Nano-imprint Lithography for the Fabrication of Injectable Stimuli-Responsive Drug Delivery Devices

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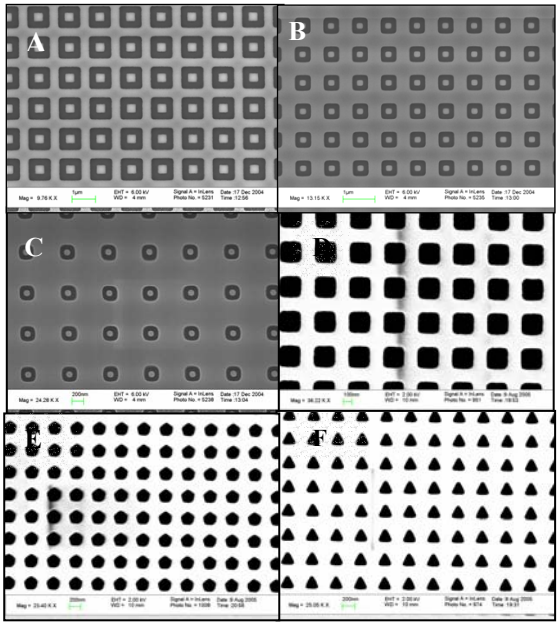
Statement of Purpose: Over the past several years therapeutic and diagnostic applications of micro and nano-fabrication technology have been gaining increasing interest. Current efforts in controlled release drug delivery suffer from a large polydisperse population of micro- or nano- particles whose physico-chemcial characteristics, drug release profiles, degradation kinetics, and material properties become hard to evaluate and reproduce in pharmaceutical scales. Our main approach is to fabricate highly monodisperse, injectable nano-particles for controlled release of drugs and injectable nano-containers with a "lid" that can effectively sense a physiological stimulus and consequently "dissolve" at a target site inside the body thereby releasing therapeutic agents. We are developing novel nanofabrication techniques using step and flash imprint lithography (S-FILTM) and thermal nano-imprint lithography to create mono-disperse, biocompatible nanoscale delivery devices having appropriate size, shape, and reservoir volume.

Methods: In order to make monodisperse drug carriers, a reusable silicon and quartz nano-imprint template with various shapes was created using e-beam lithography and reactive ion etching (RIE). Four inch silicon wafers were spin coated with ZEP520, patterned using e-beam lithography and then dry etched using a RIE to etch the silicon surface below. A two inch square quartz template had chromium evaporated on the surface and ZEP520 resist spun on top. The quartz template was patterned with e-beam lithography and then etched with two RIE processes to etch the chromium and quartz.

Depending on the polymeric material used, both the thermal nano-imprint process and SFIL process can be used to make drug delivery particles. The thermal nanoimprint process was performed on a polymethyl-methacrylate (PMMA) layer and a poly(lactic-co-glycolic acid) (PLGA) layer (300 nm thick) spun on a 4 inch silicon substrate. Each polymer was heated above its glass transition temperature using a heater chuck under the wafer and subsequently imprinted with the silicon template. Finally, residual polymer was removed using timed oxygen plasma cleaning and released into solution.

We have also employed the S-FIL method using an IMPRIO100 S-FIL tool to directly imprint peptide functionalized PEG membranes onto a silicon substrate. The step and flash process allows for high-throughput, wafer-scale patterning of the photo-linkable polymer into drug delivery vehicles. To show that the peptide functionalized PEG membranes could be photo-polymerized and imprinted using S-FIL, we imprinted the polymer using a standard template with nano-line array patterns.

Results / Discussion: Using e-beam lithography (EBL) and reactive ion etching (RIE) proved successful in creating a nano patterned Si "stamp" for use in thermal nanoimprinting. Furthermore, the novel process of creating a patterned quartz "stamp" for S-FIL proved successful. With the Si template we successfully used a thermal imprinting process to pattern PMMA nano-container features onto a Si substrate. Well-defined nano-containers (200nm, 400nm and 800nm) were patterned in the resist on a large scale with little to no variability. PMMA and PLGA nanoparticles with varying shapes (squares, triangles, pentagons) were also patterned. Using S-FIL we demonstrated that it is feasible to imprint PEG nano features.



SEM images of EBL pattern on template(A) 800nm boxes, (B) 400nm boxes, (C) 200nm boxes, (D) 400nm squares, (E) 200nm pentagons, (F) 200nm triangles.

Conclusions: We have developed top-down fabrication techniques to create highly monosdisperse biocompatible nano-devices and nano-particles. The top-down nano manufacturing approach could ensure nearly monodisperse population of drug carriers and precise control of triggered drug release. This could provide significantly improved alternatives to currently available diffusion/degradation controlled systems. We will develop methods to load drugs in the nano-containers, to incorporate stimuli sensitive polymeric "lids" with the nano-containers and to utilize our quartz template to use S-FIL to imprint polymer nano-particles.

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References: T.C. Bailey et al., *J Photopolymer Sci Tech* 15, 481 (2002).