

Nano-engineered capsules based on chemically modified polysaccharides as multicompartment drug carriers

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I - Scientific objectives and strategy

This project deals with the development of capsules of which nanoshells are made of polyelectrolyte multilayer films having tailor-made properties. These capsules are fabricated by coating colloidal templates with layer-by-layer films (resulting from the alternate deposition of polycations and polyanions) followed by dissolution of the core material.

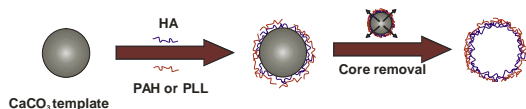


Figure 1. Synthesis of capsules using an anionic polysaccharide (HA) and a cationic polymer (PAH or PLL)

Such capsules have recently emerged as attractive materials in the field of controlled drug delivery and catalysis. However, the design and use of these core/shell systems as drug carriers for given therapeutic applications are still little explored. Elaboration of such nanoshells for biological applications requires the use of biocompatible polymers, and to date, one can notice that few realizations have been achieved from natural polymers.

In the present project, we propose to develop tailor-made capsules from biocompatible and biodegradable polysaccharides that have in addition 1) controlled mechanical properties and 2) designed nano-cavities for optimization of drug loading in the nanoshell, for the purpose of anti-HIV drug delivery.

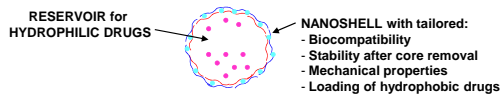


Figure 2. Hollow capsules made of LbL films

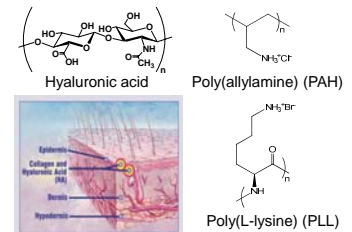
We present here our preliminary results concerning the development of conditions for the control synthesis of capsules based on hyaluronic acid, an important polysaccharide building block in the field of biomaterials.

II - Multilayer assembly based on hyaluronic acid: control of the buildup for the production of hollow capsules

Structure of the polyelectrolytes used for the multilayer assembly construction

Hyaluronic acid (HA):

- natural linear polysaccharide belonging to the glycosaminoglycan family. It consists of repeating units of D-glucuronic and N-acetyl-D-glucosamine.
- present in the synovial fluid, vitreous humor of eye, skin, cartilage...
- biocompatible, biodegradable (by enzymatic and/or chemical hydrolysis), biologically active
- used in various biomedical and cosmetic applications.



Effect of the molecular weight and concentration of HA on the buildup of the multilayer assembly.

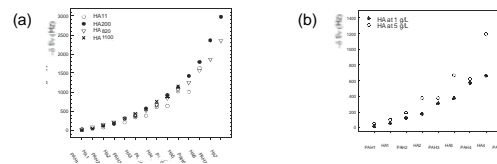


Figure 3. Analysis of film growth by quartz crystal microbalance with dissipation monitoring (QCM-D) : differences in the QCM frequency shifts measured at 15 MHz during alternate deposition of layers for (a) different M_w of HA (11×10^3 , 200×10^3 , 820×10^3 and 1100×10^3 g/mol) and (b) different concentrations of HA200 (1 and 5 g/L in 0.15 M NaCl, pH 6.5).

III - Synthesis of hollow capsules based on HA and control of their stability, biodegradability and permeability properties.

Preparation of microcapsules

The effect of the molecular weight and concentration of HA on the multilayer buildup on carbonate cores and on the morphology of capsules was investigated by microscopy techniques : transmission and scanning electron microscopy (TEM and SEM) and, confocal laser scanning microscopy (CLSM) (Figures 4 and 5).

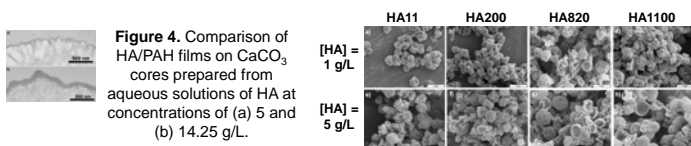


Figure 4. Comparison of HA/PAH films on $CaCO_3$ cores prepared from aqueous solutions of HA at concentrations of (a) 5 and (b) 14.25 g/L.

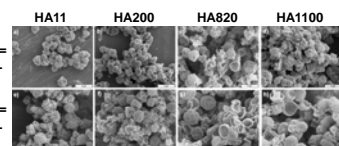


Figure 5. SEM images of capsules prepared with four HA/PAH bilayers using different HA samples.

Cross-linking of the shells and investigation of the permeability properties

Figure 6. CLSM images showing total rejection from capsules (left) or diffusion inside the capsules (right) of dextran-FITC molecules.

Conclusion and perspectives :

Our first results establish the feasibility to obtain hollow microcapsules based on the multilayer assembly of hyaluronic acid and cationic polymers (Langmuir (2008), 24, 9767-9774). This study clearly demonstrated the strong influence of the molecular weight of HA on the surface morphology of the capsules. This was mainly attributed to the porous structure of the carbonate template which allows penetration of polyelectrolytes when their size is below the maximum pore size of the carbonate template (~ 60 nm). These capsules hold promise in the controlled delivery of drugs due to their reservoir properties as well as to the large number of possible chemical modifications on HA for specific purposes such as cross-linking, grafting of drugs or cage molecules. They may also be designed for specific cell targeting. We are now working in these directions.

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