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Glucose-sensitive polyelectrolyte microcapsules based on (alginate/chitosan) pair

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ABSTRACT

Novel chemical stimulus-responsive multilayer assemblies have been elaborated through the layer-by-layer deposition of oppositely charged polysaccharides on either flat or spherical surfaces. Concentration-dependent glucose responsiveness was obtained through chemical modification of alginate, selected as polyanion, with phenylboronic acid moieties. QCM measurements showed that the alginate derivate still self-assembles though electrostatically-driven interactions with chitosan at pH 4, and that the polysaccharides multilayer assemblies, as obtained after crosslinking, exhibit improved stability versus pH (in the range 4–9) as well as swelling ability in the presence of glucose-containing solution. Glutaraldehyde-mediated crosslinking was achieved through reaction with free primary amines of chitosan. This approach was further extended to the preparation of smart capsules using $CaCO_3$ microparticles as dissolvable core templates. Success of the LbL deposition process, stability (pH range 4–9) of the multilayer assemblies and glucose-induced swelling were fully confirmed for the microcapsules. One of the major result of this study is that crosslinking prevents total dissolution of the capsules and enables modulating the permeability of the polysaccharide shell yielding controlled release on in-capsule entrapped low molecular weight molecules.

1. Introduction

Hollow particles, commonly named capsules (Shi, Shen, & Möhwald, 2004), have attracted increasing scientific interest in many fiels as for sensing, diagnosis or drug delivery (Deshmukh et al., 2013; Sukhorukov, Fery, & Möhwald, 2005), organic synthesis for catalysis, comestology to enhance permeation of active compounds through the skin, in food science and agriculture to mitigate toxicity and minimize environmental impacts of herbicides, to name but a few. This undeniable success can be rationalized by the possibility to easily access to a large range of capsules with tuneable shape, size wall thickness and permeability (Caruso, 2000; Caruso, Susha, & Caruso, 2001; Peyratout & Dähne, 2004). Moreover, the hollow core-shell structure (Johnston, Cortez, Angelatos, & Caruso, 2006) provides a container-type functionality making capsules promising carriers with programmable release (Peyratout & Dähne, 2004). Restricting the discussion to medecine, spatiotemporal control of the release profile is highly desired as it can contribute to improving therapeutic efficacy while reducing toxicity of a drug. Control release of drug can be initiated in response, or not, to an external stimuli. In the former case, the system is refer to a stimuli-responsive controlled-release delivery system. Such a smart behaviour can be combined through the judicious choice of the materials constitution the capsule's shell.

So far, many methods have been developed to construct hollow particles including pH induced micellization of a grafted polymer (Dou, Jiang, Peng, Chen, & Hong, 2003), polymerization of monomers on a liquid core, emulsion polymerization, phase separation, crosslinking of micelles, self-assembly and layer-by-layer (LbL) deposition of polyelectrolytes onto a sacrificial template (Gittins and Caruso, 2000; Gittins & Caruso, 2001). Herein, we particularly paid attention to the latter approach (Borges & Mano, 2014) as it proved efficient for the chemical modification of a plethora of substrates (Shimomura & Sawadaishi, 2001; Szarpak et al., 2010).

The overall strategy relies on stepwise film formation through repeated exposure of the colloid particle templates to polyelectrolytes with opposite charges. The polyelectrolyte excess is then removed by simply washing prior to deposition of the subsequent layer. After deposition of the desired number of polyelectrolyte layers, the sacrificial template is eliminated, through dissolution mainly, and a suspension of polyelectrolyte hollow shells is recovered (Peyratout & Dähne, 2004). To date, solid particles (Schüler & Caruso, 2001) have been widely used as cores for developing the said capsules, and one may cite as

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Table 1
Macromolecular characterization of polymers by SEC/MALS/DRI analysis.

Samples	Abbreviation	$\overline{Mn}$ (g mol^{-1})	$\overline{Mw}$ (g mol^{-1})	Đ*	DS**
chitosan	chiA	85 000	196 000	2.3	0.14 ± 0.02[a]
	chiB	78 000	174 000	2.2	0.28 ± 0.04[a]
	chiC	200 000	328 000	1.6	0.34 ± 0.04[a]
alginate	alg	270 000	380 000	1.4	–
alginate-g-boronic	alg-bor	250 000	620 000	2.5	0.20 ± 0.04[b]

*Polydispersity index (ð) Đ = $\overline{Mw}/\overline{Mn}$.
**Degree of substitution.
[a] Degree of acetylation of chitosan (estimated from ^{1}H NMR from Hirai et al. (Hirai et al., 1991), Eq. (1), Fig. S1).
[b] Grafting ratio of phenylboronic acid groups (estimated from ^{1}H NMR from Pettignano et al. (Pettignano et al., 2017) (Eq. (2)), Fig. S2 TOC/TN (Eq. (3)).

representative examples templates based on polymer (poly(styrene),poly(lactic acid), metal (Au) or metal oxide (SiO_2 or $CaCO_3$)). These organic and inorganic templates can be easily and quantitatively dissolved in organic solvents and aqueous solutions, respectively (Hu, Chen, Fang, & Wu, 2011).

Herein, we focus on calcium carbonate cores as sacrificial templates because of its easy preparation, biocompatibility, low cost, decomposition in mild conditions and intrinsic porosity (Stein, Volodkin, McShane, & Sukhorukov, 2006; Sukhorukov et al., 2004; Volodkin, Larionova, & Sukhorukov, 2004; Volodkin, Petrov, Prevot, & Sukhorukov, 2004). (Petrov, Volodkin, & Sukhorukov, 2005). Indeed, $CaCO_3$ micro-sized are easily made by mixing calcium chloride and sodium carbonate and are easily dissolved using ethylenediaminetetraacetic acid (EDTA) solution (Zhao, Mao, Gao, & Shen, 2006). They can be obtained in the micro-size range (Pechenkin, Mohwald, & Volodkin, 2012). Of particular interest, one can take advantage of the intrinsic porosity of $CaCO_3$ particles for drug loading purpose and further after LbL deposition of polyelectrolyte shell.

For in vivo drug-delivery applications, one of the most fundamental issues is the use of biocompatible and nontoxic capsule shell. Towards this aim, polysaccharides are very competitive candidates. Indeed their hydroxyl-rich chemical structure and pH-dependent charge enable, under specific conditions, LbL assembly formation electrostatic interactions in tandem with hydrogen bonds may act as driving the force for deposition of polysaccharides. We can mention the successive deposition of polysaccharides, proteins or lipids to form multilayers walls of microcapsules, e.g. chitosan/chitosan sulfate (Berth, Voigt, Dautzenberg, Donath, & Mohwald, 2002) or dextran sulfate/protamine (Balabushevich, Tiourina, Volodkin, Larionova, & Sukhorukov, 2003). Moreover, polysaccharides can be easily chemically modified to provide responsiveness to various stimuli.

Providing “stimuli- responsiveness” to drug carriers may open smart path to trigger the release upon specific changes in the surrounding medium. In the specific case of polyelectrolyte capsules, the multilayered shell governs the stimuli-responsive performances. Numerous studies reported on capsules responsive to a broad range of external stimuli such as pH, temperature, ionic strength, magnetic field or even temperature (De Geest, Sanders, Sukhorukov, Demeester, & De Smedt, 2007; Sanders, Sukhorukov, Demeester, & De Smedt, 2007; Sukhishvili, 2005). Although glucose has a crucial biological function in living systems, only few groups have considered glucose as chemical stimulus for triggering the physicochemical properties of polymer-based assemblies. (De Geest, Jonas, Demeester, & De Smedt, 2006) For instance, one of those overproduced metabolite in tumors is glucose (Brooks & Sumerlin, 2016; Wu, Wang, Yu, Wang, & Chen, 2011) and cancer cells present a very high glucose concentration as compared to normal cells (Aykin-Burns, Ahmad, Zhu, Oberley, & Spitz, 2009). Although the controlled design of glucose-responsive systems remains a challenging task (Wu et al., 2011). Glucose responsive capsules are undoubtedly promising candidates for the treatment of diabetics. Phenylboronic acids are known to form covalent bonds with polydiols such as polysaccharides (De Geest et al., 2006) and the complexation occurs efficiently in a pH range above the pKa of the boronic moities (pKa ~ 9) (Brooks & Sumerlin, 2016; De Geest et al., 2006; Wu et al., 2011).

Levy et al. have elaborated glucose-sensitive capsules, stabilized by the formation of ester bonds between mannan and phenylboronic acid moieties grafted onto poly(acrylic acid) (Levy, Déjugnat, & Sukhorukov, 2008). The competitive binding of low molecular weight saccharide and mannan with the boronic acid groups incorporate within the films control on the destabilization of the multilayered film. De Geest et al. have prepared glucose-sensitive capsules by the layer-by-layer assembly of a copolymer of dimethylaminoethylacrylate and acrylamidophenylboronic acid as polycation and poly(styrene sulfonate) as polyanion. They evidenced glucose-induced change in the electrostatic interactions between the polyanion and the phenylboronic acid-containing polycation (De Geest et al., 2006). The here-above mentionned strategies involved the total destabilisation of the film upon contact with a sugar solution above a critical concentration. Herein, we suggest a complementary approach to the sugar-induced total dissolution of multilayered films. More precisely, we report on preparation of glucose-responsive hollow polyelectrolyte multilayer capsules based on natural polyelectrolytes, namely chitosan as polycation and phenylboronic acid-functionalized alginate, as polyanion. Our strategy differs by the crosslinking of the multilayer films providing capsules with enhanced stability in a broad range of pH together and swelling ability in the presence of glucose. As such the addition of glucose does not induce total dissolution of the designed capsules but rather modify the permeability of the polyelectrolyte shell allowing for time-dependent release properties. The responsiveness of chitosan/boronic acid modified alginate derivative films has been investigated in the presence of glucose-containing solutions at varied concentrations. Effects of the average molar mass and the degree of acetylation of chitosan as well as crosslinking time are also discussed.

2. Experimental parts

2.1. Chemicals

The following chemicals were used as received: chitosan (Sigma-aldrich), alginate with mannuronic/guluronic ratio 1.4 (Cargill (Baupte, France)) (macromolecular characteristics are given in Table 1), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC, Sigma-aldrich, > 98.5%), N-hydroxysuccinimide (NHS, Sigma-aldrich, > 98%), mercaptosulfonate (Sigma-aldrich, > 89.5%), calcium chloride ($CaCl_2$, rectapur, 99%), [9-(2-carboxyphenyl)-6-diethylamino-3-xanthenylidene]-diethylammonium chloride (rhodamine b, Alfa Aesar, > 98.5%), sodium nitrate (rectapur, 99%), 4-aminophenylboronic acid hydrochloride (Alfa Aesar, 97%), acetic acid (Alfa Aesar, + 99%), sodium acetate (Alfa Aesar, 99%) and ethylenediaminetetraacetic acid (EDTA, Sigma-Aldrich, 98%). Water was purified with a Milli-Q reagent system (Millipore).