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NANOSTRUCTURED AMPHIPHILIC SYSTEMS BASED ON HYALURONIC ACID IONIC COMPLEXES

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Hyaluronic acid (HyA) is a naturally occurring biodegradable polymer which is ubiquitous in the human body. HyA has enjoyed wide success in biomedical and cosmetic applications due to its high capacity for holding water and exceptional viscoelasticity, as well as to its inherent biocompatibility and biodegradability [1]. Chemical modification of HyA is a frequent practice applied today for creating new derivatives of this polyacid which are able to satisfy new demanding applications [2]. In this sense, coupling HyA with organocationic compounds bearing long linear alkyl chains is an extremely useful tool. In fact, recent studies carried out in our group [3] on coupling of HyA with alkyltrimethylammonium surfactants have proven that comb-like ionic complexes may be readily formed and that they are well stable and able to self-assemble into amphiphilic layered nanostructures.

In this communication we wish to report on HyA ionic complexes prepared by coupling with a) choline-based surfactants (*n*ACh·HyA complexes, Fig. 1a), and b) alkylphosphonium surfactants (*n*ATMP·HyA complexes, Fig. 1b) with *n* being the number of carbons of the alkanoyl or alkyl side chain. *n*ACh surfactants are synthesized from choline and fatty acids, and distinguished because they are fully biobased and biocompatible. The *n*ATMP surfactants have been scarcely studied as counterions of polyacids in spite of being more stable to heat and less harmful than their alkylammonium analogs.

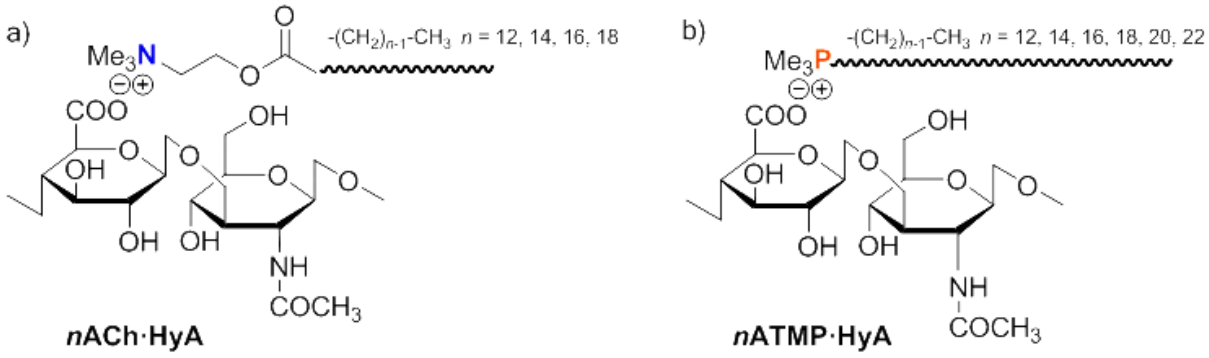
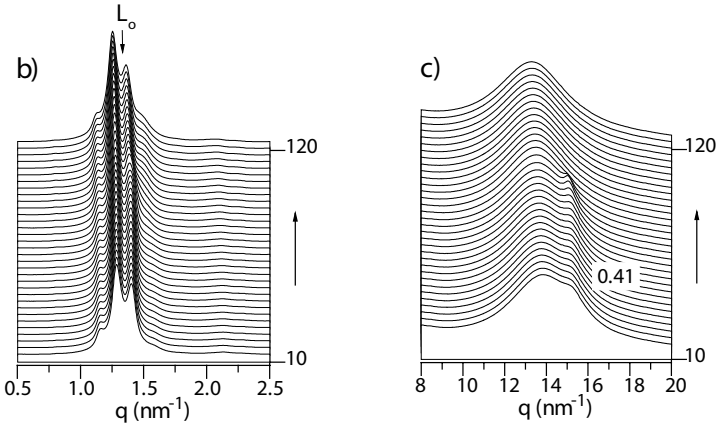


Fig. 1. Chemical structure of the two families of HyA complexes studied in this work. a) Alkanoylcholine complexes; b) Alkyltrimethylphosphonium complexes.

Complexes were synthesized by mixing equimolar aqueous solutions of the sodium salt of HyA and the respective cationic salts. The complexes spontaneously precipitated from the mixed aqueous solution and were recovered by centrifugation as white powders. These complexes were soluble in organic solvents but not in water. Degradation experiments demonstrated that they were sensitive to hydrolysis under physiological conditions, in particular in the presence of hyaluronidases.

Both, *n*ACh·HyA and *n*ATMP·HyA complexes were characterized by FT-IR and NMR spectroscopies which indicated that they are exempt of contamination and that their compositions are almost stoichiometric. The TGA essays under inert atmosphere revealed that they are thermally stable over 200 ºC. The DSC study showed well defined melting peaks arising from the paraffinic phase and taking place at temperatures within the 40-60 ºC interval

for those complexes bearing alkanoyl chains with $n \geq 16$ or alkyl chains with $n \geq 18$. Their structure, at both molecular and supramolecular levels, was studied in detail by SAXS/WAXS at variable temperature and real time (Fig. 2a).



It was found that both types of complexes adopted a layered biphasic structure with the hydrophilic main chain and the hydrophobic side chain clearly separated in organized nano-domains (Fig. 2b). Upon heating, the paraffinic phase melted without severe alteration of the layered nanostructure, and the whole structure was almost fully recovered after cooling.

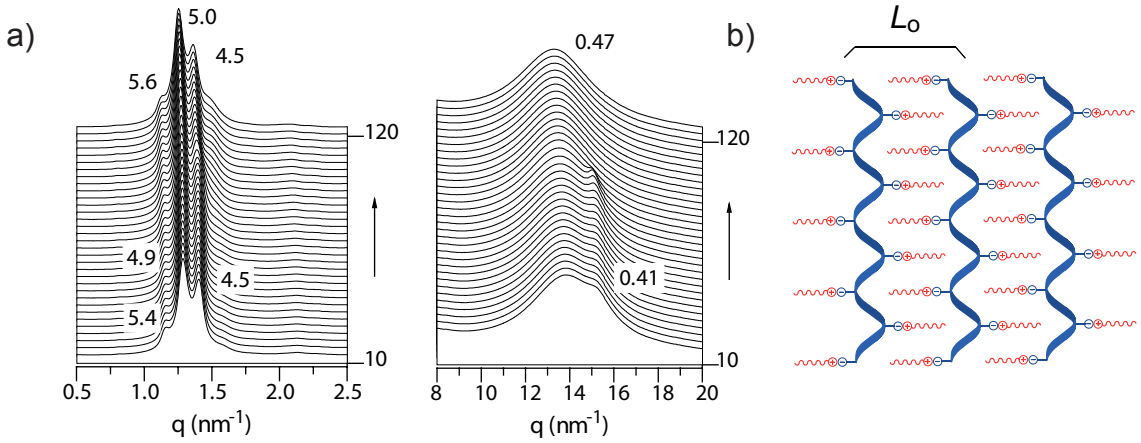


Fig. 2. a) Evolution of SAXS and WAXS profiles of 22ATMP·HyA upon heating over the 10-120 ºC interval. (Main spacings indicated in nm); b) Simplified scheme of the layered structure adopted by hyaluronic complexes.

The lamellar structure was also visualized by TEM. The repeating spacing measured for the observed periodical structured in complex films (Fig. 3a) was in agreement with the L_o spacing afforded by SAXS. The preparation of nanoparticles was feasible for some selected cases using the nanoprecipitation method. In practice, nanoparticles were formed by a self-assembly mechanism induced by the formation of the polyelectrolyte complex [4]. These nanoparticles have a diameter around 50-100 nm with a spherical to oblate or prolate shape and display the same periodical striations as the film (Fig. 3b). The detailed structure of these nanoparticles is currently under investigation.

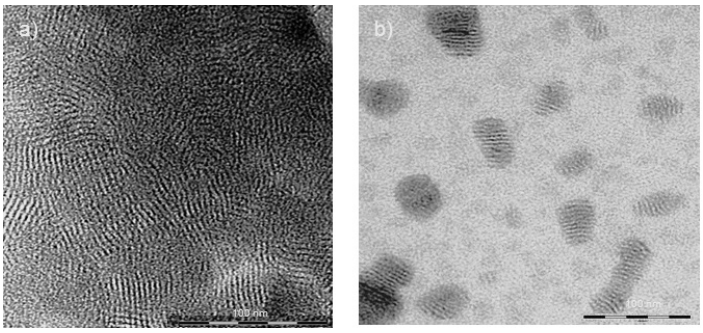


Fig. 3. TEM micrographs of 22ATMP·HyA complex. a) Film prepared by casting; b) nanoparticles created by spontaneous self-assembly in aqueous environment.

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