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Effect of chitosan coating on the swelling and controlled release of a poorly water-soluble drug from an amphiphilic and pH-sensitive hydrogel

I. Colinet[a], V. Dulong[a], G. Mocanu[b], L. Picton[a], D. Le Cerf[a,*]

[a] University of Rouen, Lab. Polymers Biopolymers Surfaces-CNRS UMR 6270 and FR 3038, 76821 Mont Saint Aignan, France
[b] "Petru Poni", Institute of Macromolecular Chemistry, Iasi, Romania

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ABSTRACT

In the present work, a new particulate controlled release system was prepared, by coating alginate-*g*-PCL/Ca^{2+} beads with chitosan. The swelling behaviour and controlled release of a poorly water-soluble drug (theophylline) model were studied in media of varying pH, by simulating human fluids at 37 °C. In a simulated gastric fluid (SGF, pH 1.2), coated beads presented weak swelling (8–22%) and weak release rates (24–32% within 120 min), and were able to protect the drug from this harsh environment. In a simulated intestinal fluid (SIF, pH 6.8), the swelling rates of amphiphilic beads (before disintegration) were strongly reduced (300–1100%) comparatively with those of uncoated beads (700–1700%). This can be explained by the strong electrostatic interactions between the amino groups of chitosan and the carboxylate groups of alginate-*g*-PCL, leading to the formation of a protective membrane of strong polyelectrolyte complex around the beads. This outermost layer effectively promoted the stability of beads under gastro-intestinal tract conditions, while the hydrophobic interactions between theophylline and PCL grafts allowed a considerable slowing down of the drug release. It was found out that combination of the protective effect of the polyelectrolyte membrane in SIF associated with the hydrophobicity of PCL grafts allowed to release a poorly water-soluble drug, in a controlled manner, for 7 h, along a simulated gastro-intestinal tract.

1. Introduction

Hydrogels are hydrophilic polymer networks which may absorb from 10 to 20% (within arbitrary limit) up to thousands times their dry weight in water. They are of interest not only for industrial applications such as cells encapsulation [1], drug delivery systems [2], separation processes [3] but also for enzymes immobilisation [4]. For biomedical applications, the systems should be biocompatible and stimuli responsive as a function of temperature, pH, etc.

These systems were largely developed for entrapment and release of hydrophilic drugs, such as peptide, protein, etc. [5]. When the drugs are hydrophobic or poorly water-soluble, systems with amphiphilic properties should be employed. Poly(N-isopropylacrylamide) (PNIPAAm) and other Low Critical Solubility Temperature (LCST) polymers can be used due to the hydrophobic character obtained at a temperature higher than LCST [6]. Grafting of an alkyl chain on the polymer backbone is another possibility yet the biocompatibility is reduced [7]. Other hydrophobic groups, such as Poly(ε-caprolactone) (PCL) or Poly(lactic acid), are potential candidates [8]. In these systems, entrapment of poor water-soluble drugs is possible if hydrophobic clusters are formed in the hydrogel.

A previous paper [9] reported results about the swelling/degradation and drug release behaviour of beads based on an amphiphilic polysaccharide (alginate-*g*-PCL) cross-linked with Ca^{2+} ions. It was found out that the release of a poorly water-soluble model drug (theophylline) is strongly slowed down within a simulated gastro-intestinal tract, compared to its kinetic release from a hydrogel based on alginate, due to the establishment of hydrophobic clusters inside the beads. The best system is obtained when the length of PCL is reduced to 530 g mol^{-1} against 1250 g mol^{-1}. For these systems, it has been shown that hydrophobic interactions give hydrophobic clusters in a preferentially intramolecular way. However, these systems are not sufficiently stable in the simulated intestinal fluid. Due to ionic exchanges, they swell and degrade rapidly, which causes a rapid release of the drug.

Many methods have been adopted by researchers to overcome the limitations imposed by the physical instability of systems based on alginate and cross-linked by calcium ions, in high pH media.

Abbreviations: PNIPAAm, Poly(N-isopropylacrylamide); LCST, Low Critical Solubility Temperature; PCL, Poly(ε-caprolactone); TPH, Theophylline; CS, Chitosan; SGF, Simulated gastric fluid; SIF, Simulated intestinal fluid; GI, Simulated gastro-intestinal tract.

* Corresponding author. Tel.: +33 235 14 65 43; fax: +33 235 14 65 43.
E-mail address: didier.lecerf@univ-rouen.fr (D. Le Cerf).

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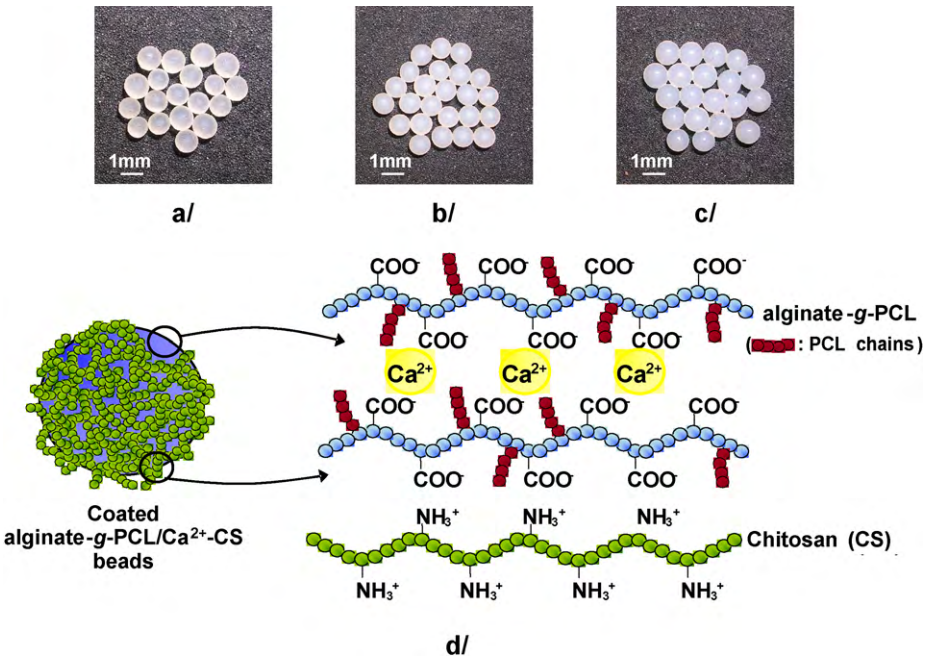

Fig. 1. Pictures of wet beads of coated alginate/Ca^{2+}-CS (a/), 530-8/Ca^{2+}-CS (b/) and 1250-13.5/Ca^{2+}-CS (c/) beads. Schematic structure of a coated alginate-*g*-PCL/Ca^{2+}-CS bead (d/).

Chitosan-alginate polyelectrolyte complexes have been especially and widely used to obtain microcapsules for cell encapsulation and devices for a controlled release of drugs or of other substances [10–14]. Chitosan is a weak cationic polysaccharide, composed mainly of (1,4) linked 2-amino-2-deoxy-β-D-glucan. It exhibits a pH-sensitive behaviour due to the large quantities of amino groups present on its chain, with a pK_a from 6.5 to 6.8 [14]. As a function of pH, the negatively charged carboxylate acid groups of alginate can form ionic bound with the positively charged amino groups of chitosan, to form a polyelectrolyte complex on the basis of their opposite charges. Thanks to these interactions, it was demonstrated that addition of chitosan in formulations based on alginate cross-linked with Ca^{2+} ions improves the physical stability of these systems in high pH medium, to alter their swelling and erosion rates, and to slow down the diffusion rates of the entrapped substances. Elaboration of alginate-chitosan blend gel beads based on calcium chloride ionic cross-linking has been reported [15–17].

There are many other advantages of chitosan coating, such as improvement of the bio-adhesive property of alginate/Ca^{2+} beads or liposomes [18,19], due to the presence of a negative charge on almost all mucous membranes of the gastro-intestinal tract, which increases the contact time of drugs with the mucosa. For example, these mucoadhesive properties of chitosan allowed to prolong the residence time of the protein drug carrier [18] or liposomes [20] in the GI tract, and to prolong [21–23] and control [24] the drug release properties. Consequently, the chitosan coating could be an efficient method to improve the stability of alginate-*g*-PCL/Ca^{2+} beads in SIF, and hydrophobic interactions between PCL grafts and amphiphilic drug might allow its release, in a controlled manner. Stable alginate-*g*-PCL/Ca^{2+} beads coated with chitosan were prepared and the swelling, stability and release behaviour of a poorly water-soluble model drug was reported in SGF, SIF and in a medium of varying pH which mimics the gastro-intestinal tract. This study has been undertaken with two major objectives: first, to increase the overall stability of alginate-*g*-PCL/Ca^{2+} beads in SIF through coating of alginate-*g*-PCL/Ca^{2+} beads with a cationic natural polymer and secondly, to evaluate their potential use as controlled release systems in pharmaceutical applications.

2. Materials and methods

2.1. Materials

The synthesis of alginate-*g*-PCL was described in detail in a previous study [25]. The copolymers are obtained without degradation (Mn = 200,000 g mol^{-1}). In the present study chitosan (CS) had a low molecular weight (M = 15,000 g mol^{-1}) (Sigma–Aldrich).

Indeed, Gåserød et al. [26] have studied the interactions between alginate and chitosan in a quantitative manner and they have found out that binding of chitosan to alginate was markedly increased by reducing the number average molecular weight of chitosan (equal or lower than 20,000 g mol^{-1}). Theophylline (TPH) and calcium chloride were purchased from Acros Organics. Hydrochloric acid (HCl) and sodium chloride (NaCl) were purchased from Sigma–Aldrich. All compounds and solvents were used without further purification. Water was purified with a Milli-Q reagent system (Millipore). Modified alginates are coded as follows: *X*–*Y* where *X* is the molecular weight of the grafted PCL and *Y* the real incorporation rate of PCL. Hydrogels were based on 530-4, 530-8 and 1250-13.5 samples [25].

2.2. Preparation of CS coated alginate/Ca^{2+} and alginate-*g*-PCL/Ca^{2+} beads

Elaboration of uncoated alginate/Ca^{2+} and alginate-*g*-PCL/Ca^{2+} beads was reported in a previous study [9]. Alginate-*g*-PCL/Ca^{2+} (and alginate/Ca^{2+}) beads coated with CS were prepared by dropping. Alginate-*g*-PCL (or alginate) was dissolved in distilled water at a concentration of 20 g L^{-1}. The pH was then adjusted to 7.0 with 0.1N NaOH, and a solution of NaCl was added, to obtain an ionic strength of 0.1 M. The gelling medium was a CS solution of 2 or 5 g L^{-1} in diluted HCl (pH 1.2). The pH of this solution was previously increased until a pH value of 4.0 (with NaOH 1N), followed by addition of $CaCl_2$ (0.15 M), and NaCl (0.1 M). The alginate-*g*-PCL (or alginate) solution was dropped into the gelation medium (CS/$CaCl_2$) using a 10 mL hypodermic syringe, under constant stirring at room temperature.