in Diverging Microchannels, *Phys. Rev. Lett.*, 2006, **96**, 114501.
3 F. A. Shaikh and V. M. Ugaz, Collection, focusing, and metering of DNA in microchannels using addressable electrode arrays for portable low-power bioanalysis, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 4825–4830.
4 T. Thorsen, R. W. Roberts, F. H. Arnold and S. R. Quake, Dynamic Pattern Formation in a Vesicle-Generating Microfluidic Device, *Phys. Rev. Lett.*, 2001, **86**, 4163–4166.
5 D. R. Link, E. Grasland-Mongrain, A. Duri, F. Sarrazin, Z. Cheng, G. Cristobal, M. Marquez and D. A. Weitz, Electric Control of Droplets in Microfluidic Devices, *Angew. Chem. Int. Ed.*, 2006, **45**, 2556–2560.