Scalable Fabrication of Polymeric and Organic Nanomaterials using Particle Replication In Non-wetting Templates (PRINT) and Imprint Lithography

B.W. Maynor,* G.M. Denison,* J.P. Rolland,* J.M. DeSimone**

* Liquidia Technologies
P.O. Box 110085, Research Triangle Park, NC 27709, ben.maynor@liquidia.com
** Departments of Chemistry, Pharmacology, and Lineberger Comprehensive Cancer Center
University of North Carolina – Chapel Hill, Chapel Hill, NC 27599
Department of Chemical and Biomolecular Engineering
North Carolina State University, Raleigh, NC 27695

ABSTRACT

We have developed scalable, "top-down" nanofabrication methodologies for the fabrication of polymeric and organic nanostructures for nanobiotechnology and materials engineering. These techniques use highly fluorinated elastomers (Florocur™) that possess superior nanoimprinting properties, including error-free nanoscale shape replication of microfabricated, self-assembled, and biological materials. We have used these materials to produce monodisperse, shape-specific organic nanoparticles of many compositions in a process that we call Particle Replication In Non-wetting Templates (PRINT™) and for the fabrication of nanostructured surfaces for microelectronics. For pharmacological applications, we are able to fabricate valuable particulate agents such as monodisperse solid drug nanoparticles, targeted therapeutic delivery vectors, and molecular imaging agents. For microelectronics, we have demonstrated the ability to pattern relevant structures such as dual-damascene patterns with nanometer-scale resolution in a single step. We have combined the robust processing capabilities of the microelectronics industry with the flexibility and sophistication of traditional organic materials chemistry to produce unique nanostructured materials that should find many applications in nanomedicine and materials science.

Keywords: nanoparticles, imprint lithography, nanobiomaterials, drug delivery, nanofabrication

1. Introduction

Emerging nanotechnologies have found important roles in applications as diverse as materials science and medicine. Unfortunately, both "top-down" and "bottom-up" nanofabrication technologies have been limited by several factors. "Top-down" methods have been hampered by limitations in enabling materials and materials flexibility, and "bottom-up" methods are limited by uniformity, precision, and scalability. Here, we report development of a series of platform technologies that use "top-down" fabrication using Fluorocur elastomers for precision surface patterning and nanoparticle manufacturing (the PRINT™ process).

2. Imprint Lithography using Fluorocur™ molds

Fluorocur elastomers are ideal as "molds" for imprint lithography because they offer superior molding properties, including minimal adhesion to molded patterns and excellent release. We have previously demonstrated error-free replication of sub-100 nm features,[1] but the ultimate replication fidelity of these materials is within 1-2 nm of the desired mold morphology. Figure 1 shows fabrication of a complex "dual-damascene" structure in a single step, demonstrating that we have excellent replication ability of important 3-dimensional nanopatterns for microelectronics applications.

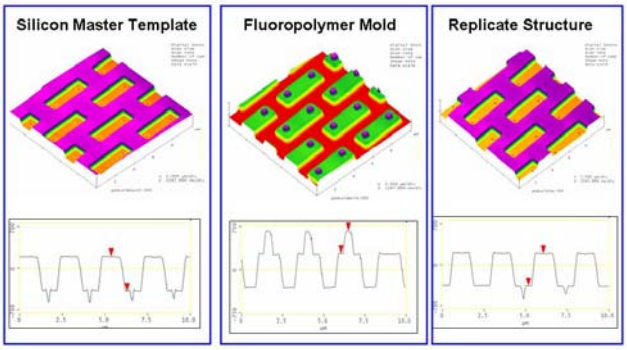

Figure 1. Dual-damascene structures fabricated using imprint lithography with PFPE molds

3. Particle Replication in Non-wetting Templates (PRINT™)

We have also used Fluorocur materials for the fabrication of nano- and micro- particles in a process called Particle Replication In Non-wetting Templates (PRINT™), where Fluorocur molds are used to "stamp" or "print" out particles in well-defined shapes that are directly derived from the shapes of the cavities in the mold (Figure 2).[2]

PRINT™ offers absolute control over particle size, shape and particle composition.

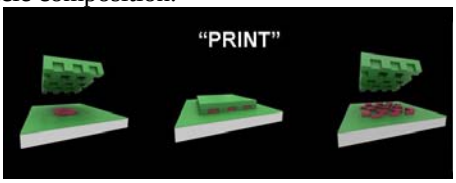

Figure 2. Schematic of the PRINT process. The green color refers to low surface-energy materials, which are used to assist the removal of residual material between objects.

The PRINT process begins with generation of a "master" template that is used to pattern the Fluorocur mold. The masters are generated using standard micropatterning and nanopatterning technologies from the microelectronics industry. Figure 3 shows a representative image of a typical micropatterned master. The Fluorocur liquid precursor is then poured over the master, where it wets the surface topography due the extremely low surface tension of the precursor material. The Fluorocur precursor is then polymerized to form a highly fluorinated, elastomeric material that adopts the morphology of the master.

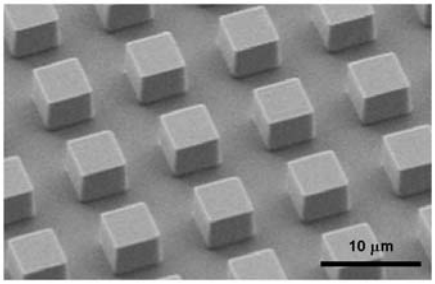

Figure 3. Representative image of a microfabricated "master" template used to pattern PFPE molds

This mold is then used to "mold" or "print" out particles that have shapes that closely resemble those on the microfabricated template. The crucial difference between PRINT and imprint lithography is that a low surface-energy substrate is used to assist removal of the residual material between objects. Because Fluorocur molds are highly chemically inert and non-interacting with hydrophilic and lipophilic compounds, nearly any organic compound can be molded to form uniform, shape-specific particles, including biocompatible materials, engineering polymers, and biological materials. Because the shapes of the particles are directly derived from the mold, nearly any particles of any shape can be fabricated simply by changing the shape of the patterns on the microfabricated master. Figure 4 shows shows a variety of uniquely shaped particles, demonstrating the breadth of morphologies that can be fabricated using PRINT.

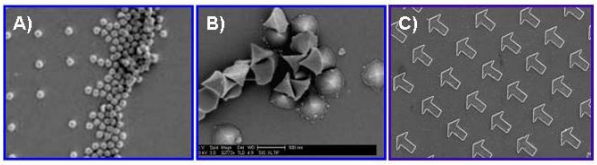

Figure 4. Demonstration of some of the particle shapes generated using the PRINT process; A) 160 nm cylindrical particles; B) 500 nm conical particles; C) arrow-shaped particles.

Using PRINT, we have fabricated monodisperse, shape-specific particles using important drug delivery systems. Monodisperse particle populations, ranging from sub-200 nm nanoparticles to complex micron-scale objects, have been fabricated and harvested in a scalable manner. Figure 5 shows a variety of important biological agents that have been incorporated into particle compositions, including DNA therapeutics, viral vectors, and chemotherapy agents. We have initiated ground-breaking studies on the combined effects of size, shape, and composition on therapeutic delivery in vitro and in vivo. These types of studies are not possible using other particle fabrication methods because they do not allow for complete control over particle size and shape.

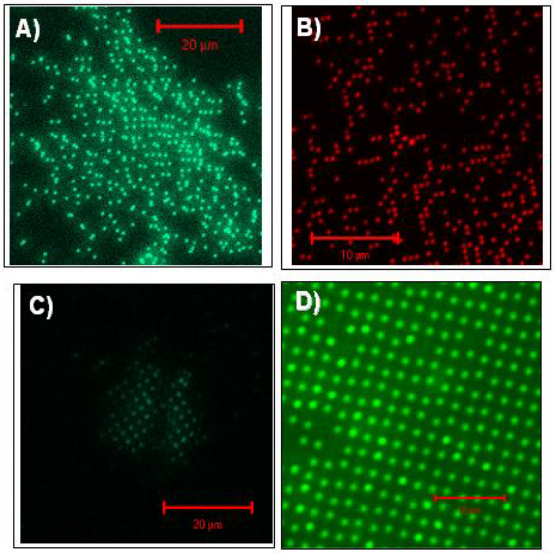

Figure 5. Fluorescent images of therapeutic agents incorporated into PRINT particles (the imaging agent is indicated in parentheses); A) avidin containing particles (fluorescein); B) DNA-containing particles (Cy-3); C) Adeno-associated virus-conatining particles (Alexa 488); D) Doxorubicin-containing particles (autofluorescent).

4. Conclusions

In conclusion, we have demonstrated that Fluorocur™ elastomers can be used for unique high-fidelity, high-value nanofabrication applications. The unique properties of these materials, such as their extremely low surface energies and

chemical tolerance allow them to have great flexibility for nanofabrication applications. In particular, we have demonstrated superior imprint lithography capability for 3-dimensional micro- and nano-patterning of surfaces and we have shown a unique application of these materials for the production of monodisperse, shape-specific organic microparticles and nanoparticles with nearly any composition (the PRINT^{TM} process).

REFERENCES

[1] J. Rolland, E. Hagberg, G. Denison, K. Carter and J. DeSimone, *Angew. Chem. Int. Ed. Engl.*, 43, 5796-5799, 2004.

[2] J. Rolland, B. Maynor, L. Euliss, A. Exner, G. Denison and J. DeSimone, *J. Am. Chem. Soc.*, 127, 10096-10100, 2005.