# Top-down Fabrication of Monodisperse Non-Spherical Polymer Composite Particles for Nanomedicine Applications

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Size and shape are fundamental properties of micro/nanoparticles that are of critital importance 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 vaguely 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 top-down engineering methods using lithography to produce monodisperse, non-spherical (rod and disc shaped) polymer composite particles for nanomedicine applications. The availability of these shape-specific and multi-functional particles will allow fundamental study of the shape effects on the aforementioned *in vivo* behavior of nano particles.

There are two requirements for lithography to be practical in producing particles for nanomedicine: 1) high-rate production with low cost, and 2) biocompatible process/ materials to transfer particles to aqueous solution. Therefore we employed photolithography and nanoimprint or their combination to pattern discrete particles on biocompatible and water-soluble sacrificial polymer substrate (Fig. 1). For disc-shaped micro-particles, photolithography is used to pattern bilayer polymer on the wafer scale, e.g. functional UV curable polymer (SU-8) containing bio-agents (Green BODIBY© fluorescence dyes and superparamagnetic iron oxide or SPIO) on a sacrificial water-soluble polymer (PVA). For rod-shaped nanoparticles, nanoimprint with large-area trench mold (Nanonex) is used to pattern nano-lines in SU-8 on the PVA coated substrate, and then the nanolines were truncated using photolithography to form uniform nanorods with a density of $10^8$ particles per $cm^2$ (Fig. 2). The residue layer formed in nanoimprint can be removed by either plasma etching or by partial molding the sacrificial polymer layer into the mold to separate the nanolines on the top. After patterning, the PVA is dissolved in water to release patterned disc or rod-shaped particles into solution. Figure 3 shows the fluorescence and TEM images of disc-shaped SU-8 particles of 2 μm in diameter and 100-200 nm in thickness. The fluorescence dyes and SPIO particles are uniformly encapsulated into the disc particles, enabling fluorescence microscopy and magnetic resonance imaging (MRI) for characterization *in vivo*. Aqueous solution of the discs (~$5\times10^7$ particles per mL) with varied doses had been injected into mice, after which blood samples were taken in different time points. The number of disc particles staying in these blood samples counted under the fluorescence microscope shown an exponential decreasing trend versus time (Fig.4), indicating the feasibility of these lithographically defined non-spherical particles for *in vivo* study under current process conditions. In the paper, we expect to show more results to elucidate the effect of particle shape on their blood circulation and bio-distribution *in vivo*.


Figure 1. Schematic of the fabrication process.

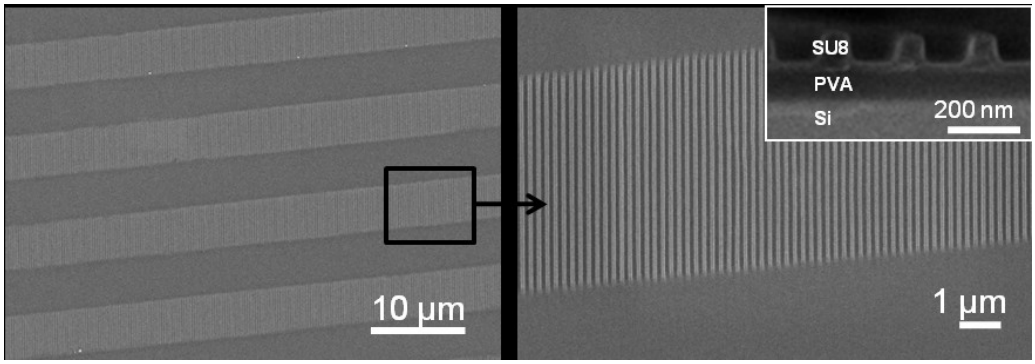


Figure 2. SEM images of SU-8 nanorods of 80-90 in diameter and 5 µm in length on top of the PVA layer. Inset shows the cross-section of the particles.

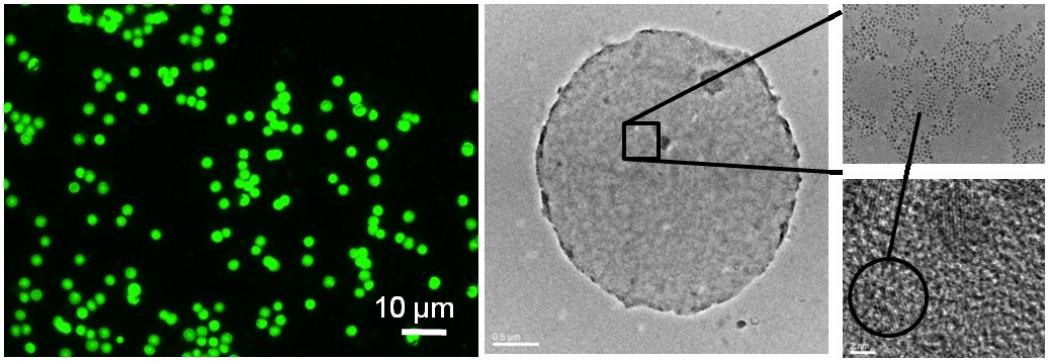


Figure 3. Fluorescence (left) and TEM (right) image of released SU-8 disc particles of 2 µm in diameter and 100-200 nm in thickness, encapsulated with SPIOs and green dyes.

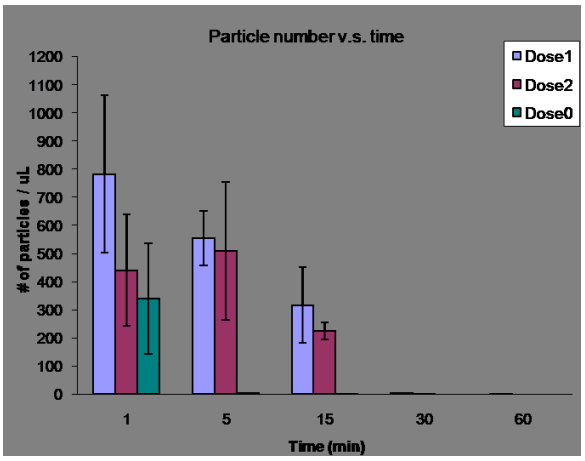


Figure 4. *In vivio* study of SU-8 disc particles in mice. a) The number of SU-8 disc particles per µL in mouse blood sample versus time, SU-8 particles are concentrated to $5\times10^7$ particles per mL in aqueous solution with PBS: Dose 0, 1, 2 are 57, 100, 160 µL injection respectively.