

Engineering thermo-responsive nano-shells

Daniel Cohn

The Casali Institute of Applied Chemistry, The Institute of Chemistry, The Hebrew University of Jerusalem, 91904
Jerusalem, Israel

Introduction

Engineering nano-sized structures such as liposomes, dendrimers and polymeric micelles, is a growing area of contemporary biomaterials science, with special interest being drawn by their use in drug and gene delivery and in the Tissue Engineering field. The objective of this study is to develop thermo-responsive nano-constructs. The approach followed in the past to render nano-particles with the ability to respond to small temperature differentials, focused on grafting thermo-responsive chains onto the surface of various nanoparticles or blending them with a non-responsive matrix. Expectedly, these nano-particles displayed a very limited ability to respond to temperature changes since a non-responsive component was a significant part of the system.

This contribution describes totally thermo-responsive hollow nano-structures, comprising only poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock. The uniqueness of these novel nano-sized constructs stems from their ability to display a remarkable and reversible change in size (up to 400 times by volume), within a narrow temperature interval. These supramolecular architectures are produced by cross-linking intramolecularly end-capped PEO-PPO-PEO dimethacrylates, while these amphiphilic triblocks are constrained to the specific spatial configuration dictated by their micellar organization.

Materials and Methods

(I) *Pluronic F-127 dimethacrylate*. The PEO-PPO-PEO triblock with methacryloyl chloride. The functionalization of the triblock was demonstrated by ¹H-NMR analysis and FTIR spectroscopy. Once F-DMA formed micelles in aqueous medium, they were crosslinked intramolecularly by free radical polymerization, using ammonium persulfate (20 mg/ g polymer) as the initiator and (5 mg/g) of both ferrous sulfate and L-ascorbic acid. Most of the work was conducted using the (EO)₉₉-(PO)₆₇-(EO)₉₉ triblock, known as Pluronic F127.

(II) *Biodegradable nano-shells* were obtained, by the ring opening polymerization of L-lactide, initiated by the terminal hydroxyl groups of F-127, followed by the incorporation of the methacrylate moieties.

(III) *Dynamic Light Scattering*. The average hydrodynamic radius of the microstructures present in the aqueous medium was measured by dynamic light scattering (HPPS, HPP5001, Malvern Instruments, U.K). The solutions concentration was 0.2% W/W.

(IV) *Transmission electron microscopy*. Samples were lyophilized with liquid nitrogen for 24 hours and then re-dissolved in water *prior* to use and dried on the grid.

Results

The cross-linking of the hydrophilic PEO shell, not only stabilized the micelles, resulting in robust nano-constructs, but rendered them also with a unique dimensional reverse thermo-responsive behavior. F127

triblocks appear as molecular unimers at low temperatures and they form a micelle, at a higher temperature. For example, at 15 °C, the size of F127 unimers is 6-7 nanometers, while its micelles attain a size of around 20 nanometers, at 37°C. Once the temperature decreases below *cmt*, the micelles disassemble, reverting to their unimeric state. In fundamental contrast to the above, the affixed nano-sized constructs generated decrease in size markedly when going from a lower temperature to a higher one, in a sharp and reversible manner. Spherical nano-shells formed at 50 °C exhibited a diameter of around 230 nanometers at 15°C, while displaying a markedly smaller size (approximately 35 nanometers in diameter) at 37°C (Figure 1).

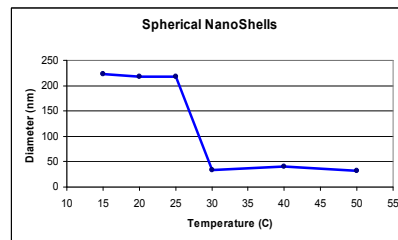


Figure 1

Since the shape and size of the micelles depend on the temperature, nano-shells having various geometries, were "sculptured" by performing the cross-linking reaction at different temperatures. Tubular nano-shells (see Figure 2) were formed by crosslinking rod-like micelles at 80°C. Their size shifted from 3,000 nanometer at 15°C, to around 300 nanometers at 37°C. Also, the nano-shells were rendered biodegradable by incorporating aliphatic oligoesters into their structure. By selecting the particular lactone (e.g. lactide, ε-caprolactone) as well as its segmental degree of polymerization, nano-shells displaying different rates of degradation, were generated.

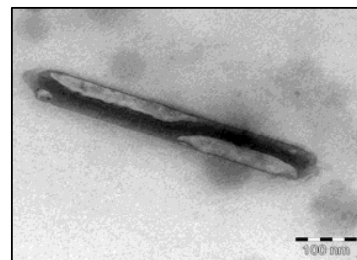


Figure 2

Conclusions

Numerous applications for these thermo-responsive nano-shells can be foreseen in various biomedical areas, such as drug delivery, sensors and Tissue Engineering.