Journées Nationales en Nanosciences et en Nanotechnologies

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

ANR-07-NANO-BIOCAPS

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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.

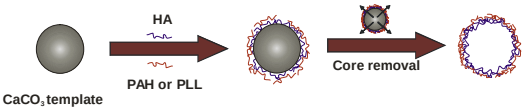


Figure 1. Synthesis of capsules using an anionic polysaccharide (HA) and a cationic polymer (PAH or PLL)

➢ 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.

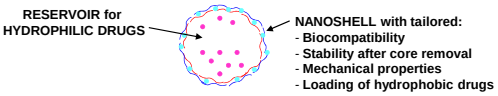


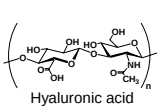
Figure 2. Hollow capsules as multicompartment drug delivery systems

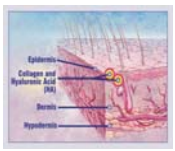
➢ We present here our work aimed at producing capsules able to encapsulate hydrophilic and hydrophobic drugs in the aqueous cavity and the multilayer wall, respectively. In this context, hydrophobically modified derivatives of hyaluronic acid (HA) were synthesized and their assembly into multilayer films form hydrophobic nanocavities was investigated. Moreover, we prepared capsules based on hyaluronic acid, by varying the nature of the polycation partner, and compared its effect on the morphology and permeability properties of capsules, as well as on their cellular uptake.

II - Synthesis of alkylated derivatives of hyaluronic acid and assembly into thin multilayer films forming hydrophobic nanocavities

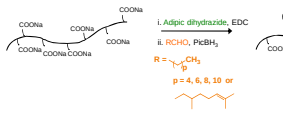
➢ Hyaluronic acid

- natural linear polysaccharide belonging to the glycosaminoglycan family.
- 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.

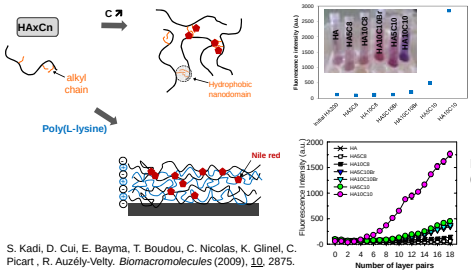




➢ Synthesis of hydrophobically modified derivatives of hyaluronic acid



HAxCn
X = DS (5 or 10 %)
n = Nb of carbon atoms of the alkyl chain
DS = degree of substitution, number of moles of substituting groups per repeating disaccharide unit



Aqueous solutions of alkylated HA (C_p = 2 g/L in PBS) containing the dye nile red at a concentration of 10 µM.

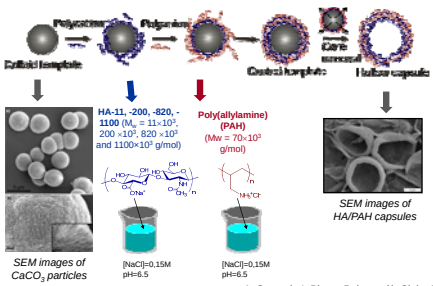
Incorporation of nile red in (PLL/alkylated HA)$_{18}$ films

S. Kadi, D. Cui, E. Bayma, T. Boudou, C. Nicolas, K. Glinel, C. Picart , R. Auzély-Velty. *Biomacromolecules* (2009), 10, 2875.

The formation of hydrophobic nanodomains could be observed both from aqueous solution of alkylated HA and from planar multilayer films. The ability of the films to entrap hydrophobic molecules was found to be tunable according to the HA derivative selected for the construction of the film and its thickness, which was related to the number of deposited layers. Similarly to results obtained in the bulk, the HA10C10 derivative lead to films able to efficiently entrap the dye nile red into hydrophobic nanodomains.

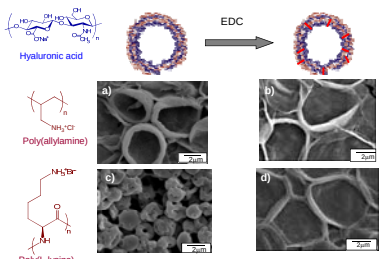
III – Synthesis of hollow capsules based on HA and manipulating the properties by chemical composition of the shell.

➢ Preparation of the capsules

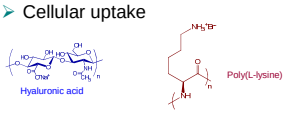


A. Szarpak, I. Pignot-Paintrand‡, Claire Nicolas, C. Picart, R. Auzély-Velty *Langmuir* (2008), 24, 9767

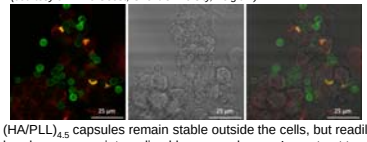
➢ Effect of the polycation on the morphology of crosslinked and non-crosslinked capsules



➢ Cellular uptake



Observation by CLSM of capsule internalization by RAW mouse macrophages (courtesy of B. De Geest, Ghent University, Belgium)



$(HA/PLL)_{4.5}$ capsules remain stable outside the cells, but readily break open once internalized by macrophages. In contrast to capsules made of synthetic polymers, which stay stable for a day or two inside the cells, the HA-based capsules readily break open when they enter the cell.

Our first results established the feasibility to obtain hollow microcapsules based on the multilayer assembly of hyaluronic acid and poly(allylamine) (A. Szarpak et al. *Langmuir* (2008), 24, 9767). As the main objective of this work was to obtain capsules able to encapsulate and release in a controlled manner hydrophilic and hydrophobic drugs, we then focused our study on the design of multilayer assemblies forming hydrophobic nanodomains. We thus demonstrated the ability of HA/PLL films to load a hydrophobic dye. Moreover, we investigated the formation and properties of HA/PLL capsules which contain fully biocompatible and degradable polymers in contrast to HA/PAH capsules. The HA/PLL capsules exhibited low mechanical properties, which required shell crosslinking. Interestingly, those capsules could be internalized by cells in which they readily break open. Such a capsule behavior upon cellular uptake has never been reported before. Considering the promising properties of the HA-based capsules as drug delivery systems, we plan in future work to investigate the incorporation and biological activity of hydrophobic drugs loaded in these carrier systems.

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