Top-down Fabrication of Uniform Non-Spherical Polymer Particles for Nanomedicine Applications

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Statement of Purpose: Size and shape are fundamental properties of micro/nanoparticles that are critically important in nanomedicine applications. Extensive studies have elucidated the effects of particle size (mostly from spherical particles) on their clearance, circulation, extravasation, and distribution *in vivo*. In contrast to size, the impact of particle shape remains poorly understood, due in large part to the lack of fabrication methods to simultaneously and precisely control the size and shape of nanoparticles. Here, we report two innovative top-down engineering methods to produce monodisperse, non-spherical polymer composite particles for nanomedicine applications. The availability of these shape-specific and multi-functional particles will allow fundamental study of the particle shape effects on their blood circulation, cell targeting, and drug release performance in vivo.

Methods: The first method is based on double-layer polymer nano-molding or nanoimprint using nanoporous anodic alumina templates (AAT) to produce polymeric nanotubular or nano-rod particles containing bio-agents. The second method is to fabricate disc-shaped polymer composite particles using photolithography on double-layer polymer systems (P-DLP). For both techniques, functional polymer (polymer composite loaded with superparamagnetic iron oxide (SPIO) particles, fluorescence dyes, and/or drugs) is deposited on a sacrificial polymer layer using spincoating. After the micro- or nano-particles are formed, the sacrificial polymer layer is selectively dissolved to release free rod or disc particles to aqueous solution. The details of both methods will be presented in the presentation.

Results: Figure 1 shows the rod shaped particles produced using double-layer polymer nanomolding process. Nanotubular SU-8 (a UV-curable epoxy polymer) particles of 80 nm diameter and 100-500 nm length have been achieved in large quantities (10^{12} particles per run). Fluoresence images of released particles demonstrate that molecular agents and drugs can be encapsulated into this non-spherical carrier system. Figure 2 shows the disc-shaped SU-8 particles of 2 μm in diameter and 100-200 nm in thickness. Green fluorescence dyes and SPIO particles are successfully and uniformly encapsulated into the disc particles. The drug release rate from these particle systems can be controlled by controlling the degree of SU8 cross-linking by adjusting UV exposure time. Currently, the throughput of the P-DLP process is about 10^9 particles per run (10 mins), which can be enhanced by using automatic wafer handling robot available in our cleanroom, or using PDMS transfer process to deposit polymer materials in a similar fashion to the roll-to-roll printing methods.

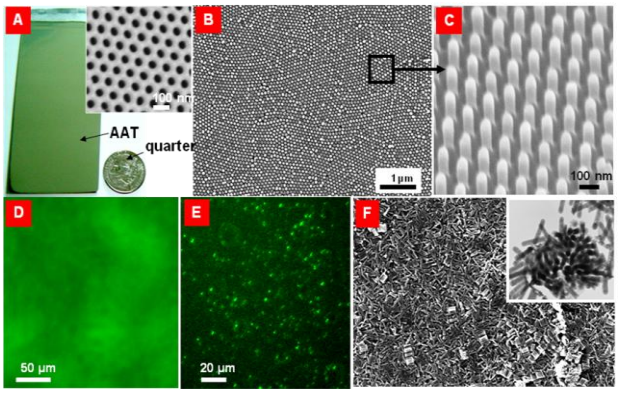

Figure 1. Manufacturing of rod shaped nanoparticles: A) nanoporous anodic alumina template; B) and C) SEM images of the molded SU-8 pillars; D) Fluorescence images of nanorods doped with green dyes before release from substrate and E) after release to aqueous solution; F) SEM image of massive rods produced (inset is TEM).

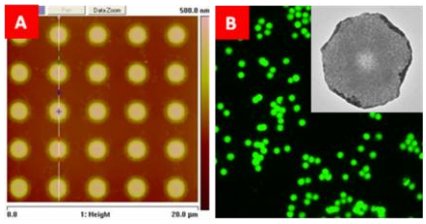

Figure 2. Manufacturing of disc shaped SU-8 particles: A) AFM of disc particles (2 μm in diameter and 100-200 nm in thickness) on sacrificial polymer layer; B) fluorescence image of released disc particles encapsulated with SPIOs and green dyes. The inset is a TEM image of individual disc particles with uniform and dense distribution of SPIOs.

Conclusions: We have developed two new fabrication methods based on nanoimprint and photolithography on double-layer polymer materials. The use of anodic alumina membrane as imprint template allows fabrication of highly packed tubular nanostructures over large area. Using nanocomposite polymer that contains therapeutic and diagnostic agents, fabrication of multi-functional rod and disc shaped particles has been demonstrated. The use of sacrificial polymer allows non-invasive collection of these particles from the substrate to aqueous solution. UV induced cross-linking of epoxy material can be well controlled to achieve desired drug release rate from the particles. These processes provide practical scale-up strategies for the application of top-down engineering approach to produce massive nanoparticles of specific and uniform shape and size. It may open up new opportunities to study the effects of particle shape on the nanomedicine performance.