Preparation of Chitosan Nanocaps for Smart, Self-disassembling Nanostructures for Targeted Drug Delivery

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Introduction

The production of chitosan nanoparticles is an integral part of an ongoing project to produce capped nano-sized "test tubes" for targeted drug delivery. Chitosan is a biocompatible polymer; thus, chitosan nanotubes have potential applications in cancer treatment, where current treatments are often prohibitively cytotoxic.

Nanotubes can be loaded with drugs, and capped using dimethyl 3,3′-dithiobispropionimidate (DTBP) to link the nanoparticles to the tubes. The tubes can then be liberated from the template in which they were prepared, and modified with specific antibodies which can biologically direct tubes to (only) diseased cells. Upon entering the cells, DTBP is cleaved at its disulfide bond, the cap is removed, and the payload is released.

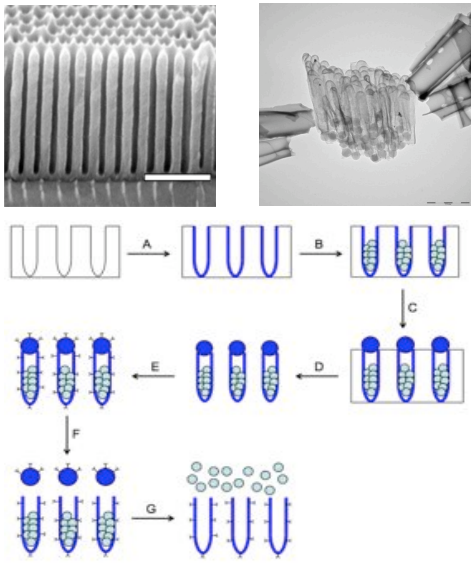

Figure 1. (Top Left) Cross section of an alumina template used to prepare nanotubes. Scale bar: 500nm. (Top Right) TEM image of chitosan nanotubes capped with commercially available latex nanospheres. Scale bar: 500nm. (Bottom) Schematic for [A] producing, [B] loading, [C] capping, [D] liberating, [E] modifying, [F] uncapping, and [G] unloading chitosan tubes.

Methods

Chitosan nano-sized caps were prepared using a reverse microemulsion technique. Briefly, a microemulsion containing a small amount of aqueous chitosan (CS) solution was prepared. A similar, separate microemulsion containing a small amount of aqueous NaOH solution and sodium dodecyl sulfate (SDS) was also prepared. The NaOH microemulsion was then added to the CS microemulsion until the pH reached 10. The particles were crosslinked with glutaraldehyde, filtered through a membranes of varying pore diameters, and collected.

Capping experiments were also performed by immersing chitosan tubes (while still in the alumina template) in an aqueous solution containing commercially available latex nanospheres. The template was dissolved, and the liberated capped tubes were collected.

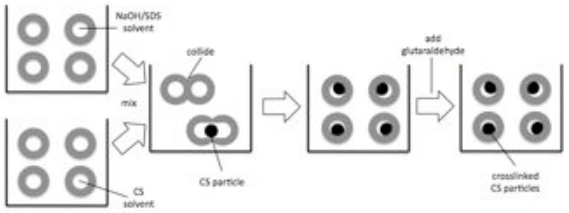

Figure 2. Reaction diagram of the preparation of chitosan nanocaps.

Results

Using a reverse microemulsion technique, spherical, monodisperse chitosan nanocaps were prepared with an average diameter of 80nm, and a sufficiently narrow size distribution. An attempt to cap chitosan tubes with the prepared chitosan caps has not yet been made.

Chitosan tubes (still in the alumina template) were successfully capped with commercially available latex nanospheres. The average in-template capping efficiency (measured by the ratio of capped tubes to total tubes) was 76%, and did not decrease significantly when the capped tubes were liberated from the alumina template.

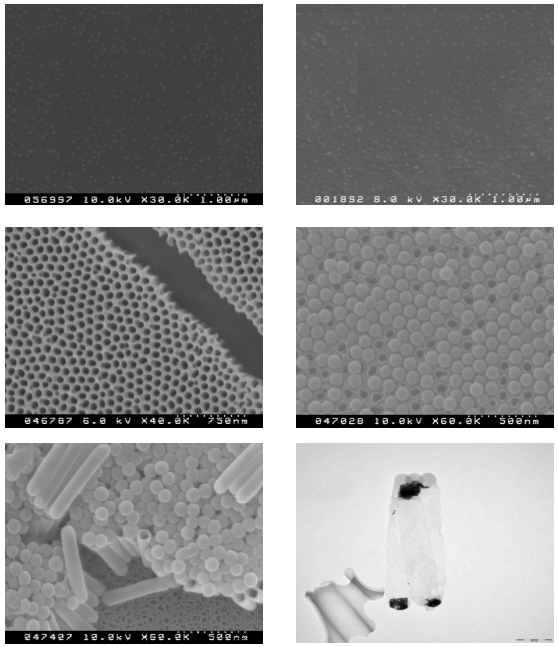

Figure 3. (Top Left) Purchased latex nanospheres. (Top Right) Chitosan nanocaps prepared using microemulsion technique. (Center Left) Blank alumina template. (Center Right) In-template chitosan tubes capped with commercially available latex nanospheres. (Bottom Left) Liberated chitosan tubes capped with commercially available latex nanospheres. (Bottom Right) Liberated, capped chitosan tubes loaded with 2nm gold particles as a drug substitute.

Further Work

While the efficient capping of chitosan tubes with latex particles is a promising start, chitosan tubes have yet to be successfully capped with chitosan particles. The latex nanospheres provide an adequate model for chitosan caps, and thus, fine-tuning a reliable method to covalently bind chitosan caps to in-template chitosan tubes is the obvious and immediate next step.

We would also like to incorporate an iron oxide (magnetic) core into the chitosan caps. This provides several advantages over pure chitosan caps. Magnetic particles can be easily directed in solution, which could lead to more efficient capping; successfully capped (magnetic) tubes could then be quickly separated from uncapped (nonmagnetic) tubes. Magnetic caps also have the benefit of being highly visible under MRI, which could be used to determine the ability of these nanostructures to locate their biological targets. Since iron oxide is noncytotoxic, the magnetic structures will still retain the advantage of being biocompatible.

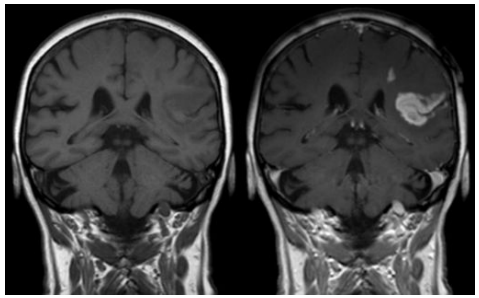

Figure 4. A defect of the blood brain barrier seen under MRI without a contrast agent (left), and with an iron oxide contrast agent (right). *Source: Hadjipanayis, EGFRvIII Antibody-conjugated Iron Oxide Nanoparticles for Magnetic Resonance Imaging-guided Convection-enhanced Deliver and Targeted Therapy of Glioblastoma. 2010*

Acknowledgements

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Selected References

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