Título: SELF-ASSEMBLING OF SYNTHETIC-POLYMERIC AND BIO-POLYMERIC SYSTEMS OF TECHNOLOGICAL INTEREST

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Fecha de lectura: 11/05/2012

Mención a doctor europeo: concedido

Programa de doctorado: CIENCIA Y TECNOLOGÍA DE MATERIALES

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> QUIMICA FISICA

> TECNOLOGIA DE MATERIALES

> FISICA DEL ESTADO SOLIDO

> TECNOLOGIA MEDICA

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> 2012juareself-.pdf

Localización: BIBLIOTECA XERAL USC

Resumen: In the present work, we investigated the micellization, gelation and the structure of aggregates of three poly(ethylene oxide)-poly(styrene oxide)-poly(ethylene oxide) block copolymers (EO12SO10, EO10SO10E10 and EO137SO18EO137, where E represents the oxyethylene unit, S the oxystyrene unit, and the subscripts correspond to the number of monomeric unit constituting the polymeric chain) in solution. We also investigated the adsorption process and the surface properties of these block copolymers at the air-water (a/w) and chloroform-water (c/w) interfaces. Since these copolymers possess a more hydrophobic middle block ¿the styrene oxide unit, they should gives rise to more efficient drug delivery systems, in which geometry might play a

key role for drug solubilisation and cell uptake. For these reasons, a detailed characterization of the physicochemical properties of these copolymers is required.

In this work, the spontaneous formation of vesicles by the block copolymer EO12SO10 without the need of external energy input has been observed In aqueous bulk solution. This is the first time that vesicle formation for styrene oxide based-block copolymers is reported. These vesicular structures are in coexistence with spherical micelles, as confirmed by dynamic light scattering (DLS), polarized optical microscopy and transmission and cryo-scanning electron microscopies. Meanwhile, for block copolymers EO10SO10E10 and EO137SO18EO137 only one species is found in solution, assigned to elongated and spherical micelles, respectively. The adsorption kinetics of these block copolymers at both (a/w) and (c/w) interfaces were determined by the pendant drop method. Measurements of their interfacial rheological behaviour showed that the adsorption layer at the (a/w) interface manifests solid-like properties in the whole accessible frequency range, whereas a viscous fluid-like behaviour is displayed at the (c/w) interface. The adsorption isotherm for the block copolymer EO137SO18EO137 displays the four classical regions (pancake, mushroom, brush, and condensed states), whereas for EO12SO10 and EO10SO10E10 copolymers only two regions were observed. Probably, these observed differences in the monolayer isotherms arose from their different hydrophobic/hydrophilic block ratios and block lengths.

On the other hand, the fibrillation propensity of the protein human serum albumin (HSA) was analysed under different solution conditions (varying pH, temperature, ionic strength and solvent composition). Fibrillation is an important self-assembly mechanism of proteins which allows them to achieve an energy state even lower than their own native state. Also, the presence of protein fibrils has been related to the appearance and development of more than 20 neurodegenerative and non-neurodegenerative diseases, known as amyloid diseases. Hence, a profound knowledge about the fibrillation mechanisms and the structure of the resulting protein assemblies is required to develop new therapeutical strategies, but also to exploit the special structural properties of such protein aggregates in new technological fields.

In this way, the kinetics of HSA fibril formation under different solution conditions and the structures of resulting fibrillar aggregates were determined. It was observed that fibril formation is largely affected by electrostatic shielding: At physiological pH, fibrillation is more efficient and faster in the presence of up 50 mM NaCl. In contrast, under acidic conditions a continuous progressive enhancement of HSA fibrillation is observed as the electrolyte concentration in solution increases. The fibrillation process is accompanied by a progressive increase in ß-sheet and unordered conformations at the expense of ¿-helix one as revealed by CD, FT-IR and tryptophan fluorescence spectra. The presence of structural intermediates in the aggregation pathway, such as oligomeric clusters (globules), bead-like structures, and ring-shaped aggregates suggest that fibril formation takes place by the competent-association of these aggregates. The resultant fibrils are elongated but curly, and differ in length depending on solution conditions. In addition, very long incubation times lead to a complex morphological variability of amyloid fibrils, such as long straight fibrils or flat-ribbon structures, amongst other. In addition, the formations of ordered aggregates of amyloid fibrils, such as spherulites, which possess a radial arrangement of the fibrils around a disorganized protein core, or fibrillar gels were also observed. All these observations lead to the conclusion that HSA can be used as a suitable model to study protein fibrillogenesis.

On the other hand, the utility of the obtained HSA fibrils as building blocks to construct new and useful

nanomaterials as tested. We reported a method to obtain metallic Au nanowires by using lysozyme protein fibrils as bioscaffolds to generate a complete gold coating layer on the biotemplate surface by the attachment of gold seeds and subsequent overgrowth of the coating layer by sequential addition of gold salt growth solution (seeded-mediated mechanism). We decided to use lysozyme fibrils since these display a straight and uniform core, which is more suitable for the generation of nanowires. To obtain full coverage of the protein fibril, suitable [Au]/[protein] molar ratio and number of sequential additions of Au ions must be chosen. The hybrid metallic fibrils have been proved to be useful as catalytic substrates, provided their great catalytically activity when incorporated in the reduction reaction of p-nitrophenol to p-aminophenol by NaBH4. On the other hand, we also reported a method to obtain magnetic Fe3O4 nanowires by using HSA and lysozyme protein fibrils as bioscaffolds to generate a magnetic Fe3O4 coating layer on the biotemplate surface by the in situ controlled Fe nanoprecipitation method. The magnetic properties of the magnetic nanowires have been tested by using a superconducting quantum interference device (SQUID), and their potential applicability as MRI contrast agents was analysed by means of magnetic resonance imaging at different Fe doping concentration in phantoms.