Fabrication of Gold/Chrome Microparticles to be Used in Drug Delivery Applications

Arthur K. Kuehl, Materials Sciences & Engineering, University of Arizona
NNIN REU Site: Minnesota Nanotechnology Cluster, University of Minnesota

NNIN REU Principal Investigator: Steven Campbell, Electrical Engineering, University of Minnesota
Contact: akuehl53@yahoo.com, campbell@ece.umn.edu

Abstract:

The norm in drug delivery carriers is a polymeric shell that encapsulates drugs and escorts them to a targeted area. Metallic particles have the advantage of being smaller than polymeric carriers, and they are less likely to be removed from the body due to recognition as a foreign object. In this work, a process for making micron-sized metallic particles for use as drug delivery carriers was evaluated. These particles were gold and chromium coated silicon nitride made using known technologies such as photolithography and dry etching procedures. The scope of the project included analyzing the particles to find their stiffness, but this was not accomplished due to a lack of adhesion between the free particles and the sampling substrate.

Introduction:

There are many challenges that must be overcome to construct a biopharmaceutical or biotechnological drug that is effective in the human body. Some of these challenges are: poor drug solubility, short half-life, poor bioavailability and drug targeting. Up to 90% of intravenously delivered drugs may be gathered up by macrophages within the first five minutes inside the body. Many other drugs simply cannot stand up to the environment of the blood and will break apart before reaching their targets [1].

The standard answer to this problem is to encapsulate and protect the drugs inside a carrier molecule. Many of these carrier molecules are polymeric micelles that are functionalized to limit recognition by the body's mononuclear phagocytic system (MPS), which is useful to increase half-life within the body, and also to place a targeting moiety on the particles [2].

A more novel answer to this problem would be to use a metallic microparticle as the drug carrier. These particles could have high affinity to biological molecules, and thus adhere very strongly, as well as slip through smaller channels. It is also advantageous to have the drug connected to the particle surface rather than inside a polymer matrix. Some metallic particles (e.g. magnetite, Fe_3O_4) also have the advantage of being able to be targeted through the use of magnetic fields [3].

The scope of this project included evaluating a procedure for fabricating microparticles and secondarily, characterizing the stiffness of the particles produced. Existing techniques used for photolithography, dry etching, wet etching, and metal deposition were employed.

The Atomic Force Microscope (AFM) was used to try to measure the stiffness of the fabricated particles. This device operated the cantilever in a mode in which the tip of the cantilever would come into contact with the surface of the sample. The stiffness of the material could be determined from force vs. displacement data gathered with the AFM.

Experimental Procedure:

The beginning materials for this process were 4-inch Si wafers with phosphosilicate glass and low-stress nitride layers on the surface. The process used to fabricate these particles consisted of two separate photolithography procedures separated by metal deposition, and then a dry and a wet etch. The first photolithography left uncovered the shapes of the metallic layers on the nitride. The metal was deposited and the remaining photoresist was removed, thereby lifting off the unwanted metal. The second photolithography procedure left uncovered channels between the particles, which were dry-etched in order to eat the nitride out from between the particles. After this etch, an HF vapor etch was done to release the particles from the PSG layer beneath the nitride. The result of this final etch was an aqueous solution of gold/chrome microparticles on a nitride backing.

The particles fabricated were then spun onto wafers patterned with trenches in order to hold the particles for AFM sampling. The AFM was used to try and sample the stiffness of these particles.

Results and Conclusions:

Metal-based particles in the micron-size range could provide an attractive alternative drug carrier for the biotechnology industry. In this work, a procedure utilizing well-known processes used in microchip production was developed to fabricate these particles. The procedure—including photolithography, and wet and dry etching—has proven to be effective in making particles on the micron scale with specific geometries. All four geometries—filled rectangles, filled circles, rectangular rings and circular rings—were successfully produced and harvested from the original wafer substrates.

Future Work:

The main work remaining within the scope of this project is to image the particles produced, and determine their stiffness using the AFM. Using the probing tip of the AFM, force versus displacement data can be taken, and from this information, the stiffness of the particles can be calculated. This information about the stiffness of the particles is important in determining whether the nitride/metal microparticles could survive inside the body.

Acknowledgements:

Thanks to Dr. Steve Campbell, Mark Fisher, and the NFC staff. Also, thanks to Greg Haugstad and the CharFac for their assistance. I also thank the NSF and the NNIN for providing funding. A very special thanks to the other REU students at UMN for making this a wholly wonderful summer experience.

References:

[1] Muller, R. H. and C. M. Keck. "Challenges and Solutions for the Delivery of Biotech Drugs - A Review of the Drug Nanocrystal Technology and Lipid Nanoparticles". Journal of Biotechnology. 113 (2004) 151-170.

[2] Rosler, A., G. W. M. Vandermuelen, and H. Klok. "Advanced Drug Delivery Devices View Self-Assembly of Amphiphilic Block Copolymers". Advanced Drug Delivery News. 53 (2001) 95-108.

[3] Chattopadhyay, P. and R. B. Gupta. "Supercritical CO2 Based Production of Magnetically Responsive Micro- and Nanoparticles for Drug Targeting". Ind. Eng. Chem. Res. 41 (2002) 6049-6058.

[4] Madou, Marc J. Fundamentals of Microfabrication: The Science of Miniaturization. CRC Press, LLC. Boca Raton, FL 2002.

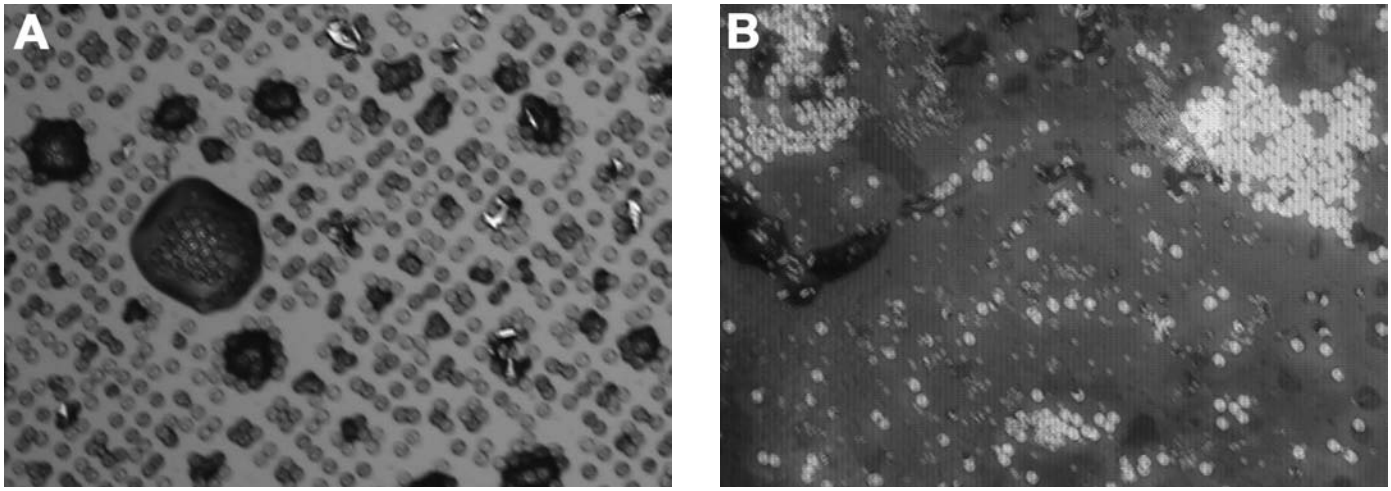

Figure 1: SEMs ~300 µm across. A. Clumped particles previous to removal from substrate wafers. B. The wafer after the etching procedure was done to release the particles, showing how the particles continue to coagulate.