

Chitosan (or alginate)-coated iron oxide nanoparticles: A comparative study



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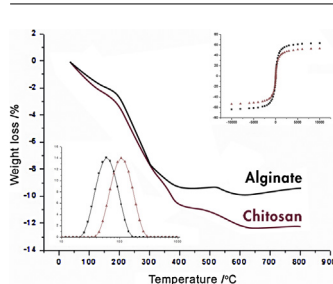
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HIGHLIGHTS

- Ferrofluid formed by adsorption of unmodified alginate or chitosan.
- Optimal concentration of polymer for recovering the particles has been determined.
- The polymer coating avoids the formation of clusters.
- Alginate-coated nanoparticles exhibit the highest stability in biological medium.

GRAPHICAL ABSTRACT



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ABSTRACT

The preparation and characterization of stable aqueous suspensions of superparamagnetic iron oxide nanoparticles stabilized with chitosan (CHI) or with alginate (ALG) are reported.

Particles of iron oxide were synthesized via a controlled co-precipitation method. The particles obtained had a diameter ~ 12 nm; a value that ensures superparamagnetic properties and their suitability for biomedical applications. The optimal concentration of polymer needed for coating the nanoparticles was determined using adsorption isotherms. When the magnetic nanoparticles were coated with CHI and ALG, their properties were compared through the following measurements: hydrodynamic ratio; ζ -potential; content of polymer coating the particles, by thermogravimetry; magnetic properties; high-resolution transmission electron microscopy; and, finally, their stability in biological media. The ALG-coated nanoparticles had a mean diameter of 50–55 nm, whereas that of the CHI-coated nanoparticles was 80–120 nm. Both types of particles showed similar values of saturation magnetization (59.3 emu g^{-1} for ALG-coated nanoparticles; 56.8 emu g^{-1} for CHI-coated ones); however, when in contact with human multiserum at 37°C , significant differences were observed between the two. The ALG-coated nanoparticles were stable for up to 9 days, while the CHI-coated nanoparticles were stable for only 2 days. Agglomeration and phase separation were the main effects observed.

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1. Introduction

The development of highly effective medicine requires continuous and timely monitoring of medical treatment processes. The combination of monitoring (also called imaging or diagnostics) and therapeutics allows for a considerable degree of control over treatment efficacy in different individuals and is now commonly referred to as “theranostics” [1]. The combination of therapeutic and diagnostic capability in a single agent is anticipated to give rise to new protocols that will adapt treatment to test results, thereby providing more specific and efficient systems for curing disease. Such combined agents are materials capable of detecting and treating diseases in one single procedure. Emerging nanotechnology offers great opportunities to design and generate such agents, wherein detection is allowed to run not only before or after, but also during a treatment regimen [2]. Due to the presence of a large percentage of surface atoms, inorganic nanoparticles (NPs), especially those in the <20 nm range, have unique physical and chemical properties that are not observed in their bulk forms [3]. This, plus their size, makes inorganic NPs ideal probes for theranostic applications. Among various NPs studied so far, magnetic NPs containing ferromagnetic iron (Fe) and cobalt (Co), as well as their alloys and oxides, have been shown to be the most promising probes for theranostics, promising the desired imaging sensitivity and therapeutic efficacy [4–7]. Thus, iron oxide nanoparticles are advantageous due to their inherent biocompatibility and relatively low cost. In order to confer colloidal stability on the particles and to protect them from aggregation, NPs may be embedded in other crystalline or amorphous nanoscale materials, resulting in what are known as ferrofluids. Ferrofluids are used in medical science, especially as contrast agents for magnetic resonance imaging (MRI) and in hyperthermia [8]. Among the embedding materials, hydrophilic polymers, such as dextran and its derivatives [9–11], polyvinyl alcohol (PVA) [12], polyethylene glycol [13–17], alginate (ALG) [18] and chitosan (CHI) [19–21], have been used to stabilize bare magnetic nanoparticles. The surfaces of the NPs can be coated with a polymer by adsorption or grafting. Adsorption is the most versatile attachment mechanism and is applicable to a broad range of particles and polymers [8].

CHI and ALG are two of the more common naturally occurring polysaccharides that are increasingly being studied in the biomedical field, particularly in the area of drug delivery [22]. CHI is a deacetylated derivative of chitin, a polycationic polymer found in the shells of crustaceans. With one amino group and two hydroxylic functions in repeating glycosidic residues it is structurally similar to hyaluronic acid [23]. Moreover, CHI has remarkable affinity with many biomacromolecules. ALG is an anionic polymer extracted from brown algae and contains carboxylic acid groups that may introduce negative charge to the polymer at appropriate pH values [24]. ALG is now known to be a whole family of linear copolymers containing blocks of (1,4)-linked β -D-mannuronate (M) and (1–4)-linked β -D-guluronate (G) residues. The blocks are composed of consecutive G residues (GGGGGG), consecutive M residues (MMMMMM) and alternating M and G residues (GMGMGM). ALGs extracted from different sources differ in the length of each block [24]. CHI and ALG could have major applications in the fields of biotechnology, biomedicine, food ingredients and cosmetics [25,26]. In this study, we examine and compare the properties of magnetic particles stabilized with ALG or with CHI. We compare the characteristics of the coatings of magnetic cores consisting of these polymers under the same experimental conditions. It is known that the properties of the initial iron nanoparticles determine the stability of the resulting nanoparticles. Hence, this study allows us to identify real differences and similarities between the coating capacities of the polymers.

2. Materials and methods

All the chemicals were reagent-grade and used without purification. Ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$), ferrous chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), CHI (molecular weight: 91.1 kDa) and ALG (molecular weight: 12 kDa, medium viscosity) were purchased from Sigma–Aldrich (St. Louis, MO). Ammonium hydroxide (NH_4OH , 25%) was supplied by Panreac (Barcelona, Spain). Deionized Millipore Milli-Q water was used in all the experiments. A strong neodymium–iron–boron ($\text{Nd}_2\text{Fe}_{12}\text{B}$) magnet (1.2 T) was obtained from Halde GAC (Barcelona, Spain).

2.1. Preparation of magnetite

Magnetite (Fe_3O_4) NPs were synthesized via a controlled chemical co-precipitation method [27]. Briefly, they were prepared in aqueous solution by addition of 1 mL of FeCl_2 2 M solution to 4 mL of FeCl_3 1 M solution (1:2, molar ratio) under constant magnetic stirring. Then, 60 mL of 0.5 M ammonia was added drop by drop and the mixture was stirred vigorously for 15 min more, until a precipitate formed. This precipitate was then washed with MilliQ water, and a magnet used to eliminate excess ammonia. As ammonia is a good ligand to iron, the absence of ammonia was confirmed by measuring the pH of the rinsing. When pH reached a constant value (≈ 6), ammonia was supposed to be eliminated from iron. This fact is achieved after five cleaning steps.

2.2. Determination of the optimal concentration of polymer

The optimal amount of polymer needed to coat the magnetic particles was determined by the solution depletion method [28]. Suspensions were prepared by adding an appropriate aliquot of polymer stock solution to an aliquot of magnetite stock solution; then, the tubes containing the samples were immediately closed and shaken. Each suspension contained 0.2 g magnetite and a polymer concentration in the range 50–2500 mgL^{-1} for a total suspension volume of 20 mL in a 50 mL falcon tube. The samples were rotated end over end at 30 rpm for 24 h at room temperature in a test tube rotator (L-29, Labinco, Netherlands). The suspension was then centrifuged for 180 min at 3600 rpm (Didacem II, Orto-Alresa, Spain) to separate the coated particles from the supernatant. The supernatant was carefully removed and filtered through 0.45 μm membranes. The concentration of non-adsorbed polymer in the supernatant was determined spectrophotometrically: ALG by means of the anthrone method [29] and CHI according to the reaction of *o*-phthaldehyde (OPA) and β -mercaptoethanol with primary amines [30]. The adsorbed mass was calculated from the difference between the initial and final polymer concentrations. The concentration of iron in each suspension was measured by the Kiwada method [31]. A multiplicative factor of 1.38 was used to convert the measured mass of iron to an equivalent mass of magnetite, which takes into account the oxygen content of magnetite. Each value for the adsorbed mass corresponds to the average of measurements performed in triplicate.

2.3. Preparation of ferrofluid

Both kinds of ferrofluid (ALG- and CHI-coated) were prepared following the same method. Briefly, the optimal amount of polymer determined according to the adsorption isotherms was solubilized (in water for ALG; in acetic acid at a pH of 5.5 for CHI). Then, 20 mL of the polymer solution was added to the NPs and the mixture was stirred at increasing temperatures: at 45 °C for 60 min, then at 60 °C for 15 min and, finally, at 70 °C for 15 min.

After this, the coated NPs were poured into a beaker and the vessel was placed on a permanent magnet. The coated NPs were

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