Microstructured Materials

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Multicompartmental Materials by Electrohydrodynamic Cojetting**

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While multicomponent micro- and nanoscale structures and even atomically blended materials have been in use for centuries in various bulk forms ranging from metal-nanoparticle-doped glasses to crystalline alloys, recent advances in top-down and bottom-up fabrication processes have allowed for improved control over the structure of micro- and nanoscale multicomponent materials. These multicomponent microstructured materials are important in imaging, drug delivery, sensing, and tissue engineering. A simple example of such a material is the core–shell particle, where the shell could improve the compatibility with the surrounding environment in imaging applications, provide for a controlled release profile in drug delivery, or give tuneable absorption properties in plasmonic particles. While the core–shell configuration has its utility, there is ample room for more complex configurations. In drug delivery and diagnostics, for example, it would be attractive to have a platform where multiple compartments of a microstructured material could be used to: 1) target the desired cells, 2) deliver the desired drug(s) at the desired rate(s) for the required duration(s), and 3) label the treated cells for diagnostic evaluation.

Various techniques have been utilized to fabricate multicomponent microstructured materials with core–shell,[1] nested,[2] Janus,[3] and/or granular architecture.[4] Figure 1 depicts examples of multiphase microstructures patterned by various techniques, including the microfluidic sheath flow of granular Janus particles (Figure 1a),[4] laser direct writing of a trapped colloidal fluid (Figure 1b),[5] electrospinning of inorganic–organic hybrid materials in core–sheath and side-by-side configurations (Figure 1c and d),[6,7] and the electrospray and cellular uptake of water-stable Janus particles (Figure 1e).[8] While the solution-phase syntheses of particles can be scaled up readily, they have not been well suited for the arbitrary placement of multiple components on the microscale. Standard lithographic approaches are also limited as a result of their layer-by-layer additive and subtractive processing requirements, which can be wasteful and tedious as complexity increases. Directed assembly approaches have been gaining popularity as they often use relatively simple building blocks, and do not require repetitive layer-by-layer processing to form useful microstructures. Direct writing through a robotically controlled nozzle is a powerful technique for the direct assembly of three-dimensional structures, but it so far suffers from low throughput and has not been used to date for co-

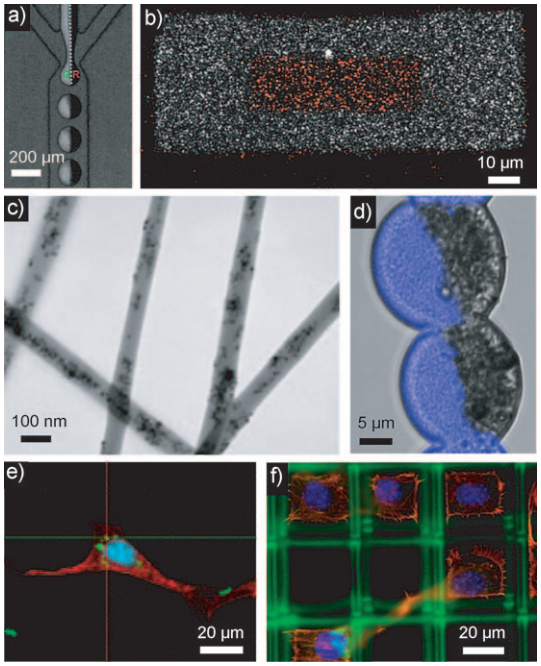

Figure 1. Multicomponent microstructures patterned by a) the microfluidic sheath flow of granular Janus particles,[4] b) laser direct writing of a porous-walled microcavity with trapped colloidal fluid (in red),[5] c), d) the electrospinning of inorganic–organic hybrid bicompartmental fibers with core–sheath (c) and Janus (d) configurations,[6,7] e) the electrospray and cellular uptake of water-stable, fluorescently labeled Janus particles (reprinted from ref. [8] with permission from Elsevier), and f) the robotic direct write assembly of scaffolds showing compartmentalized cell morphology.[14] Images in (a), (e), and (f) are fluorescence micrographs, (b) is a reflectance-mode laser scanning confocal micrograph (LSCM), (c) is a TEM micrograph, and (d) is an overlay of fluorescence-mode LSCM and differential interference contrast (DIC) micrograph cross-sections.

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deposition of multicomponent microstructured materials. The microfluidic laminar co-flow of various input streams in side-by-side or nested configuration has been used to form particles with multiple components and complex microstructure.[2] Electrospinning, electrospray, and scanning e-jet printing approaches are rapid directed assembly techniques which have been used to form fibers, particles, and droplets on the micro- and nanoscale. These techniques, which rely on the formation of an electrified jet of liquid, have been receiving increased attention in the past decade because of their simplicity and versatility. Electrospinning in particular has been used to form filtration membranes, smart fabrics, nanofiber reinforced composites, sensors, optical devices, enzyme and catalyst supports, and cell scaffolds for tissue engineering.[6,9]

Electrospinning, electrospray, and e-jet printing approaches rely on the ejection of an electrohydrodynamic jet from a suspended droplet at the tip of an electrically charged syringe or capillary, and the collection of this ejected material onto a counter electrode. The liquid droplet (often called an ink in e-jet printing) can be a complex fluid or a simple solution or melt. In the typical electrospray process, an ejected jet from a low-viscosity liquid breaks up into tiny droplets as a result of instabilities associated with the jet's large surface charge and the long path length between emitting and collecting electrodes. In e-jet printing, jet breakup into droplets is typically avoided by moving the emitter and collector into close proximity. In electrospinning, jet breakup is avoided by increasing the viscosity of the fluid. As the solvent evaporates or the liquid cools, the charged jet solidifies into a filament and is collected on the counter electrode. Fiber diameters can be reliably controlled from tens of microns to less than 100 nm by utilizing solvent evaporation and filament stretching induced by electrostatic repulsion. To align the fibers, the collector surface can be moved rapidly with respect to the nozzle (typically a rotating cylinder, or the edge of a rotating disc is used), or the collector counter electrode can be split to direct the filament back and forth in the desired direction.[6,9]

Xia and Li have demonstrated the electrospinning of multicomponent coaxial fibers with core–sheath cross sections using electrohydrodynamic cojetting of nested capillaries in an approach very similar to those used in microfluidics to form core–shell particles.[6] Recently Lahann and co-workers have successfully applied side-by-side microfluidic co-flow concepts to the electrospray and electrospinning techniques.[8,10–12] In their cojetting electrospray process, several viscous polymer solutions are pumped at low flow rates in side-by-side capillaries or syringes and brought together into a common tube at low Reynolds number, resulting in laminar flow. The droplet that forms at the end of the tube maintains the distinct geometrical arrangement of the fluid phases. A voltage of several kV is applied to the fluid through the syringes or capillary, resulting in ejection of an electrohydrodynamic jet. Laminar flow is retained despite jet stretching, breakup, and solvent evaporation, allowing for the collection of colloidal particles containing distinct compartments filled with the various polymer feeds. Using this cojetting electrospray approach (depicted in Figure 2), Lahann and co-workers have successfully fabricated spherical particles with two or three distinct compartments loaded with various grafted dyes or biomolecules for potential use as multifunctional imaging probes. They have demonstrated the ability to selectively functionalize one of the compartments using the ultrastrong biotin–streptavidin interaction.[10–12] Short-term biocompatibility and cellular uptake (see Figure 1e) of the multicompartmental imaging probes was also demonstrated.[8]

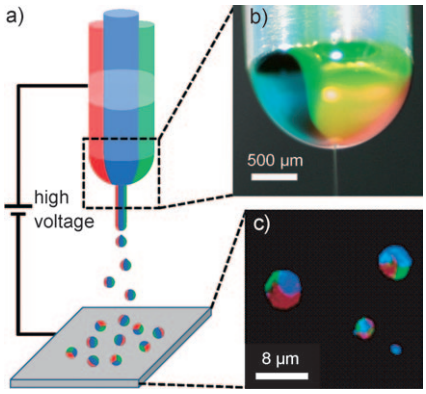

Figure 2. Fabrication of spherical particles by a cojetting electrospray process: a) schematic, b) suspended droplet with electrohydrodynamic jet emission, c) tricompartmental particles. Parts (b) and (c) adapted from reference [11] with permission from the publisher.

Very recently, Lahann and co-workers extended their cojetting technique to include the electrospinning of aligned biodegradable poly(lactide-*co*-glycolide) (PLGA) multicompartmental microfibers with narrow polydispersity.[7] Further cryosectioning of these fibers into multicompartmental particles (see Figure 3) provides a route towards multifunctional imaging probes and/or targeted drug-delivery systems.[13] However, the sheets of aligned fibers themselves have applicability as microstructured cell scaffolds. Typical electrospun materials for cellular scaffolds have random orientation, but recent studies have shown that cells can align and orient owing to both chemical and physical micropatterning (see Figure 1f for an example of the latter),[14] and that this can effect cell signalling and migration.[15] The highlighted work of the Lahann group targets the production of multicomponent cell scaffolds with both physical and chemical microscale

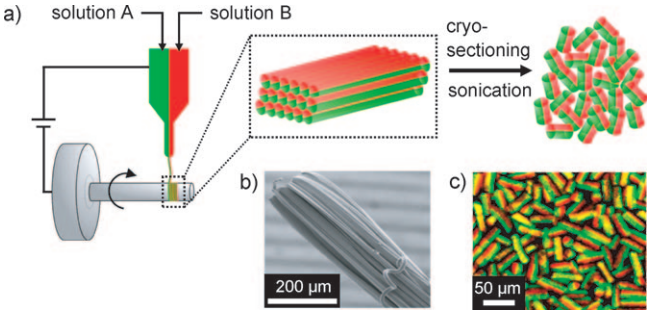

Figure 3. a) Schematic representation of the electrospinning of bicompartmental fibers and cryosectioning into cylindrical particles. b) SEM image of a fiber bundle. c) Fluorescence micrograph of bicompartmental particles. All images adapted from reference [13].

alignment.[7] Figure 4 presents fluorescence-mode laser scanning confocal micrographs (LSCMs) of frozen sections from aligned sheets and loose bundles of electrospun multicompartmental microfibers with side-by-side (Figure 4a and b), pie-shaped (Figure 4c), asymmetric (Figure 4d), striped (Figure 4e), and rosette (Figure 4f) compartment configurations. The Lahann group has further supplemented their exquisite

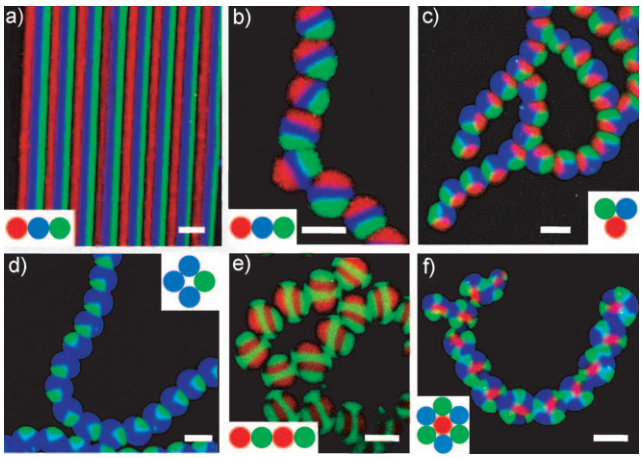

Figure 4. Fluorescence-mode LSCMs of frozen sections from a) aligned sheets and b)–f) loose bundles of electrospun multicompartmental microfibers with a), b) side-by-side, c) pie-shaped, d) asymmetric, e) striped, and f) rosette compartment configurations. Insets depict coflow bundling configuration. Scale bars = 20 μm. All images adapted from reference [7] with permission from the publisher.

control over fiber (and particle) compartmental organization and size by demonstrating the following: 1) selective removal of one compartment based on solubility differences in the starting polymer feedstock,[13] 2) the ability to sequester an inorganic phase (iron oxide) inside one compartment for potential imaging applications (see Figure 1d),[7] 3) selective click-chemistry functionalization of one compartment with active biomolecules,[13] and 4) the ability to selectively label one compartment with a target molecule using a simple bioconjugation approach.[12,13]

Several technical challenges seem to remain if the stated goal of multicomponent cell scaffolds with both physical and chemical microscale alignment is to be implemented for biological studies. To improve porosity in thick fiber mats for studies of cell migration and signaling in three dimensions, at least one component of the microstructured fibers must be removed (this has already been demonstrated in particle form).[13] Alternately, cross-hatched fiber mat designs with the required porosity could be formed by utilizing a pair of split electrodes in a crosslike configuration.[6] One limitation of electrospinning is that arbitrary fiber placement is not possible. In addition, long-range order might be disturbed if the jet or filament were to rotate en route between the emitter and collector. This would induce a stacking faultlike defect where the compartments are not all oriented in the same direction. Borrowing principles from the related direct write assembly and e-jet printing techniques could allow for improved control over fiber placement. For example, by bringing a miniaturized emitter nozzle close to the collector surface and switching the emitter voltage above and below the critical level for electrohydrodynamic jetting while scanning,[16] one might form complex structures composed of striped fibers or particles of controlled in-plane orientation and length. This would enable not only studies in biology but could also have interesting applications in electronics and other areas. Potential complications of this approach might include mixing and spreading upon impact with the substrate. Proper ink and system design would be critical to promote rapid solidification before impact yet still avoid clogging of the tip. More viscous polymer solutions or inks (perhaps even cross-linked) might be required. An alternate approach to control fiber placement would be to use electromagnetic condensing and objective lenses (as in scanning electron microscopy) to direct the jet/filament to the desired location. Ring electrodes were already reported to improve jet stability.[17] Incorporation of a magnetic fiber compartment could allow for stable control over jet/filament orientation all the way to the collector substrate. This might also allow for helical multicompartmental fiber architectures.

The practicality of the earlier electrospray techniques demonstrated by the Lahann group and others[18] might be limited by the reproducibility of particle size and architecture. The recently demonstrated cryosectioning of multicompartmental fibers (see Figure 3) is an interesting choice for the fabrication of multicomponent microparticles of low polydispersity, with potential application as multifunctional cellular imaging probes or in targeted drug-delivery systems (see Figure 1e, for example). Perhaps throughput could be improved by patterning the fibers into cylindrical particles using two-beam interference lithography in a single parallel step, instead of the serial sectioning technique that is currently in use. This of course would require that the fiber compartments be composed of polymers compatible with photolithography. Fine-tuning of the sensitivity of each compartment might be required if uniform sectioning were desired. Throughput could also be improved by electrospinning from multiple nozzles simultaneously.[19]

The work described herein represents important progress in the development of multicomponent microstructured materials and has special relevance to biological imaging, drug delivery, tissue engineering, and colloidal physics. Other intriguing materials that have been deposited recently using the more traditional forms of electrospray and electrospinning include living cells and white-light luminescent (utilizing energy transfer) DNA nanofibers.[20,21] Perhaps the printing of adjacent compartments loaded with living cells and various drugs for screening of gradient and combinatorial effects is next, or maybe it will be red–green–blue multicompartmental white-light luminescent structures.

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