Microfabrication

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Fabricating Complex Polymeric Micro- and Nanostructures: Lithography in Microfluidic Devices**

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There is currently considerable interest in fabricating polymeric microparticles and nanoparticles, and complex three-dimensional polymeric structures that are patterned at micron or submicron length scales,[1–5] for applications ranging from photonics to tissue engineering and the design of diagnostic assay systems.[6–10] Consequently, numerous innovative strategies have been developed to fabricate such structures, including bottom-up approaches based on the assembly of molecules or colloids, top-down approaches based on techniques such as photolithography, and other approaches including molding in templates, the stretching of particles, and fabrication within microfluidic systems. The synergistic use of these techniques may help achieve the long-term goal of developing simple and scalable methods to construct arbitrarily complex micro- and nanostructures.

Self-assembly is an approach for fabricating complex architectures that is ubiquitous in nature. Self-assembly has been described as the autonomous organization of components into patterns or structures without human intervention and is one of the few practical strategies for assembling macroscopic structures from nanoscale building blocks.[11] Approaches for fabrication based on the assembly of peptides and proteins[12] and DNA[5,13] have been reviewed. The self-assembly of block copolymers enables the generation of complex nanostructures, including wormlike micelles,[14] vesicles,[15] and cylindrical nanostructures.[16,17] Complex structures have also been formed by the assembly[18,19] or crystallization[20] of colloids, and by the assembly of non-spherical particles defined by lithography, illustrating the power of the combined use of lithography and self-assembly.[21] However, self-assembly cannot as yet provide arbitrary control over the geometry of a three-dimensional structure.

Another approach to generating complex polymeric structures involves the use of templates. For instance, Jiang et al.[22] have used colloidal crystals to generate polymer templates, which in turn have been used to generate monodisperse polymer colloids. Other examples include the generation of nanocapsules by colloidal templating,[23] the formation of polymer nanotubes within porous templates,[24] the use of soft lithographic microfabrication techniques,[1,25,26] and of nonwetting templates for the fabrication of micro- and nanoparticles of various shapes.[27]

The stretching of spherical polymer particles provides an interesting approach to generating complex micro- and nanoparticles. Ellipsoidal polymer particles had previously been generated by the stretching of spherical particles.[28,29] Recently, Champion et al.[30] developed a simple, inexpensive, and versatile method that uses spherical polymeric particles as the starting point to fabricate particles of more than 20 distinct shapes and with characteristic features ranging from 60 nm to 80 μm.

In addition to the fabrication methods described above, numerous top-down methods have been developed which provide precise control over the size and shape of polymeric structures. For instance, a direct-write process using concentrated polyelectrolyte inks enables the generation of complex three-dimensional polymer microstructures.[31] Multiphoton absorption enables the fabrication of complex three-dimensional structures with tremendous control over geometry;[32,33] however, the serial nature of this technique may limit throughput and make it difficult to pattern over large areas or to generate a large number of structures.[34]

Multibeam interference lithography is an attractive top-down method for fabricating three-dimensional periodic polymer microstructures rapidly and over large areas.[6,35–38] This method uses the interference of noncoplanar laser beams in a film of photoresist to generate periodic structures.[6] The use of high-resolution conformable phase masks provides an approach for the generation of complex three-dimensional nanostructures using only a single collimated beam of light; passing light through the mask generates a complex three-dimensional distribution of light intensity, thereby exposing selected regions of the photoresist.[34] This approach enables the generation of both periodic and aperiodic structures.[34] However, unlike multiphoton lithographic procedures, these methods cannot generate structures with arbitrary geometries.

An emerging area of research involves microfabrication within microfluidic devices.[39] Microfluidic devices have been used to generate monodisperse microparticles with control

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over size, shape, and composition,[40] functional microgels,[41] double emulsions,[42] and polymer vesicles.[42] Approaches to microfabrication within microfluidic devices can exploit the laminar nature of fluid flow at low Reynolds numbers; under these conditions, parallel streams of fluid can maintain sharp boundaries with mixing taking place only by diffusion across the interface.[39]

These fabrication capabilities have been significantly extended by recent creative work involving the synergistic use of microfluidics and photolithography.[9,10,43–46] Dendukuri et al.[45] used the precise shape control provided by microscope projection lithography in combination with the continuous processing and laminar flow[39] properties provided by microfluidic devices to continuously form morphologically complex and chemically anisotropic microparticles. Particles were formed by exposing a flowing solution of oligomer containing a photosensitive initiator to controlled pulses of ultraviolet light through a transparency mask; particle shape was determined by the shape of the features used on the mask. The continuous nature of the process enabled the high-throughput generation of polymer particles (400 000 particles h^{-1}).[45] Furthermore, the diffusion-limited mixing characteristic of laminar flow[39] could be exploited to form chemically anisotropic particles by polymerizing across the interface of coflowing solutions having different compositions. The use of stop-flow lithography,[43] in which a flowing stream of oligomer is stopped prior to polymerization, provided increases in both resolution and particle throughput.

The above methods, based on the use of transparency masks, could only fabricate microparticles composed of solid two-dimensional shapes. Recent work by Thomas, Doyle, and co-workers[10] significantly enhances the range of structures that can be fabricated within microfluidic channels by making use of phase-mask interference lithography. This new technique—stop-flow interference lithography (SFIL)—enables the high-throughput fabrication of complex three-dimensional and chemically anisotropic microstructures (Figure 1).

A particularly promising application of SFIL is to generate particles for use in sensing and diagnostic assays. Pregibon et al.[9] have already used continuous flow lithography to generate multifunctional polymeric microparticles containing distinct probe-loaded regions (to capture target molecules) and graphically encoded regions (to encode analytes). Libraries of such encoded particles can be used for the multiplexed detection of fluorescently labeled DNA oligomers rapidly, and with high specificity and sensitivity. In this context, the use of SFIL enables the generation of polymer microparticles with an even greater ratio of surface area to volume, thereby increasing the sensitivity for sensing and diagnostic applications.[10] The ability of SFIL to generate porous structures may be useful for applications ranging from separations to mixing and designing catalyst supports.[10,34]

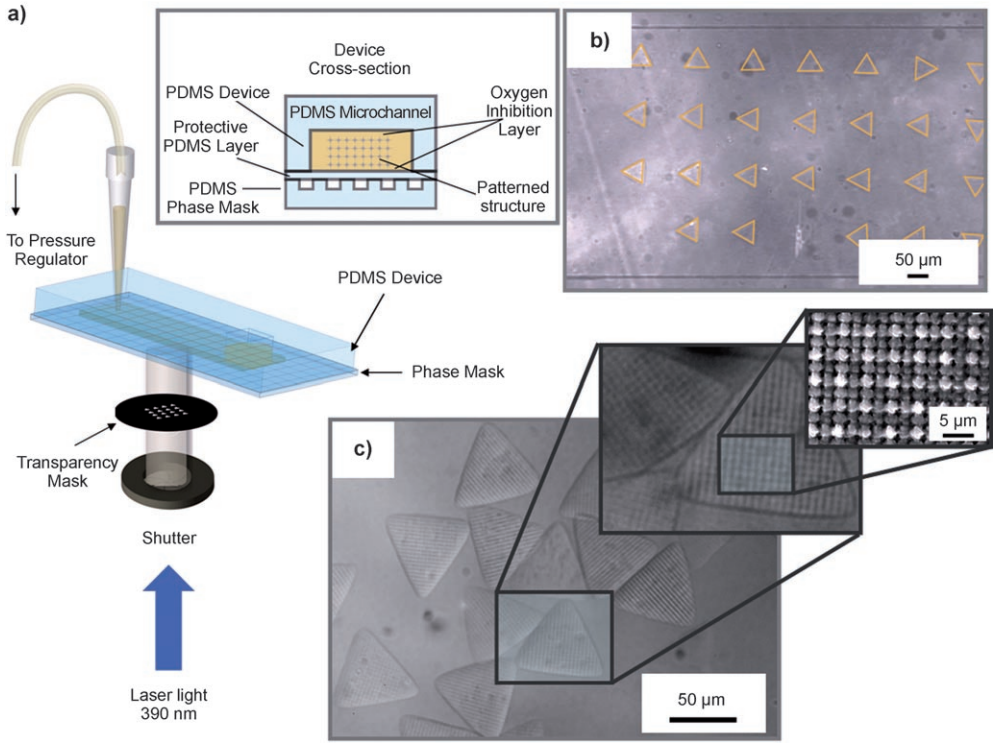

Figure 1. Fabrication of complex three-dimensional microstructures by SFIL. a) Schematic illustration of the SFIL experimental setup. Transparency-mask-defined light passes through a poly(dimethylsiloxane) phase mask into a stationary oligomer film in the microfluidic device. This process results in the formation of an array of structures, each containing a three-dimensional pattern defined by the phase mask. b) Brightfield image of an array of patterned triangles (delineated in yellow) with sides 60 µm formed in a 600 µm wide and 30 µm tall microfluidic device. c) Differential interference contrast image of the triangles shown in b) after they have been suspended in ethanol. The patterned grid-like structure formed by the phase mask is visible on the surface of the particles, and is shown more clearly in the inset view obtained by scanning electron microscopy at the top right corner. Reproduced from Thomas, Doyle, and co-workers[10] with permission.

Another important application of SFIL would be as a tool for studies of cell biology and tissue engineering.[7,8] Microfabrication techniques have already provided fundamental insight into how the cellular microenvironment (e.g. cell shape, the composition of the extracellular medium, etc.) influences cellular function.[7,8] The ability of SFIL to generate three-dimensional chemically anisotropic hydrogels may be particularly useful given the increasing emphasis on three-dimensional cell culture.[47] Cleaving the initially continuous three-dimensional microstructures formed by SFIL may also enable the generation of three-dimensional submicron particles having complex shapes.[48] Such particles would be useful for both fundamental studies as well as for applications in biotechnology,[30] as particle shape can influence particle phagocytosis[49] and the persistence of particles in the circulation.[50]

The results discussed above clearly illustrate the advantages of the synergistic use of microfluidics and lithographic techniques. SFIL, however, may also enable the generation of chemically anisotropic "patchy" particles, which could self-assemble under the right conditions into structures that would be difficult to form using traditional materials.[51] Synergistic use of SFIL with this third powerful fabrication technique—self-assembly—may pave the way to applications that are truly limited only by one's imagination!

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